

## Evaluation of the Pediatric Patients with Primary Vesicoureteral Reflux- Single Center Study

### Primer Vezikoüreteral Reflü İle İzlenen Pediatrik Hastaların Değerlendirilmesi- Tek Merkez Çalışması

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#### ABSTRACT

**Objective:** Vesicoureteral reflux (VUR) with bladder and bowel dysfunction (BBD) predispose to recurrent urinary tract infections (UTIs), thus increase the risk of kidney damage. In this study, we retrospectively evaluated the clinical characteristics and outcomes of children with primary VUR.

**Methods:** 115 patients diagnosed with primary VUR were enrolled. The patients were grouped according to VUR stages and demographic characteristics, laboratory and imaging studies, medical and surgical treatment options were evaluated.

**Results:** Majority of the patients were females (82.6%). Mean follow-up time was 3.6±1.1 years. At admission, 60% and 62.6% of the patients had recurrent UTIs and BBD, respectively. There was grade I-II VUR, grade III VUR and grade IV-V VUR in 26.8%, 51.7% and 21.5% of 149 renal units, respectively. Ultrasonographic abnormalities and scarring on technetium (Tc)-99m dimercaptosuccinic acid (DMSA) were significantly higher in high grade VUR (p=0.001 and p=0.04, respectively). Patients with scarring had significantly more recurrent UTIs, BBD and ultrasonographic abnormalities (p=0.03, for all). 22.6% of the patients underwent surgery. Control voiding cystourethrography (VCUG) of 67 renal units showed spontaneous resolution in 38.8%, whereas surgical correction/regression was detected in 53.7%. Patient outcomes were favorable with decreased recurrent UTIs (15.6%) and no progression into chronic kidney disease (CKD).

**Conclusion:** Risk of renal scarring, an important finding of reflux nephropathy and subsequent CKD, was significantly higher in patients with high grade VUR, recurrent UTIs and BBD. Urinary ultrasonography was reliable in predicting scarring. Children with recurrent UTIs and/or BBD as well as urinary ultrasonography (USG) abnormalities should be evaluated for VUR.

**Keywords:** Vesicoureteral reflux, renal parenchymal scarring, urinary tract infections, bladder bowel dysfunction, chronic kidney disease, children

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#### ÖZET

**Amaç:** Vezikoüreteral reflü (VUR) ve eşlik eden mesane-barsak disfonksiyonu (MBD) tekrarlayan idrar yolu enfeksiyonlarına (İYE) yol açarak, böbrek hasarı olasılığını artırır. Bu çalışmada, primer VUR ile izlenen çocuklarda klinik özellikler ve izlem sonuçları retrospektif olarak değerlendirildi.

**Yöntem:** Primer VUR ile izlenen 115 hasta çalışmaya alındı. Hastalar VUR evrelerine göre gruplandırılarak, demografik özellikleri, laboratuvar ve görüntüleme tetkik bulguları, tıbbi ve cerrahi tedavi yöntemleri incelendi.

**Bulgular:** Olguların çoğunluğunu kız hastalar oluşturmaktaydı (%82,6). Ortalama izlem süresi 3,6±1,1 yıldır. Başvuru anında hastaların sırasıyla %60 ve %62,6'sinde tekrarlayan İYE ve MBD saptandı. Toplam 149 renal ünitenin %26,8'inde evre I-II VUR, %51,7'inde evre III VUR ve %21,5'inde evre IV-V VUR mevcuttu. Yüksek evreli VUR saptanan hastalarda ultrasonografik bozuklukların ve teknisyum (Tc)-99m dimercaptosüksinik asit (DMSA) sintigrafisiyle belirlenen skar varlığının anlamlı yüksek olduğu görüldü (sırasıyla p=0,001 ve p=0,04). Skarı olan hastalarda olmayanlara göre tekrarlayan İYE, MBD ve ultrasonografik anormallikler anlamlı düzeyde yüksekti (hepsi için p=0,03). Hastaların %22,6'sine cerrahi uygulandı. Kontrol işeme sistoüretrografi (İSÜG) 67 renal ünitenin %38,8'sinde spontan rezolüsyon olduğu, %53,7'sinde ise cerrahi ile düzelleme/gerileme elde edildiği belirlendi. İzlemede elde edilen sonuçlar yüz güldürücü olup, hastaların sadece %15,6'sinde tekrarlayan İYE'nin devam ettiği ve hiçbir hastada kronik böbrek hastalığı (KBH) gelişmediği görüldü.

**Sonuç:** Çalışmamızda yüksek dereceli VUR olan, tekrarlayan İYE ve MBD ile izlenen olgularda hem reflü nefropatisi hem de sonrasında KBH gelişiminde önemli rolü olan renal skarlaşma riskinin anlamlı yüksek olduğu görüldü. Bu hastalarda üriner ultrasonografinin skarlaşma riskini belirleme güvenli olduğu belirlendi. Sonuç olarak, tekrarlayan İYE ve/veya MBD ile izlenen ve üriner ultrasonografi (USG) bozuklukları olan hastaların VUR açısından değerlendirilmesi gerektiğini düşünüyoruz.

**Anahtar Sözcükler:** Vezikoüreteral reflü, renal parankimal skar, idrar yolu enfeksiyonları, mesane-barsak disfonksiyonu, çocuk

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## INTRODUCTION

Vesicoureteral reflux (VUR) is the most common anatomic abnormality of the urinary system in children (1). It is defined as the reflux of urine from the bladder towards the ureters and frequently to the collecting systems due to ureterovesical (UV) junction insufficiency (2-3). VUR is classified as primary or secondary. Primary VUR occurs as a result of developmental and functional abnormalities of the UV junction, whereas secondary VUR refers to reflux resulting from disorders with increased intravesical pressure (1). Prevalence of VUR in the general pediatric population is 1-3%. On the other hand, the prevalence is higher in certain groups. For example, it was reported that 10% of neonates with antenatal hydronephrosis and 30-40% of the children with recurrent urinary tract infections (UTIs) under 5 years of age had VUR (4). The genetic predisposition to VUR is also well-defined with reported rates of positive parental history of 27-51%, and 25-45% increased risk in the siblings (5-7).

Delay in the diagnosis or treatment of VUR can predispose to recurrent UTIs, and these two entities may cause kidney damage due to scarring; so called 'reflux nephropathy'. The end result of reflux nephropathy is hypertension and proteinuria, and eventually it progresses into chronic kidney disease (CKD) and cause growth retardation (8-10). It was shown that 30-60% of the patients with VUR had renal scarring, and of these hypertension and CKD developed in 17-30% and 5-12%, respectively (11). VUR and reflux nephropathy is the underlying etiology in 7-17% of the children with end-stage renal failure in the world. Unfortunately, this percentage is much higher in our country (approximately constituting 32% of all cases) (12-13).

Two treatment options are applied for VUR: medical and surgical treatments. It is known that VUR prevalence decreases due to spontaneous resolution as the child gets older (14-15). Besides, bladder and bowel dysfunction (BBD), which can accompany the patients with VUR, is also known to predispose to recurrent UTI, induce and perpetuate VUR, and may result in permanent renal damage (10). Considering these, conservative approach includes different options such as the follow-up of the patient without medications, or intermittent or continuous antibiotic prophylaxis, and/or bladder and bowel rehabilitation, if present (16). Surgical options should be considered for high grades of VUR depending on several factors like the patient's age, renal function, duration of follow-up, etc. Meanwhile, recent studies have revealed that there is no convincing evidence that UTI in the presence of VUR predicts renal injury or that the use of long-term anti-microbial prophylaxis or surgical intervention prevents renal scarring or its progression. Therefore, until proven otherwise, regardless of the grade of VUR, it is advisable to treat each patient on individual basis (10).

In this cross-sectional study, we retrospectively evaluated the demographic characteristics, clinical and laboratory findings, imaging studies and treatment outcomes of children with VUR. We aimed to evaluate the clinical course and prognosis of the disease and compare the experience of a single center with the literature. By this way, we also aimed to gain information that could guide us in the follow-up and treatment of VUR, considering its importance in the etiology of CKD in our country.

## METHODS

Children aged 0-18 years with the diagnosis of primary VUR who were regularly being followed-up for a duration of at least one year in the Pediatric Nephrology Department of Keçiören Research and Training Hospital between September 2011-2016 were recruited. Patients with irregular follow-up, secondary causes of VUR, other structural kidney abnormalities (such as multi-cystic dysplastic kidney, renal agenesis, or ureteral ectopia) or renal diseases accompanying VUR, or use of immunosuppressive or nephrotoxic drugs were excluded. Patients' medical reports were evaluated respectively, and their demographic findings including gender, age at presentation and VUR diagnosis, recurrent UTIs and definite UTIs (febrile/afebrile episodes with positive culture results) during their follow-up, family history of primary VUR in the parents and/or siblings, findings of bladder dysfunction (with lower urinary tract symptoms (LUTS) including

daytime incontinence, enuresis, urgency, frequency, hesitancy, dribbling, straining, voiding postponement, urinary holding maneuvers or urinary retention) and bowel dysfunction (constipation and/or encopresis) were noted (17). Recurrent UTIs were defined as follows: history of  $\geq 2$  acute pyelonephritis/upper UTIs, or 1 acute pyelonephritis/upper UTI plus 1 cystitis/lower UTI, or 3 cystitis/lower UTIs (18). Constipation was defined as infrequent bowel movements (less than 3 defecations per week), with presence of hard stools and painful straining, or voluntary holding of defecation. Rome III criteria was also used to define constipation in the patient group (19).

Anthropometric measurements (body weight and height), blood pressure and any other abnormal physical examination findings were recorded. Systolic and/or diastolic blood pressures  $\geq 95$  for age, height and gender were accepted as hypertension (20). Laboratory test results including blood urea nitrogen (BUN) and serum creatinine, urine analysis, urine culture and spot urine protein/creatinine ratio were noted. Glomerular filtration rate (GFR) was estimated using Schwartz formula (21). Spot urine protein/creatinine ratio  $>0.2$  was considered as proteinuria.

Findings of imaging studies (urinary ultrasonography (USG) data including presence of unilateral/bilateral decline in renal parenchymal thickness and/or scarring and/or dilations in the collecting system, technetium (Tc)-99m dimercaptosuccinic acid (DMSA) scintigraphy data including unilateral/bilateral renal parenchymal scarring, and voiding cystourethrography (VCUG) data including degrees of VUR (grade I-V) in the renal units), treatment methods (including antibiotic prophylaxis and surgical procedures like ureteroneocystostomy (UNC) or subureteric teflon injection) and clinical outcomes (spontaneous or surgical resolution rates, presence of CKD) were recorded.

Results of VCUG studies were graded according to the International Reflux Study Standardization report (22). The patients were subgrouped as group 1: Group 1: patients with grade I-II VUR, Group 2: patients with grade III VUR, Group 3: patients with grade IV-V VUR. The patients in VUR groups were also divided into subgroups according to the presence or absence of renal scars on DMSA scans. Results of patient subgroups were compared in respect to the demographic findings, clinical and laboratory findings, radiologic investigations, outcomes of treatment and follow-up.

All the urinary system USG and VSUG examinations were performed in our center. On the other hand, DMSA scintigraphies were obtained from different centers. Therefore, the results of DMSA scans were not graded.

### Statistical Analysis

Relationship between categorical variables were evaluated using Chi-square analysis. Mean  $\pm$  standard deviations, numbers and percentages were given for definitive statistics. IBM SPSS for Windows version 20.0 software program was used for statistical analysis. P value  $<0.05$  was considered as statistically significant.

### Ethical Consent

Ethical approval was obtained from University of Health Sciences Ankara Keçiören Research and Training Hospital (date: 08/02/2017, number: 1333)

## RESULTS

This study included 115 pediatric patients with primary VUR. Majority of them were females (82.6%, n=95). Mean follow-up time was  $3.6 \pm 1.1$  years (14 months-4.9 years). Mean age at VUR diagnosis was  $57.22 \pm 38.65$  months (2-168 months). Majority of the cases diagnosed less than one year of age (n=13) were boys (53.8%, n=7), as expected. Past history revealed recurrent UTIs in 60% (n=69) of the patients. Family history of VUR was detected in 17.4% (n=20, Table 1).

**Table 1.** Demographic findings of the study group at presentation

| Characteristics                    | Number (%) | Mean ± SD     | Min-Max             |
|------------------------------------|------------|---------------|---------------------|
| Sex                                |            |               |                     |
| Female                             | 95 (82.6)  |               |                     |
| Male                               | 20 (17.4)  |               |                     |
| Mean follow-up time (years)        |            | 3.6 ± 1.1     | 14 months-4.9 years |
| Mean age at presentation (months)  |            | 53.19 ± 49.48 | 1-158 months        |
| Mean age at VUR diagnosis (months) |            | 57.22 ± 38.65 | 2-168 months        |
| Age at diagnosis                   |            |               |                     |
| <1 year of age                     | 13 (11.3)  |               |                     |
| (girls/boys)                       | 6/7        |               |                     |
| >1 year of age                     | 102 (88.7) |               |                     |
| (girls/boys)                       | 88/13      |               |                     |
| Recurrent UTIs at presentation     | 69 (60)    |               |                     |
| Uropathogens                       |            |               |                     |
| ESBL (-) <i>E. coli</i>            | 53 (46.1)  |               |                     |
| <i>Klebsiella spp.</i>             | 14 (12.1)  |               |                     |
| ESBL (+) <i>E. coli</i>            | 11 (9.6)   |               |                     |
| Others                             | 11 (9.6)   |               |                     |
| Negative                           | 26 (22.6)  |               |                     |
| Family history of VUR              | 20 (17.4)  |               |                     |
| BBD at presentation                | 72 (62.6)  |               |                     |
| Constipation                       | 43 (37.4)  |               |                     |
| Hypertension                       | 13 (11.3)  |               |                     |
| Proteinuria                        | 10 (8.7)   |               |                     |

VUR; vesicoureteral reflux, UTIs; urinary tract infections, BBD; bladder bowel dysfunction, ESBL; extended-spectrum beta lactamase

At admission, none of the patients had growth retardation or other signs of CKD in physical examination. Serum BUN and creatinine levels were in normal ranges in all the patients with mean estimated GFR  $\geq 90$  ml/min/1.73 m<sup>2</sup>.  $\geq 1$  symptoms compatible with BBD were present in 62.6% (n=72) of the cases. It was remarkable that over one third of all patients had constipation (37.4%, n=43). Extended-spectrum beta lactamase (ESBL) (-) *E.coli* was the most common microorganism detected in the urine cultures (46.1%, n=53). After correction of UTIs, it was observed that 8.7% (n=10) of the patients had persistent proteinuria (Table 1).

Voiding cystourethrography showed VUR in 149 renal units with high grade (grade IV-V) VUR in 21.5% (n=32). High grade VUR was detected in 21.7% of the patients (n=25, Table 2).

Majority of the patients had unilateral VUR (70.4%, n=81). Urinary system USG was performed in all the patients and showed abnormal findings including dilations in the collecting system, decreased renal parenchyma and/or scarring in total of 47 renal units in 28.7% (n=33) of all patients. Tc-99m DMSA scintigraphy was available in 74.7% of the patients (n=86) and revealed renal parenchymal scarring in 57 renal units in 50% (n=43) of the patients (with bilateral scarring in 37.2% (n=32) of the cases). All the patients with proteinuria were the ones with unilateral or bilateral scarring. On the other hand, 3 except all patients with hypertension also belonged to the group of patients with scarring. The other 3 patients were hypertensive due to obesity. All the proteinuric and hypertensive patients were treated with angiotensin converting enzyme inhibitors (ACEI).

**Table 2.** Clinical characteristics of the study group

|                                  | Low grade VUR n (%) | Moderate VUR n (%) | High grade VUR n (%) | Total (n) | p        |
|----------------------------------|---------------------|--------------------|----------------------|-----------|----------|
| Patients                         | 36 (31.3)           | 54 (46.9)          | 25 (21.7)            | 115       |          |
| Renal units                      | 40 (26.8)           | 77 (51.7)          | 32 (21.5)            | 149       |          |
| Recurrent UTIs                   | 26/36 (72.2)        | 31/54 (57.4)       | 12/25 (48.0)         | 69        | p=0.248  |
| BBD                              | 19/36 (52.7)        | 39/54 (72.2)       | 15/25 (60.0)         | 73        | p=0.575  |
| Constipation                     | 18/36 (50.0)        | 17/54 (31.4)       | 8/25 (32.0)          | 43        | p=0.044* |
| USG abnormalities in renal units | 6/40 (15.0)         | 15/77 (19.4)       | 26/32 (81.2)         | 47        | p=0.001* |
| Scarring in renal units          | 11/36 (30.5)        | 28/77 (36.3)       | 18/32 (56.2)         | 57        | p=0.040* |

VUR; vesicoureteral reflux, UTIs; urinary tract infections, BBD; bladder bowel dysfunction, USG; ultrasonography

There was no significant difference between the patients with different grades of VUR in respect to positive history of recurrent UTIs and presence of symptoms of bladder dysfunction (p=0.248 and p=0.575, respectively). However, constipation was significantly higher in patients with low grades of VUR (p=0.044). Abnormal USG findings and renal parenchymal scarring were significantly higher in renal units with high grades of VUR compared to moderate and low grades (p=0.001 and p=0.04, respectively, Table 2).

On the other hand, patients with parenchymal scarring had significantly more recurrent UTIs, BBD and urinary system USG abnormalities (p=0.03 for all). Additionally, patients with BBD had more recurrent UTIs (p=0.015), as expected.

During the follow-up, majority of the patients received antibiotic prophylaxis (66.1%, n=76). Antibiotic prophylaxis was mostly preferred in the patients with moderate and high grades of VUR. Conservative management with antibiotic prophylaxis or interventions towards BBD was most preferred treatment method in the study group (77.4%, n=89).

However, surgical procedures were applied in the rest (subureteric injection 18 renal units in 13 patients (11.3%) and ureteroneocystostomy (UNC) in 19 renal units in 13 patients (11.3%), Table 3). None of the patients with low grades of VUR had undergone surgery. Subureteric teflon injections (STING procedure) were applied to 77.7% (n=14), 16.6% (n=3) and 5.5% (n=1) renal units with Grade III, IV and V VUR, respectively, whereas UNC was performed to 47.3% (n=9),

47.3% (n=9) and 5.3% (n=1) renal units with Grade III, IV and V VUR, respectively. DMSA scans were available in all except one patient in UNC group and revealed scarring in 83.3% (n=10). On the other hand, 11 patients who underwent subureteric injection had DMSA scans which showed scarring in 54.5% (n=6). At this period, recurrent UTIs were detected in only 15.6% of the patients (n=18), and besides, none of them had decreased eGFR.

**Table 3.** Treatment modalities in the study group

| Treatment modality                | n (%)        |
|-----------------------------------|--------------|
| Ab prophylaxis                    | 76 (66.1)    |
| Low grade VUR                     | 9/36 (25)    |
| Moderate grade VUR                | 42/54 (77.7) |
| High grade VUR                    | 25/25 (100)  |
| Type of Ab                        |              |
| TMP-SMX                           | 57 (49.5)    |
| Nitrofurantoin                    | 17 (14.8)    |
| Amoxicillin                       | 2 (1.7)      |
| Ab ± BBD treatment                | 89 (77.4)    |
| Surgery                           | 26 (22.6)    |
| Subureteric injection             | 13 (11.3)    |
| UNC                               | 13 (11.3)    |
| Control VSUG (renal units)        | 67           |
| Spontaneous resolution/regression | 26/67 (38.8) |
| Surgical correction/regression    | 36/67 (53.7) |
| VUR persistence                   | 5/67 (7.4)   |

AB; antibiotic, VUR; vesicoureteral reflux, TMP-SMX; trimethoprim-sulfamethoxazole, BBD; bladder bowel dysfunction, UNC; ureteroneocystostomy, VSUG: voiding cystourethrography

Of note, there were only two patients (one boy and one girl) over 10 years of age at the time of VUR diagnosis. They were the ones hospitalized with acute pyelonephritis. The girl (aged 12.5 years) had unilateral grade IV VUR with parenchymal scarring and decreased function in the left kidney. She underwent UNC operation. The boy (aged 14 years) had unilateral Grade III VUR with complete loss of function in the right kidney. He was given medical treatments.

Control VSUG was available in 44.9% (n=67) of the renal units with VUR (50 patients) which showed spontaneous resolution or regression in VUR in 38.8% (n=26) of the renal units. Surgical correction/regression was detected in 53.7% (n=36, Table 3). Complete recovery was observed in 94.0% (n=18) of renal units with UNC (in 92.3% (n=12) of the patients), whereas regression to Grade I VUR was detected in one renal unit (in one patient) in this group. Complete recovery was detected in 77.7% (n=14) of the renal units with subureteric injection (in 69.2% (n=9) of the patients) while regression in VUR grades and persistence in VUR were noticed in 16.6% (n=3) and 5.5% (n=1) of the renal units, respectively in this group.

## DISCUSSION

There is a vast number of studies focusing on VUR in the pediatric literature, however, the clinical evaluation and the management of the disease is still a matter of debate. Various approaches and treatment strategies have been used in children with VUR, with the final goal of preventing renal injury (10). Clarification of which children would benefit from diagnosis or different treatment or modalities remains the greatest challenge to the clinician (7). In this study, we retrospectively analyzed the clinical characteristics and outcomes of pediatric patients with primary VUR being followed-up a single center in order to evaluate the efficacy of our approach towards the management of the disease.

Prevalence of VUR is approximately four times greater in girls than boys (2.2% vs 0.8) investigated for UTIs in children over one year of age. This is attributed to increased frequency of UTIs in girls in these age groups. Reversely, the prevalence is higher in boys under one year of age due to screening of prenatal hydronephrosis (23-25). Similarly, majority of the patients with primary VUR >1 years were the girls (girls/boys=6,8/1) in our study. The prevalence was higher in boys under one year, as expected (girls/boys =1/1,2).

A strong inheritance pattern exists for primary VUR which was defined as 15-51% in different studies. The rate may increase up to 66% in the offspring of affected individuals (15). In our study, family history of VUR was detected in 17.5% of the patients, in line with the literature.

Primary VUR is regarded as a risk factor for UTIs and renal scarring in children (26). In our study, the prevalence of recurrent UTIs was 60%, but we couldn't demonstrate a significant difference between the VUR grades in respect to recurrent UTIs. Children with high grade VUR show more renal damage at diagnosis than those with low grade VUR (26). For example, children who have high-grade VUR were shown to be approximately five times more likely to have renal scarring than those who have low-grade VUR and are nine times more likely than children who have no VUR (3). In our study, renal parenchymal scarring was detected in 50% of the patients who underwent 99mTc-DMSA scintigraphy. Similarly, renal parenchymal scarring was significantly higher in patients with high grade VUR than the patients with low and moderate VUR grades.

Presence of BBD is another risk factor for UTIs. In the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study, it was demonstrated that 51% of children with BBD had a recurrent UTI, compared with 20% of children without BBD (27). It is well-known that BBD can also be associated with VUR. A recent study indicated that among patients presenting with UTI, the prevalence of BBD was higher in patients with primary VUR compared to the ones without primary VUR (49% vs 41%) (28). In our study, although there was no difference between different VUR grades in respect to presence of BBD, overall prevalence of BBD was 62.6%, which was considerably higher than the results of the previous studies. Moreover, patients with primary VUR and BBD had significantly more recurrent UTIs compared to the ones without BBD. It is shown that presence of BBD is associated with renal scarring as well as prevention of the spontaneous resolution of VUR and decrease in the success rate of medical and/or surgical treatments (28-29). Similarly, the patients with parenchymal scarring in our study had significantly more recurrent UTIs and BBD compared to the other groups. Our results demonstrate that presence of BBD is a definite risk factor for recurrent UTIs and subsequent scarring in patients with VUR, therefore we can conclude that proper diagnosis and treatment of this condition carries great importance.

Constipation, a component of BBD, can increase bladder storage pressures and post-void residual urine volume by compressing the bladder neck (19). Besides increasing recurrent UTIs, it is shown that chronic constipation also adversely affected the spontaneous resolution of VUR and decreased the surgical success rates (19, 30). In our study, 37.4% (n=43) of the patients had chronic constipation. It was significantly more common in the patients with low grades of VUR compared to moderate and high grades of VUR. Moreover, constipation as an isolated finding, was not found to be associated with increased renal scarring. The higher prevalence of constipation in patients with low and high grades of VUR was attributed to the predominant number of these groups in our study.

Urinary USG is the first step imaging technique in the evaluation of children with UTIs. It is quite valuable in the detection of hydronephrosis, renal duplication and renal parenchymal scarring. However, it is considered to have low sensitivity for VUR diagnosis (31-32). In a study by Zamir et al. (33) all the patients with UTI had renal USG and VSUG in the following 2-6 months, and despite the presence of urinary abnormalities in only 13% of the cases, VUR was detected in 62%. Therefore, it was concluded that USG was not reliable in screening for VUR in children. Reversely, all the patients in our study group had USG examination, and it was found that both the patients with high grades of VUR and the renal units with scarring in DMSA scintigraphy had significantly more abnormalities in USG compared to other grades of VUR and renal units with normal scintigraphy, respectively. For this reason, we may conclude that ultrasonographic findings can be helpful in detecting the children with high grades of VUR and/or kidneys with scarring. On the other hand, considering the fact that the majority of the study group consisted of patients with low and moderate degrees of VUR and only 17.9% of them had abnormal ultrasonographic findings, we may also conclude that urinary USG itself is not a reliable technique for VUR screening in the whole patients under risk.

The strategies in VUR treatment include prevention of recurrent UTIs, renal parenchymal scarring and other undesired complications. Main treatment options are long-term antibiotic prophylaxis (mostly with TMP-SMX) and nitrofurantoin) and surgical correction. (34). The results of multicenter RIVUR study on 607 children aged 2-71 months reveal that although antibiotic prophylaxis significantly decreased the recurrent UTIs in children with Grade I-IV VUR, it could not prevent new scar formation (35). On the other hand, according to the recommendations of American Academy of Pediatrics (AAP), prophylactic antibiotics are applicable to the children with high grades of VUR (31). Similarly, prophylactic antibiotics were preferred mostly in the patients with moderate and high grades of VUR in our study.

The natural history of VUR is to improve or resolve completely with time in parallel to the growth in most of the patients. As the child grows, the length of the submucosal ureter increases, the ureterovesical junction is reorganized in favor of stabilization of the anti-reflux mechanism. The degree and the age at VUR diagnosis affects spontaneous resolution. It was shown that newborns and infants with VUR have shorter times of resolution. Besides, low grade and unilateral VUR have increased chance of spontaneous resolution (82%, 80% and 46% spontaneous resolution rates in Grade I, II and III VUR, respectively (36-37). Reversely, it was reported that spontaneous resolution in Grade IV and V VUR 5 years after diagnosis was 30% and 11%, respectively (38). During the follow-up period of mean 3.5 years, control VSUG was available in 67 renal units (44.9%) with VUR which demonstrated spontaneous regression/resolution in 38.8%. Although spontaneous resolution rates seem to be lower in our study compared to the data in the literature, this may stem from various reasons including the retrospective nature of the study, relatively short follow-up time of the patients and availability of control VSUG examinations mostly in patients with high grades of VUR.

Open surgical techniques (UNC) has a quite high success rate (95-97%) in VUR treatment (39), whereas subureteric teflon injection has success rates in decreasing numbers as the VUR degree rises (90-100%, 93-99% and 50-60% in Grades I-II, Grade III and Grades IV-V VUR, respectively) (40). In our study, 13 patients with moderate and high grades of VUR had UNC with a high correction rate (92.3%), but surgical correction with subureteric injections remained lower (69.2%), consistent with the ratios given in the literature. It was remarkable that presence of scarring in the renal unit was determinative in the decision of the surgery type as UNC was mostly performed in the renal units with scarring.

During a mean follow-up time of 3.6 years, the prognosis of our patients with VUR were acceptable. None of the patients progressed into CKD or end-stage renal failure.

The patients with hypertension or proteinuria due to scarring were successfully managed with ACE inhibitors. Majority of the patients did well with antibiotic prophylaxis and bladder-bowel rehabilitation, while surgical procedures were reserved for the ones with the patients with moderate or high grades of VUR with renal scarring. The frequency of recurrent UTIs decreased to greater extent via these appropriate interventions.

In summary, the risk of renal scarring, which is an important finding of reflux nephropathy and subsequent CKD, is significantly higher in patients with higher grades of VUR, recurrent UTIs and BBD in our study. Moreover, urinary USG was found a reliable technique to predict scarring in the patients with VUR. Therefore, it is strongly recommended that children with recurrent UTIs and/or BBD as well as abnormalities in urinary USG should be evaluated for VUR. As majority of the patients were successfully managed by antibiotic prophylaxis and bladder-bowel rehabilitation, surgery options should only be considered for the patients for high grades of VUR and scarring.

#### Conflict of interest

No conflict of interest was declared by the authors.

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