



# Sonoelastography Findings of Permanent Damage Due to Chronic Urinary Infection and Vesicoureteral Reflux Seen in Childhood

Çocuklarda Görülen Kronik İdrar Yolu Enfeksiyonu ve Vezikoüreteral Reflünün Böbrekte Yarattığı Kalıcı Hasarın İzlenen Sonografik Elastografi Bulguları

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## Abstract

**Objective:** Sonoelastography findings of permanent damage due to chronic urinary infection and vesicoureteral reflux seen in childhood. Early and non-invasive detection of permanent kidney damage secondary to chronic urinary infections and vesicoureteral reflux in childhood, instead of DMSA.

**Material and Methods:** We prospectively evaluated 83 patients with chronic urinary infection and/or vesicoureteral reflux that applied our hospital's medicine department of radiology ultrasonography unit between January 2015-January 2016 and 100 healthy individuals as control group, and performed strain elastography and gray-scale ultrasonography in the same session. Our study is a prospective study.

**Results:** The strain index (SI) values between the control group and the patient-non-scarred group were analyzed with the Mann-Whitney U test. A statistically significant difference was found only in terms of upper pole SI values for the right kidney. The mean SI value for the control group was  $4.08 \pm 6.36$ , and  $17.63 \pm 43.60$  for the patient-non-scarred group ( $p=0.006$ ). As a result of receiver operating characteristic (ROC) analysis for right kidney upper pole SI values obtained between the control and patient-unscarred groups, cut-off values, sensitivity, specificity, positive predictive values and negative predictive values according to 60-70% and 82% sensitivities values were calculated. The SI value obtained in the control and patient-non-scarred groups was found to have 82% sensitivity, 42% speci-

## Öz

**Giriş:** Çocukluk çağında görülen kronik üriner enfeksiyon ve vezikoüreteral reflüye bağlı kalıcı hasarın sonoelastografi bulgularını paylaşmayı ve çocukluk çağında kronik üriner enfeksiyonlara ve vezikoüreteral reflüye sekonder kalıcı böbrek hasarının DMSA yerine erken ve non-invaziv tespitini sunmayı amaçladık.

**Gereç ve Yöntemler:** Ocak 2015-Ocak 2016 tarihleri arasında kronik üriner enfeksiyon ve/veya vezikoüreteral reflü şikayetiyle hastanemiz radyoloji ultrasonografi ünitesine başvuran 83 hasta ve kontrol grubu olarak 100 sağlıklı bireye aynı seansta strain elastografi ve gri skala ultrasonografi yapıldı. Çalışmamız prospektif bir çalışmadır.

**Bulgular:** Kontrol grubu ile hasta-skarlı grup arasındaki strain indeksi (SI) değerleri Mann-Whitney U testi ile analiz edildi. Sağ böbrek için sadece üst pol SI değerleri açısından istatistiksel olarak anlamlı bir fark bulundu. Ortalama SI değeri kontrol grubu için  $4.08 \pm 6.36$  ve hasta-skarlı grup için  $17.63 \pm 43.60$  idi ( $p=0.006$ ). Kontrol ve hasta-skarlı grupları arasında elde edilen cut-off değerleri, sensitivite, spesifite, pozitif prediktif değerler ve negatif prediktif değerlere göre %60-70 ve %82 sensitivite değerleri hesaplandı. Kontrol ve hasta-skarlı grup elde edilen gerilim indeksi değerinin 1.15 cut-off değerinde %82 duyarlılık, %42 özgüllük, %36 pozitif öngörü değeri ve %64 negatif öngörü değeri olduğu bulundu. Ne yazık ki hasta-skarlı grubu ile diğer gruplar arasında yaptığımız karşılaştırmada anlamlı bir sonuç elde edemedik.

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ficity, 36% positive predictive values, and 64% negative predictive values at the cut-off 1.15. Unfortunately, we could not obtain a meaningful result in the comparison between the patient scarred group and the other groups.

**Conclusion:** The SI values of scar tissues were high formed secondary to chronic urinary infections and vesicoureteral reflux.

**Keywords:** Urinary tract infection, vesicoureteral reflux, strain elastography, strain index, SI

## Introduction

Urinary tract infection (UTI) is a common cause of morbidity in childhood. Early diagnosis and early initiation of treatment are important in order to have a successful treatment of UTI. Vesicoureteral reflux (VUR) is low or high pressure, infected or sterile reflux of urine towards the kidney. VUR is diagnosed by voiding cystourethrography. The frequency of VUR in children with recurrent urinary tract infection varies between 21.7% and 61% (1,2). Kidney damage occurs due to both reflux and infections (3). Afterwards, the presence of scar can be evaluated with technetium 99-m dimercaptosuccinide acid scintigraphy (DMSA) and the function of each kidney with diethylene triamine pentaacetic acid scintigraphy (DTPA). Today, the gold standard diagnostic method in revealing the scar tissue in the kidneys is the DMSA examination (4).

Strain elastography (SE) is a semi-static and semi-quantitative method used in recent years. This method is based on measuring the stiffness of the lesion by applying a compressive force to the tissue. Lesion hardness is coded on a color scale in qualitative assessment, while strain rate is obtained in semi-quantitative assessment. Strain index (SI) is the ratio of the strain value around the examined tissue to the strain value of the examined tissue. Studies been reported that malignant lesions are harder than benign lesions. The application of strain elastography in the kidney parenchyma is limited in the literature (5,6).

In this study, we aimed to detect noninvasively the permanent damage caused by chronic urinary tract infection and vesicoureteral reflux in children by strain elastography.

## Materials and Methods

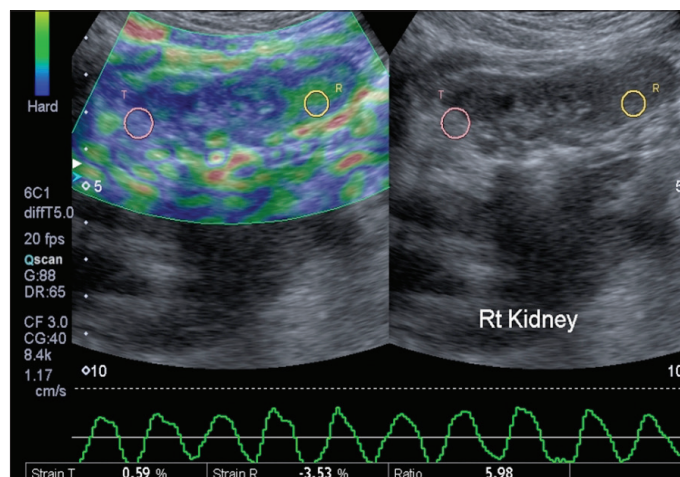
This study was approved by the the hospital ethics committee (2014/501). Between January 2015 and January 2016, 83 patients with chronic urinary infection and/or vesicoureteral reflux were enrolled in this prospective study. All of these patients underwent DMSA (technetium-99m-dimercaptosuccinic acid) scintigraphy examination. A control group of 100 healthy children was also evaluated in the study. Strain elastography was applied to these patients in the same session as renal ultrasound (US). The control group consisted of healthy individuals undergoing US for any reason. Consent forms were obtained from the families of all patients and healthy individuals.

**Sonuç:** Kronik üriner enfeksiyonlara ve vezikoureteral reflüye sekonder skar dokularının strain indeksi değerleri yüksekti.

**Anahtar Kelimeler:** İdrar yolu enfeksiyonu, vezikoureteral reflü, strain elastografi, strain indeksi, SI

Patients who had previously undergone kidney surgery, a renal mass or calcification, unilateral renal agenesis, ureteropelvic junction obstruction or urolithiasis, acute or chronic renal failure were excluded. Children with secondary VUR, such as neurogenic bladder or posterior urethral valve, and those with such severe hydronephrosis and cortical atrophy that the renal cortex was unmeasurable were also excluded from the study.

All patients were examined simultaneously with gray-scale US and SE with Aplio 500 (Toshiba, Japan) 6-14 MHz broad band matrix convex transducers by two experienced radiologists. SE was performed in prone position for patients and control group individuals. The probe was positioned to view the kidney in the sagittal plane. In this technique, the area of interest is compressed with the probe (Figure 1). Probe compression was applied using the free hand technique. Probe compression was tried to be done slowly and at equal intervals. Minimum and constant pressure was applied to create a sinusoidal wave. When measuring the strain value, it is preferable to measure from the decompression wave monitored on the monitor because no external force is applied to the tissue during the decompression wave phase. Therefore, strain values of hard tissues are low. Generally, hard tissues are seen in blue, soft tissues in red, and intermediate hard tissues in green. SI is the ratio of the strain value around the examined tissue to the strain value of the examined tissue. This value obtained is called SI (7-14).



**Figure 1.** A 12-year-old female patient, followed up for chronic urinary tract infection, DMSA showed scar tissue in the upper pole of the right kidney, SI value of 5.98, transversal plane.

SI measurements were applied to the areas where renal scar was seen on scintigraphy. SI values were measured ten times in kidneys with scar tissue and average values were obtained. SI value is the ratio of strain value of normal renal cortex tissue (strain R) to strain value of cortical scar tissue (strain T), which is automatically calculated by the US device. SI in healthy patients with non-scarred tissue was calculated by proportioning the strain values obtained from middle pole of the kidney (strain R) and the strain values obtained from upper and lower poles (strain T).

DMSA kidney scintigraphy images were obtained 2-4 hours after intravenous injection of Tc99m DMSA at the dose calculated by the 'dosage card' published by the European Nuclear Medicine Association, with the lowest dose of 0.3 millicurie (mCi) and the highest dose of 3 mCi. In imaging, posterior, anterior, right and left posterior oblique, five-minute planar images were taken with a gamma camera (Siemens Symbia E). Differential renal function was calculated by geometric mean from anterior and posterior images. The localization, morphology, size, localization and number of cortical damage, and whether there was a diffuse reduction in involvement were stated in the report.

### Statistical Analysis

All data were evaluated via SPSS (Statistical Package for Social Sciences, version 18.0, Lead Technologies Inc., USA) program. The conformity of continuous variables to the normal distribution was evaluated with Kolmogorov-Smirnov Test. Mann-Whitney-U test was used to compare non-parametric continuous variables independent groups. The patient-scarred group and the patient-non-scarred group were compared with the control group. Unfortunately, only a significant result emerged between the patient-non-scarred group and the control group.

### Results

There were 83 pediatric patients (27 males, 56 females; 166 kidneys) with a mean age of 7.6 years and 100 normal children (50 males, 50 females; 200 kidneys) with a mean age of 10 years. We separated VUR patients scarred and non-scarred by DMSA. We did not grade them separately. Renal scar was detected in DMSA in 41 (49%) of the patients. Age range of the patient-scarred group was 1-15 years (mean  $8.36 \pm 3.52$ ), that of the patient-non-scarred group was 1-15 years (mean  $6.88 \pm 4.67$ ), and that of the healthy control group was 1-15 years (mean  $10.08 \pm 3.12$ ). Majority of the patients in the patient group scarred and non-scarred were girls.

The underlying etiological factor was chronic urinary tract infection and VUR (Tables 1, 2).

SI values of the upper and lower poles were higher comparing to middle pole of each kidney in the scarred group.

**Table 1.** Distribution of groups by etiology

Group name		n	%
Patient-scarred	UTI	28	68.30
	VUR	12	29.26
	UTI + VUR	1	2.44
	Total	41	100
Patient-non-scarred	UTI	32	76.19
	VUR	10	23.81
	Total	42	100

UTI: Urinary tract infection, VUR: Vesicoureteral reflux.

**Table 2.** Distribution of groups by etiology and sex

Sex	Group name	n	%	
Female	Patient-scarred	UTI	22	53.65
		VUR	8	19.51
		UTI + VUR	1	2.44
		Total	41	100
	Patient-non-scarred	UTI	20	76.92
		VUR	6	23.08
Total		26	100	
Male	Patient-scarred	UTI	6	60
		VUR	4	40
		Total	10	100
	Patient-non-scarred	UTI	12	75
		VUR	4	25
		Total	16	100

UTI: Urinary tract infection, VUR: Vesicoureteral reflux.

The reason for this is that the upper and lower poles of the kidneys are more affected due to VUR and UTI.

SI value was calculated from all three groups. For the scarred pole of each kidney, ten values were taken and analyzed with mean values. In the 41 scar group, the number of patients with scar only in the right kidney was 16, the number of patients with scar only in the left kidney was 23, and the number of patients with scarring in both kidneys was two. The number of patients affected by more than one pole was 18. The lower pole of the left kidney and the upper pole of the right kidney were the most affected. In our study, the incidence of scar tissue in the right kidney was 35.82% and 64.18% in the left kidney. The incidence of scar tissue observed in DMSA in both kidneys is higher in the upper-lower poles than in the middle pole (Table 3).

### Discussion

Recurrent UTI and VUR can cause renal parenchymal scarring and irreversible kidney damage. In daily practice, DMSA, which is an invasive method that includes low-dose radiation

**Table 3.** Distribution of strain index values according to kidney poles in the scarred patient group

Strain index (SI)		Right kidney upper pole SI	Right kidney middle pole SI	Right kidney lower pole SI	Left kidney upper pole SI	Left kidney middle pole SI	Left kidney lower pole SI
Scarred patient	n	16	3	5	13	7	23
	Average	5.0000	1.8800	4.6900	6.3200	2.2200	4.0000
	Median	3.8300	2.0500	4.1800	3.9000	1.2200	2.5600
	Standard deviation	5.7300	1.6700	3.0000	6.7600	2.3600	3.8600
	Minimum	0.4900	0.1300	0.7300	0.2000	0.5000	0.2600
	Maximum	23.6500	3.4600	8.7600	21.3700	7.1200	14.8100

and uses radiopharmaceuticals, is used to detect renal parenchymal scarring. Therefore, it is necessary to develop non-invasive, harmless methods that do not contain radiation. In this study, we aimed to investigate the role of strain elastography in detecting scar tissue.

In our study, SI values were higher in children with scarring on DMSA scintigraphy compared to the control group; which was similar to the literature (15,16). Since the SI values obtained in the renal-scarred group were not homogeneous in the distribution according to the poles and the numbers were significantly less in some poles, statistical comparative analysis could not be performed, and therefore only descriptive evaluation could be made. We found that the highest value was in the left kidney in the upper pole and the lowest in the right kidney in the middle pole ( $6.32 \pm 6.76$  and  $1.88 \pm 1.67$ , respectively) (Table 3). In the comparative SI values among the groups, a significant result was obtained only between the non-scarring group and the control group. A statistically significant difference was found only in terms of upper pole SI values for the right kidney. Mean SI value for the control

group was  $4.08 \pm 6.36$ , and  $17.63 \pm 43.60$  for the patient-non-scarred group ( $p= 0.006$ ) (Table 4). As a result of receiver operating characteristic (ROC) analysis for right kidney upper pole SI values obtained between the control and patient-non-scarred groups, cut-off values, sensitivity, specificity, positive predictive values and negative predictive values were calculated according to 60-70% and 82% sensitivities (Figure 2). The SI value obtained in the control and patient-non-scarred groups was found to have 82% sensitivity, 42% specificity, 36% positive predictive values, and 64% negative predictive values at the cut-off value of 1.15 (Table 5). Specificity was low due to high standard deviation. The reason for high standard deviation was attributed to the heterogeneous structure of the kidney parenchyma in accordance with the literature (17).

In the literature, one of the few studies on this issue is Menzilcioglu et al.'s strain elastography study for chronic kidney patients and healthy control group. They have found the SI value to be higher in chronic kidney patients than in the healthy control group (1.81 in chronic kidney patients, 0.52 in the healthy control group) (16). Göya et al. have used a different

**Table 4.** Distribution of strain index (SI) values according to kidneys between the control group and the non-scarred patient group

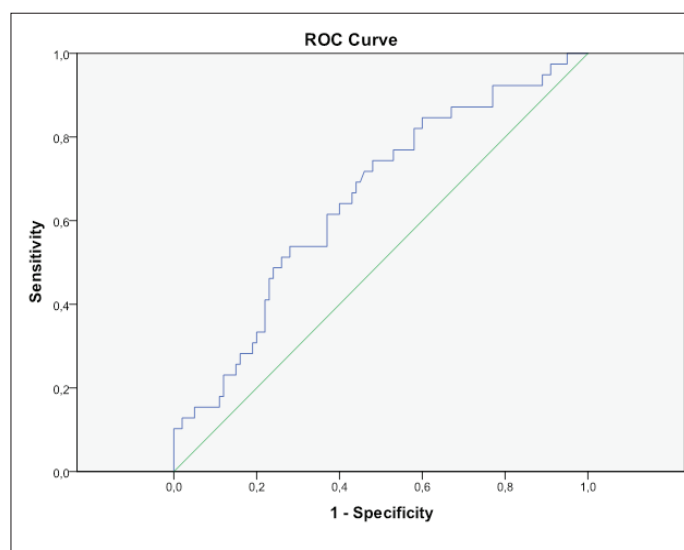
Group name		Right kidney upper pole SI	Right kidney lower pole SI	Left kidney upper pole SI	Left kidney lower pole SI
Control	n/(%)	100/(72)	100/(72)	100/(71)	100/(71)
	Average	4.0883	2.6410	6.9052	3.8847
	Mean	1.3821	1.1725	1.9946	1.2474
	Standard deviation	6.3604	4.3438	24.1110	11.3790
	Minimum	0.0100	0.0200	0.0500	0.0300
	Maximum	29.6700	26.3800	228.5000	96.6700
Patient non-scarred	n/(%)	39/(28)	39/(28)	41/(29)	41/(29)
	Average	17.6359	3.1649	7.4720	4.4676
	Mean	3.2500	1.0353	1.1687	1.2034
	Standard deviation	43.6095	6.2020	27.0794	11.8191
	Minimum	0.1100	0.0500	00.0041	0.0039
	Maximum	218.6700	32.4300	174.0000	73.0000
Total number of people		139	139	141	141
p		0.006	0.981	0.283	0.658



**Table 5.** Cut-off, sensitivity, specificity, positive predictive and negative predictive values according to the right kidney upper pole strain index values obtained between the control and non-scarred patient groups

Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
1.15	82	42	36	64
1.70	70	55	38	63
2.32	60	63	39	61

p= 0.006.

**Figure 2.** The area under the curve in the ROC analysis for the right kidney upper pole strain index values was 65%, p= 0.006, (confidence interval= 0.551-0.752).

method to detect kidney scar tissue. ARFI elastography was used as the method and found the shear wave velocity (SWV) value to be higher in the control group than in the severely damaged kidneys ( $2.39 \pm 0.23$  in the healthy control group,  $1.51 \pm 0.34$  in the damaged kidney) (15). As an example of other studies in this field, Lee et al. have found with ARFI method in healthy children that the strain value in the right kidney was  $2.19 \pm 0.03$  and  $2.19 \pm 0.03$  in the left kidney (18). Grenier et al. have found cortex elasticity value higher than kidney medulla elasticity value in kidneys with shear wave technique (19). In order to detect moderate fibrosis, Gao and friends have found sensitivity and specificity as 92.9% and 94.7%, respectively, according to the cut-off value of 0.975 (20). Costanza et al. have examined scarred kidney and contralaterally performed shear wave elastography in the kidney and normal control group. They have found mean ARFI values of "affected" kidneys with secondary reflux ( $6.59 \pm 1.45$ ) significantly higher than those with primary reflux ( $5.35 \pm 1.72$ ) (21).

In a recent study, areas under the ROC curves for the detection of tubulointerstitial fibrosis were 0.75 (95% CI 0.61-0.89), 0.85 (95% CI 0.75-0.95) for cortical, medullary, and they estimated 0.65 (95% CI 0.53-0.78) for tissue stiffness and serum creatinine, respectively (22). In another study with shear wave

elastography, mean renal cortical and pyramidal stiffness in patients with stable renal function was  $28.48 \pm 4.27$  kPa and  $21.97 \pm 3.90$  kPa, respectively after renal transplantation (23). For shear wave elastography study on contrast-induced nephropathy, the cut-off value of cortical stiffness obtained by the ROC curve analysis was 7 kPa for the CIN development (sensitivity= 74.5%, specificity= 72.5%) (24).

We also found that 65.20% of the patients with VUR were females and 34.80% were males (8,15).

Since the elastography technique and unit are different in all these studies, the data obtained are also different.

The fact that it depends on the subjective evaluation of the practitioner can be counted as a limitation of the review. In the literature, studies investigating inter-observer interpretation differences in elastographic evaluation have been reported (25).

Among the limitations of our study; the pressure applied to the probe is person-dependent, the applied pressure comes at a right angle to the middle pole while the upper and lower poles are at a more oblique angle. Difficulty in breathing and movement control during ultrasound and elastography, and inability to make a comparative analysis of SI value in the patient-scarred group were other limitations of our study. In future studies, it was thought that the reference tissue for the kidney could be chosen as perinephritic adipose tissue or renal sinus rather than the cortex.

## Conclusion

The scarred group and the non-scarred group were compared with the control group. Unfortunately, only a significant result emerged between the non-scarred group and the control group. We did not achieve the results we hoped for with strain elastography. Studies with larger patient groups and using more standardized elastography methods may provide guidance for more comprehensive evaluation and validation of results and findings in the future.

**Ethics Committee Approval:** This study was approved by Adnan Menderes University Faculty of Medicine Noninvasive Clinical Research Ethics Committee (Decision no: 21, Date: 25.12.2014).

**Informed Consent:** Patient consent was obtained.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept- YDP; Design- MK; Supervision- YDP; Resource- FS; Data Collection and/or Processing- DY, AC; Analysis and/or Interpretation- MK; Literature Search- MK; Writing- MK; Critical Review- YDP.

**Conflict of Interest:** All authors declare that they have no conflicts of interest or funding to disclose.

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