International Urology and Nephrology (2019) 51:1727–1734
https://doi.org/10.1007/s11255-019-02229-8

UROLOGY - ORIGINAL PAPER

Evaluation of the urinary podocalyxin and nephrin excretion levels to determine a safe time interval between two sessions of SWL for renal stones: a non randomized exploratory study

Hüseyin Kocatürk[1] · Nursen Atasoy[1] · Fevzi Bedir[1] · İbrahim Karabulut[1] · Engin Şebin[2] · Kemal Sarica[3]

Received: 12 May 2019 / Accepted: 5 July 2019 / Published online: 18 July 2019

Abstract

Objectives We aimed to evaluate the role of nephrin and podocalyxin in determining the intervals between shock wave lithotripsy (SWL) sessions and how soon the kidney damage was recovered.

Methods This work was a prospective study that included 30 patients with unilateral kidney stones. The patients' midflow urine samples were collected before SWL and 1 h, 1 day and 1 week after the procedure. Nephrin and podocalyxin levels in the urine samples were measured by the enzyme-linked immunosorbent assay method.

Results Among the 30 patients who underwent SWL, 19 were males and 11 were females. The mean age of the SWL group was 34.7 ± 13.2. Both biomarkers did not correlate with age, creatinine values, body mass index, stone side, stone size, energy, frequency and shock numbers. Nephrin and podocalyxin levels were significantly higher at the pre-SWL point ($p < 0.05$). After the procedure, a significant decrease was observed in both biomarker levels ($p < 0.05$). At the end of first day, these levels started to increase progressively up to the end of the first week ($p > 0.05$).

Conclusions Nephrin and podocalyxin may help to determine early period kidney damage associated with SWL. Post-SWL podocalyxin and nephrin values may be used to determine the interval between SWL sessions.

Keywords Shock wave lithotripsy · Kidney injury · Nephrin · Podocalyxin

Abbreviations

BMI	Body mass index
SWL	Shock wave lithotripsy
SD	Slit diaphragm
HESW	High-energy shock waves
ERPF	Effective renal plasma flow
ROS	Reactive oxygen species
RIRS	Retrograde intrarenal surgery

✉ Hüseyin Kocatürk
kocaturk78@hotmail.com

1 Department of Urology, Health Sciences University, Erzurum Regional Training and Research Hospital, Palandöken, Erzurum, Turkey

2 Department of Biochemistry, Health Sciences University, Erzurum Regional Training and Research Hospital, Erzurum, Turkey

3 Department of Urology, Faculty of Medicine, Biruni University, Istanbul, Turkey

Introduction

As a globally important health problem, the incidence and prevalence of urolithiasis increased prominently in the past 3–4 decades [1]. Regarding the management of kidney stones, as a result of the technological advancements, treatment principles have changed to a considerable extent where minimally invasive procedures gradually replaced the open surgical approach. However, published data so far in the literature have clearly indicated that each of these options is associated with certain advantages and disadvantages. As the least invasive and anesthesia-free alternative, following its clinical introduction in the early 1980s, SWL has been applied as the only non-invasive and effective method in the majority of such stones. However, accumulated experience with SWL demonstrated that repeated treatments performed in a certain percent of these cases make the total duration of the treatment longer than the other approaches. Moreover, published data so far indicate that high-energy shock wave (HESW) application may cause adverse effects on the function and morphology of the treated kidneys. Related with this issue, after SWL, while increased excretion of small proteins (b2- and a1-microglobulin), decreasing the enzyme (*N*-acetyl-b-glucosaminidase) and Tamm-Horsfall protein excretion have been reported as signs of proximal tubular impairment [2, 3]. Studies also showed certain histopathologic alterations including bleeding, endothelial cell damage, glomerular atrophy and sclerosis, and interstitial fibrosis in the treated kidneys [4, 5]. In other words, aside from the acute tubular alterations HESW application may also affect the integrity as well as function of renal glomeruli.

As the most important basic functioning units of kidneys responsible for filtration and urine formation, renal glomeruli are composed of capillary rings, basement membranes and epithelium cells (podocytes). Of these structural units, podocytes are highly differentiated glomerular epithelial cells and they are attached to the outer part of the glomerular ring with pedigree extensions (pedicel). These cells are also connected to the glomerular basement membrane through actin filament bundles. Furthermore, by providing a large filtering surface through the slit diaphragm (SD) structure, podocytes also stabilise the glomerular architecture against the distention of the glomerular basement membrane. Furthermore, in addition to the crucial interaction between podocyte foot extensions controlling the glomerular filtration [6], studies have demonstrated that certain proteins, namely nephrin, podocin and podocalyxin also play an important role in the regulation of glomerular filtration. Among these proteins, while podocalyxin has been shown on the podocyte cell surface, nephrin has been found to be a SD protein [7].

Podocalyxin is a type I transmembrane sialoglycoprotein of the CD34 family released abundantly on the luminal surface of epithelial cells (podocytes) of renal glomeruli [7, 8]. Through its strong negative charge and heavy sulphation as well as sialylation, podocalyxin is considered to play a role in preserving the structural regulation of renal glomeruli. During normal plasma filtration. Podocalyxin is also secreted from non-renal tissues like multipotent hematopoietic progenitor cells, vascular endothelium or heart cells [9, 10]. Several types of tumour cells have also been found to secrete podocalyxin proportional to the grade of malignancy [11]. The physiological role of podocalyxin released from tissues outside of the kidney is obscured despite its large release [12].

Nephrin is a 180-kDa transmembrane protein that is released from the podocyte SD. It is an integral part of podocyte cells and forms a glomerular filtration barrier with the endothelial cells as well as basement membrane [13]. Nephrin is found in the pancreas, brain, spinal cord and lymphoid tissues, but its role in these tissues has not yet been fully established [14].

In this present study we aimed to determine the minimal time period needed for a second session for a safe SWL application in an individualized manner by assessing the urinary excretion levels of podocyte proteins (nephrin, podocalyxin) which were found to reflect the presence as well as the duration of acute renal tissue injury in a reliable manner.

Patients and methods

Patients

Between February 2018 and April 2018, a total of 30 patients treated with SWL for the first time because of unilateral kidney stones were included in this prospective study. Prior to study process, a written informed consent was obtained from each case and depending on the renal functional status patients with chronic renal disease, urinary infection, hydronephrosis, history of renal surgery, solitary kidney, renal tumour, congenital anomalies and a treatment of nephrotoxic drugs that would affect renal function were excluded from the study program. In addition to the demographic data including age, body mass index (BMI) and gender, stone size, laterality, serum creatinine levels as well as treatment-related parameters (number of shocks, energy and frequencies) were all assessed and recorded in all cases.

SWL technique

A single session of SWL was applied to one of the kidneys (unilateral) with the same lithotripter (Richard Wolf PiezoLith 3000, Knittlingen, Germany). All procedures were performed by a urologist with the patient in supine position under real-time fluoroscopic image for stone localization. Treatment was started at a low power of 5.4 kV, 102 MPa and 0.86 mJ/mm^2 and gradually increased in 0.4-kV steps every 300 SWs to a maximum power of 8.3 kV, 116 MPa and 1.54 mJ/mm^2, depending on the tolerance level of the patients. The frequency of shock wave application was 120 pulses per minute, with a maximum of 4.000 shock waves per session. The subsequent sessions of SWL were completed to 3 sessions of SWL in patients without stone free. After 3 sessions of SWL, patients with residual stones underwent auxiliary retrograde intrarenal surgery (RIRS).

Collection of urine specimens

Midflow urine samples of the patients were obtained before SWL, 1 h, 1 day and 1 week after the procedure. Urine (10 mL) was collected in plastic tubes, without any specific preservative. The urine samples obtained from all cases were centrifuged at 3000 rpm for 20 min at + 4 °C. The supernatant urine samples were transferred to Eppendorf tubes. The samples were kept in a deep freezer system at − 80 °C until analysis.

Measurement of nephrin and podocalyxin in the urine

The urinary nephrin and podocalyxin levels were measured with enzyme-linked immunosorbent assay (ELISA) method by using the human podocalyxin ELISA kit (SunLong Biotech, Cat. no: SL1429Hu, HangZhou, China) and the human nephrin ELISA kit (SunLong Biotech, Cat. no: SL1246Hu) in accordance with the manufacturer's instructions. The analysis was performed with a BioTek ELx50 microplate reader device (BioTek Instruments, Inc.; Winooski, USA). Each sample was measured in duplicate and the obtained values were expressed as ng/L.

Statistical methods

Statistical analyses of the values were carried out using SPSS (Statistical Package for Social Sciences) 22.0 statistical software package. The distribution of the variables was measured by the Kolmogorov–Smirnov test. Variables with normal distribution were indicated as the mean and standard deviation. Variables without normal distribution were shown as the median and minimum–maximum values in addition to mean and standard deviation. A linear association between parameters is evaluated using Spearman's correlation coefficient. Paired sample *t* test was used to determine whether the mean difference between before and after treatment values. $p < 0.05$ was considered as statistically significant. The data are represented as box-and-whisker drawings.

Table 1 Patients' demographic features and SWL characteristics

	Mean ± SD/*n* (%)	Median (min–max)
Age	34.7 ± 13.2	
Gender		
Male	19 (63.3)	
Female	11 (36.7)	
BMI	23.5 ± 2.4	
Stone side		
Right	10 (33.3)	
Left	20 (66.7)	
Stone size (mm)	9.0 ± 2.7	9.0 (5.0–15.0)
Creatinine levels (μmol/L)	78.7 ± 14.1	
SWL Characteristic		
Shocks	2763 ± 546	3000 (2000–4000)
Energy (kV)	6.7 ± 0.7	6.8 (5.4–8.3)
Frequency (Hz)	2.2 ± 0.4	2.0 (2.0–3.0)

BMI body mass index, *SWL* shock wave lithotripsy

Table 2 Correlation of pre-SWL podocalyxin and nephrin levels with age, BMI and creatinine levels

	Podocalyxin		Nephrin	
	r	*p*	*r*	*p*
Age	− 0.105	0.581	0.070	0.715
BMI	0.292	0.118	0.045	0.813
Creatinine levels	− 0.170	0.368	− 0.160	0.399

BMI body mass index, *r* correlation coefficient (Spearman's), *p* level of significance

Results

Patient demographics data, stone laterality, creatinine levels and SWL related parameters are presented in Table 1. Evaluation of the possible relationship between the pre-SWL nephrin and podocalyxin levels and the patient age and BMI values as well serum creatinine values demonstrated no significant correlation ($p > 0.05$) (Table 2). Similarly, evaluation of podocalyxin and nephrin levels after SWL revealed a distribution in a wide range, and as a result of this distribution (although expected) no significant correlation was present between their levels and stone size as well as treatment-related parameters including energy level, frequency and the number of shock waves ($p > 0.05$) (Table 3). Variation of pre and post-SWL nephrin and podocalyxin values on a follow-up time period based manner is being given in Table 4. However, there was a significant decrease observed in both nephrin and podocalyxin levels following SWL procedure ($p < 0.05$). Regarding the urinary nephrin levels, there was a significant decrease during 1 h and 1 day evaluation after SWL ($p < 0.001$ and $p = 0.003$, respectively). While evaluating the level of decrease on a time period based manner, a statistically significant difference was found between the evaluation during 1 h and 1 day as well as between the evaluations during 1 day and 1 week ($p < 0.001$, $p = 0.001$), respectively. Close follow-up of the changes clearly showed that a progressive increase was noted at the end of 1 day until the end of 1 week with no significant difference observed between the levels noted during pre-SWL and the 1-week evaluation ($p = 0.446$). In the podocalyxin levels again a significant decrease was noted during 1-h and 1-day evaluation after SWL ($p < 0.001$, $p = 0.004$, respectively). There was a statistically significant difference between the levels assessed during 1 h and the 1 day and that of between the 1-day and the 1-week levels ($p < 0.001$, $p = 0.001$), respectively. However, no statistically significant difference with respect to these values was observed between pre-SWL levels and the 1-week levels ($p = 0.200$). Box-and-whisker plots for the nephrin and podocalyxin levels during different follow-up periods are being shown in Fig. 1.

Table 3 Correlations between the amount of change in podocalyxin/nephrin levels and SWL characteristics

SWL characteristics	Δ^1 Podocalyxin		Δ^2 Podocalyxin		Δ^3 Podocalyxin		Δ^1 Nephrin		Δ^2 Nephrin		Δ^3 Nephrin	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Size	0.186	0.325	0.008	0.965	0.246	0.189	0.060	0.753	−0.011	0.954	0.053	0.781
Shock	0.262	0.161	0.064	0.738	0.267	0.154	0.067	0.724	0.05	0.792	0.269	0.151
Energy	0.325	0.079	0.133	0.484	0.313	0.092	−0.022	0.907	0.001	0.999	0.167	0.377
Frequency	0.068	0.720	0.023	0.905	−0.077	0.684	−0.287	0.124	−0.196	0.300	0.014	0.943

SWL shock wave lithotripsy, Δ^1 the difference in values before and after SWL first hour, Δ^2 the difference in values before and after SWL first day, Δ^3 the difference in values before and after SWL first week, *r* correlation coefficient (Spearman's)

Table 4 Patients' nephrin, podocalyxin and *p* values

	Mean ± SD	Δ Mean ± SD Median (min/max)	% Change Mean ± SD Median (min/max)	p^1	p^2
Nephrin levels (ng/L)					
Before SWL	2635.7 ± 643.8				
After SWL (first hour)	1605.2 ± 375.4	− 1030.5 ± 736.6 − 759.2 (− 2569/141)	− 35.7 ± 19.7 − 31.5 (− 72/9)	< 0.001	
After SWL (first day)	2118.6 ± 508.2	− 517.1 ± 867.5 − 468.4 (− 1993/1051)	− 14 ± 32 − 17.4 (− 52/66)	0.003	< 0.001
After SWL (first week)	2596.4 ± 562.5	− 39.3 ± 278.8 − 107.8 (− 470/638)	− 0.2 ± 12 − 4.3 (− 15/35)	0.446	0.001
Podocalyxin levels (ng/L)					
Before SWL	566.6 ± 163.7				
After SWL (first hour)	432.5 ± 123.8	− 134.1 ± 177.5 − 149.2 (− 426/294)	− 17.6 ± 35.8 − 25.3 (− 77/104)	< 0.001	
After SWL (first day)	504.8 ± 111.8	− 61.8 ± 109.2 − 76.2 (− 334/179)	− 7.1 ± 21.7 − 13.9 (− 42/63)	0.004	< 0.001
After SWL (first week)	603.3 ± 151.5	36.7 ± 153 − 10.9 (− 281/550)	11.8 ± 32.9 − 1.9 (− 38/110)	0.200	0.001

% Change = percentage of change in values before and after SWL; (Δ/value before treatment) × 100

Δ the difference in values before and after SWL

p = level of significance/^{1}difference with before SWL/^{2}difference with previous measurement (paired sample *t* test)

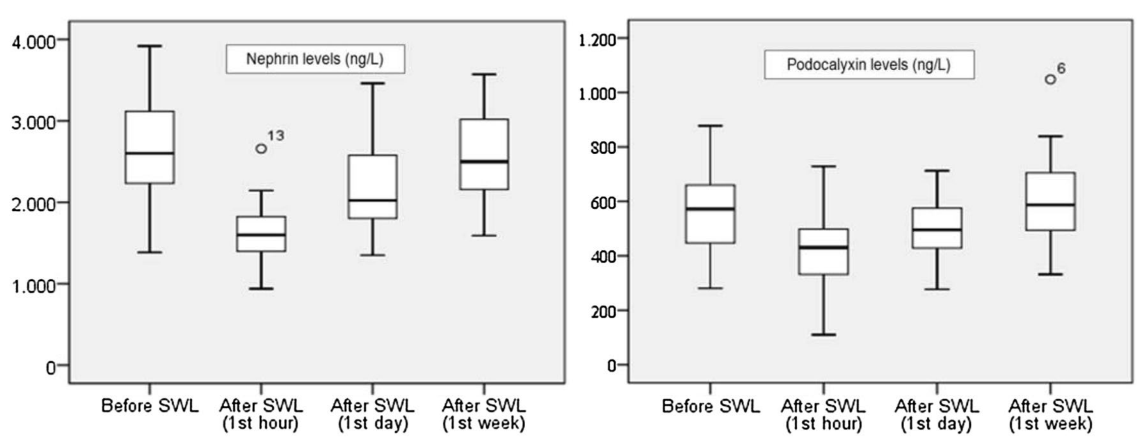

Fig. 1 Box-and-whisker plots for the nephrin and podocalyxin levels at different time points in the study

Discussion

In addition to certain histomorphological changes demonstrated by animal model studies [15, 16], investigations dealing with the immediate vascular supply and total effective renal plasma flow (ERPF) to kidneys treated with SWL indicated a transient decrease in renal perfusion, which might be related to shockwave-induced trauma in these kidneys [17–21]. While prolonged parenchymal transit time following HESW application was regarded as obstruction and ischaemia formation due to vascular pathologies [17, 19, 20, 22], concerning the pathophysiology of postischaemic renal dysfunction, reactive oxygen species (ROS) and vasoconstrictive substances (endothelin, renin, angiotensin II, thromboxane) were found to play important roles [23–25]. Additionally, these studies demonstrated well that above mentioned pathologic alterations could be responsible in the formation of histopathologic changes in both tubular as well glomerular structures.

Application of the shock waves during SWL to disintegrate the stone(s) will also affect podocytes as the most sensitive cells forming the glomerular filtration barrier due to their unique, complex cellular organisation and many specific functions. With respect to the extent of trauma, podocyte count is a critical determinant of glomerular integrity and scar formation where a decrease in glomerular podocyte number (podocytopaenia) was shown to lead to progressive renal failure. Therefore, the number of glomerular podocytes has become an important predictor of prognosis in glomerular diseases. Podocytes are the targets of injury in many forms of human and experimental glomerular diseases, such as minimal change disease, gene mutations, protein overload situations, toxins (adriamycin), infections (HIV), lupus nephritis and unknown causes (idiopathic focal segmental glomerulosclerosis). Furthermore, podocytes are the targets of injury in the secondary forms of focal segmental glomerulosclerosis, such as hypertension, diabetes and tubule-interstitial disease [6, 7, 26–28]. Urinary excretion of some molecules like podocalyxin and nephrin have been found to be elevated indicating the injury to podocytes in the majority of these diseases. Regarding this issue, in their study on 59 children with various renal diseases, Hara et al. found that the urinary podocalyxin values were negligible in those patients with glomerular disease in comparison with those cases demonstrating no glomerular disease [29]. In their experimental animal study again, Andersson et al. found that the selectivity of glomerular permeability was also disrupted during an acute renal injury induced by mild (15 min) renal ischaemia–reperfusion [30]. These findings let us to propose that the selectivity of glomerular permeability is directly related to the degree of podocyte damage which may be well demonstrated by the varying urinary levels of podocalyxin and nephrin depending on the duration, severity and frequency of the exposure to endogenous or exogenous stimuli. In their original study conducted on 48 patients with acquired renal disease leading to podocyte damage, Koop et al. investigated the protein and mRNA expressions of podocyte-related molecules (nephrin, podocalyxin, CD2-associated protein and podocin) and found that the glomerular levels of these molecules were lower than those of the control group cases with an increase in the mRNA levels. However, the authors did not find any relationship between the degree of proteinuria and the expression of these proteins [31]. In a study on patients with type 2 diabetic nephropathy, Jim et al. found that the expression of nephrin and other podocyte-related proteins (synaptopodin, podocin, etc.) decreased in the kidney biopsy materials, which was associated with a deteriorated glomerular filtration and late onset of proteinuria [32]. Working on rat crescentic glomerulonephritis by using the vascular endothelial growth factor inhibitor, Hara et al. found that nephrin expression decreased and proteinuria increased [33]. These animal- and human-based studies have clearly shown that the decrease in glomerular proteins (required for normal basal membrane functions and glomerular filtration) indicates a SWL-associated acute renal (glomerular) damage during early follow-up. As a result of such changes, the glomerular mRNA expression of these proteins tends to increase which leads to an active synthesis with elevated urinary levels. Another reason for the decrease in these molecules in the early period is that the podocytes synthesising these proteins can be damaged by shock waves, thus rendering them unable to perform these specific functions.

Related with this critical issue, in their study on the swine model by performing histopathological examination of the renal tissue samples taken within minutes (about 20 min) after SWL, Shao et al. found that shock waves may disrupt the basement membranes and cells of tubular as well as glomerular units by causing cellular breakdown and necrosis. These effects were noted throughout all segments of the nephron from the glomerulus to the collective tubules where the result was nephron destruction [34]. Regarding the role of such proteins from this aspect, Zhu et al. [26] assessed well the urinary nephrin and podocalyxin levels by ELISA method in 107 adult patients with nephrotic syndrome (27 proliferative nephritis, 77 non-proliferative and 3 amyloidosis) and found that levels of urinary nephrin and podocalyxin were significantly elevated. Similarly, Wang et al. [35] reported significantly higher levels of urinary nephrin and podocalyxin as measured using by ELISA in women with preeclampsia. In this current study, by using ELISA method, we measured the urinary levels of podocalyxin and nephrin proteins (which play an important role in the regulation of glomerular filtration,) on a time-dependent manner to evaluate the presence and degree of direct damaging effects of shock waves on the glomerular structures.

A series of biomarkers have been discovered in the recent years for the early detection of acute kidney injury to predict the likelihood of kidney damage development in some certain problematic clinical situations. Furthermore, serum and/or urine levels of such biomarkers may enable us to estimate the cause, severity and duration of kidney damage along with the possible response to the management. Kidney injury molecule-1, cystatin C, interleukin-18, neutrophil gelatinase-associated lipocalin, intercellular adhesion molecule-1, monocyte chemoattractant protein-1 and β2-microglobulin are some of the molecules used in the diagnosis and follow-up of kidney damage after certain situations [36–38]. As mentioned above, SWL can cause glomerular injury by way of the alterations in podocytes and the evaluation of the urinary levels of above mentioned proteins may help us to detect the possible early renal damage caused by the application of high-energy shock waves. We studied these podocyte proteins for the first time in the literature to determine the possible intervals between SWL sessions and we were able to find that the podocalyxin and nephrin levels returned to the pre-SWL levels after about 1 week. These findings let us to propose that a time interval of 1 week could be a safe period between two consecutive SWL sessions for the physicians to apply this modality in safe manner in clinical conditions. Related with this issue, while a relatively short interval (1-day) between treatment sessions for ureteral stones (1-day intervals) is commonly accepted [39], no consensus has been proposed and reported in the guidelines so far on the optimum time period between two SWL sessions for kidney stones in order to perform a safe application. However, depending on the clinical experience accumulated so far, patients are recommended to wait 10–14 days between two consecutive SWL sessions to limit the extent of trauma on the kidney. Related with this issue a study showed that the mean duration of time for the recovery of kidney tissue contusions is approximately 2 weeks [40]. As studied for the first time in our study, following a significant rise, the excretion levels of both podocalyxin and nephrin returned to the baseline values after 1 week, indicating the normalization (recovery) of the transient kidney damage induced by high-energy shock waves within this period. The extent of the trauma induced on the kidney after shock wave application may vary from patient to patient depending on the functional capacity, morphological characteristics as well as the total antioxidant capacity of the kidneys. Thus, in the light of this fact, the assessment of urinary excretion levels of podocalyxin and nephrin in an individualized manner will enable the responsible physician to determine the minimum time period needed to elapse for a second session to perform SWL in a safe manner.

Our study is limited by the fact that we did not compare the podocalyxin and nephrin levels with the glomerular filtration rate, creatinine clearance and other oxidative stress markers in order to correlate the reliability of these markers for the presence and degree of renal damage on a comparative manner.

Conclusion

Although SWL is accepted to be an effective and non-invasive treatment method for kidney stones, it may be associated with some certain potential transient adverse effects on the function as well as morphology of the treated kidneys. Our results have clearly demonstrated that as reliable biomarkers of transient kidney injury, the assessment of urinary podocalyxin and nephrin excretion levels may be used to determine the extent as well as duration of acute glomerular changes in the SWL-treated kidney. Furthermore, our current findings indicate well that period of "1 week" between two consecutive SWL sessions seems to be appropriate for a safe application to overcome above mentioned adverse effects. This evaluation will certainly enable us to assess the optimal time interval between SWL sessions for a safe application in these patients in an individualized manner.

Author contribution KH: project development, data collection, data analysis, manuscript writing. BF: project development, data collection. AN: data collection, manuscript editing. Kİ: data collection, manuscript editing. ŞE: project development, data collection, data analysis, manuscript editing. SK: data analysis, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflicts of interest. There was no funding for this study.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol (2018/01-01) was approved by the ethics committee of the Health Sciences University Erzurum Regional Education and Research Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Romero V, Akpinar H, Assimos DG (2010) Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol 12(2–3):e86–e96

2. Cohen TD, Durrani AF, Brown SA, Ferraro R, Preminger GM (1998) Lipid peroxidation induced by shockwave lithotripsy. J Endourol 12(3):229–232
3. Willis LR, Evan AP, Connors BA, Blomgren P, Fineberg NS, Lingeman JE (1999) Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. J Am Soc Nephrol 10(8):1753–1762
4. Lingeman JE, McAteer JA, Kempson SA, Evan AP (1988) Bioeffects of extracorporeal shockwave lithotripsy: strategy for research and treatment. Urol Clin N Am 15:507
5. Recker F, Hofmann W, Bex A, Tscholl R (1992) Quantitative determination of urinary marker proteins: a model to detect intrarenal bioeffects after extracorporeal lithotripsy. J Urol 148(3):1000–1006
6. Mundel P, Shankland SJ (2002) Podocyte biology and response to injury. J Am Soc Nephrol. 13:3005–3015
7. Camici M (2007) Urinary detection of podocyte injury. Biomed Pharmacother 61(5):245–249
8. Kerjaschki D, Sharkey DJ, Farquhar MG (1984) Identification and characterization of podocalyxin–the major sialoprotein of the renal glomerular epithelial cell. J Cell Biol 98(4):1591–1596
9. Kerosuo L, Juvonen E, Alitalo R, Gylling M, Kerjaschki D, Miettinen A (2004) Podocalyxin in human haematopoietic cells. Br J Haematol 124:809–818
10. Kershaw DB, Beck SG, Wharram BL, Wiggins JE, Goyal M, Thomas PE, Wiggins RC (1997) Molecular cloning and characterization of human podocalyxin-like protein. Orthologous relationship to rabbit PCLP1 and rat podocalyxin. J Biol Chem 272:15708–15714
11. Casey G, Neville PJ, Liu X, Plummer SJ, Cicek MS, Krumroy LM, Curran AP, McGreevy MR, Catalona WJ, Klein EA, Witte JS (2006) Podocalyxin variants and risk of prostate cancer and tumor aggressiveness. Hum Mol Genet 15:735–741
12. Larrucea S, Butta N, Arias-Salgado EG, Alonso-Martin S, Ayuso MS, Parrilla R (2008) Expression of podocalyxin enhances the adherence, migration, and intercellular communication of cells. Exp Cell Res 314:2004–2015
13. Kestilä M, Lenkkeri U, Männikkö M, Lamerdin J, McCready P, Putaala H, Ruotsalainen V, Morita T, Nissinen M et al (1998) Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome. Mol Cell 1:575–582
14. Aström E, Rinta-Valkama J, Gylling M, Ahola H, Miettinen A, Timonen T, Holthöfer H (2006) Nephrin in human lymphoid tissues. Cell Mol Life Sci 63:498–504
15. Karalezli G, Gögüş O, Bedük Y, Köküuslu C, Sarica K, Kutsal O (1993) Histopathologic effects of extracorporeal shock wave lithotripsy on rabbit kidney. Urol Res 21(1):67–70
16. Sarica K, Ozer G, Soygür T, Yaman O, Ozer E, Ustün H, Yaman LS, Göğüş O (1997) Preservation of shock-wave-induced renal histologic changes by dermatan sulfate. Urology 49(1):145–150
17. Krysiewicz S (1992) Complications of renal extracorporeal shock wave lithotripsy reviewed. Urol Radiol 13(3):139–145
18. Biri H, Oztürk HS, Büyükkoçak S, Kaçmaz M, Cimen MY, Unal D, Birey M, Bozkirli I, Durak I (1998) Antioxidant defense potential of rabbit renal tissues after ESWL: protective effects of antioxidant vitamins. Nephron 79(2):181–185
19. Kaude JV, Williams CM, Miliner MR, Scott KN, Finlayson B (1985) Renal morphology and function immediately after extracorporeal shock-wave lithotripsy. AJR Am J Roentgenol 145(2):305–313
20. Bomanji J, Boddy S, Britton KE, Nimmon CC, Whitfield HN (1987) Radionuclide evaluation pre and post-extracorporeal shock wave lithotripsy for renal calculi. J Nucl Med 28(8):1284–1289
21. Sarıca K, Kosar A, Yaman O, Bedük Y, Durak I, Göğüş O, Kavukçu M (1996) Evaluation of ischemia after SWL: detection of free oxygen radical scavenger enzymes in renal parenchyma subjected to high-energy shock waves. Urol Int 57(4):221–223
22. Neal DE Jr, Kaack MB, Harmon EP, Puyau F, Morvant A, Richardson E, Thomas R (1991) Renin production after experimental extracorporeal shock wave lithotripsy: a primate model. J Urol 146(2 (Pt 2)):548–550
23. Strohmaier WL, Carl AM, Wilbert DM, Bichler KH (1996) Effects of extracorporeal shock wave lithotripsy on plasma concentrations of endothelin and renin in humans. J Urol 155(1):48–51
24. Yurdakul T, Kulaksizoglu H, Pişkin MM, Avunduk MC, Ertemli E, Gokçe G, Barişkaner H, Byükbaş S, Kocabas V (2010) Combination antioxidant effect of α-tocoferol and erdosteine in ischemia-reperfusion injury in rat model. Int Urol Nephrol 42(3):647–655
25. Thamilselvan S, Byer KJ, Hackett RL, Khan SR (2000) Free radical scavengers, catalase and superoxide dismutase provide protection from oxalate-associated injury to LLC-PK1 and MDCK cells. J Urol 164(1):224–229
26. Zhu B, Li XF, Zhu XL, Lin Y, Zhong S, Zhu CF, Tang XL, Hu YQ, Cheng XX, Wang YJ (2014) ELISA analysis of urinary nephrin and podocalyxin standardized by aquaporin-2 in adult patients with nephrotic syndrome. J Nephrol 27(4):411–417
27. Matovinović MS (2009) Podocyte ınjury in glomerular diseases. eJIFCC 20(1):21–27
28. Whiteside C, Porutis K, Cameron R, Thomson J (1989) Glomerular epithelial detachment not reduced charge density correlates with proteinuria in adriamycin and puromycin nephrosis. Lab Investig 61:650–660
29. Hara M, Yamamoto T, Yanagihara T, Takada T, Itoh M, Adachi Y, Yoshizumi A, Kawasaki K, Kihara I (1995) Urinary excretion of podocalyxin indicates glomerular epithelial cell injuries in glomerulonephritis. Nephron 69:397–403
30. Andersson M, Nilsson U, Hjalmarsson C, Haraldsson B, Nystrom JS (2007) Mild renal ischemia-reperfusion reduces charge and size selectivity of the glomerular barrier. Am J Physiol Renal Physiol 292:F1802–F1809
31. Koop K, Eikmans M, Baelde HJ, Kawachi H, De Heer E, Paul LC, Bruijn JA (2003) Expression of podocyte-associated molecules in acquired human kidney diseases. J Am Soc Nephrol 14(8):2063–2071
32. Jim B, Ghanta M, Qipo A, Fan Y, Chuang PY, Cohen HW, Abadi M, Thomas DB, He JC (2012) Dysregulated nephrin in diabetic nephropathy of type 2 diabetes: a cross sectional study. PLoS One 7(5):e36041
33. Hara A, Wada T, Furuichi K, Sakai N, Kawachi H, Shimizu F, Shibuya M, Matsushima K, Yokoyama H, Egashira K, Kaneko S (2006) Blockade of VEGF accelerates proteinuria, via decrease in nephrin expression in rat crescentic glomerulonephritis. Kidney Int 69(11):1986–1995
34. Shao Y, Connors BA, Evan AP, Willis LR, Lıfshıtz DA, Lıngeman JE (2003) Morphological changes induced in the pig kidney by extracorporeal shockwave lithotripsy: nephron injury. Anat Rec A Discov Mol Cell Evol Biol 275(1):979–989
35. Wang Y, Zhao S, Loyd S, Groome LJ (2012) Increased urinary excretion of nephrin, podocalyxin, and βig-h3 in women with preeclampsia. Am J Physiol Renal Physiol 302(9):F1084–F1089
36. Obermüller N, Geiger H, Weipert C, Urbschat A (2014) Current developments in early diagnosis of acute kidney injury. Int Urol Nephrol 46(1):1–7
37. Sirota JC, Klawitter J, Edelstein CL (2011) Biomarkers of acute kidney injury. J Toxicol 2011:328120
38. Aydin HR, Irkilata L, Aydin M, Daggulli M, Taskin MH, Demirel HC, Adanur S, Moral C, Atilla MK, Sancaktutar AA (2016) The application of kidney injury molecule-1 to determine the duration between shock wave lithotripsy sessions. J Endourol 30(1):109–113

39. Turk C, Petrik A, Seitz C, Skolarikos A, Thomas K, Neisius A et al (2018) Guidelines on urolithiasis (limited text update March 2017), pp 1–81. http://uroweb.org. 13 Mar 2017
40. Kira VM, Fagundes DJ, Bandeira CO, Fagundes AT, Ortiz V (2007) The repeated extracorporeal shockwaves and the renal parenchyma injury on normal and diabetic rats. Acta Cir Bras 22(4):285–290