Urinary Beta-2Microglobulin: An Indicator of Renal Tubular Damage after Extracorporeal Shock Wave Lithotripsy

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Purpose: This study aims to determine extracorporeal shock wave lithotripsy (ESWL)-induced renal tubular damage and the affecting factors by measuring urinary beta2microglobulin (β2M) excretion.

Materials and Methods: This is a cross-sectional study conducted on 91 patients with renal stones who underwent ESWL during 2012. Urinary beta2microglobulin was measured immediately before and after the procedure for each patient and analyzed based on different variables to evaluate factors affecting ESWL-induced renal tubular injury.

Results: Mean ± SD urinary beta2-microglobulin values, before and after ESWL were 0.08 ± 0.07 and 0.22 ± 0.71 mg/dL respectively, the average difference between which was equal to 0.14 ± 0.07 mg/dL. These figures exhibited a 166.66% rise in the urinary β2M concentration after ESWL which was statistically significant ($P < .001$). Multivariate analysis showed that hypertension ($P = .05$) and the history of ESWL ($P = .02$) were predictive factors of higher post-ESWL urinary beta2-microglobulin excretion.

Conclusion: Urinary excretion of beta2-microglobulin increased significantly immediately after ESWL. These changes could indicate that ESWL is a contributing factor to renal tubular damage. It also seems that in patients with hypertension and a previous history of ESWL the likelihood of this injury is higher than others.

Keywords: acute kidney injury; beta2-microglobulin; extracorporeal shock wave lithotripsy; urinary stone

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is one of the most effective methods available for the treatment of urinary stones. It is a non-invasive procedure that does not require general anesthesia and can be used for outpatients. The mechanism of ESWL is to use the shock wave energy to break the stones into small particles that can easily pass into the urinary tract[1]. The effectiveness of this mechanism depends on various factors and all the treatments are not successful[2]. On the other hand, studies have shown that treatment with ESWL could have adverse effects and be followed by tissue damage in the kidneys.[3]

Urinary beta2-microglubulin is a sensitive marker of renal tubular injury,[4-6] the increased excretion of which after ESWL represents the proximal tubule cell damage and dysfunction following the treatment.[7,8] It is a low molecular weight protein easily filtrated by the glomerulus and reabsorbed by about 99.9% in the proximal tubules of the kidney. Beta2-microglobulin reuptake process is so effective that its urinary excretion is less than 400 ng per day.[9] For this reason, any disturbance in reabsorption of this protein in kidneys leads to higher excretion of urinary beta2-microglobulin and can represent subtle changes in renal tubular function. On the other hand, Glomerular Filtration Rate (GFR) is the most important factor affecting serum beta2-microglobulin level. Therefore, serum beta2-microglobulin level can be useful in detecting slight decline in GFR levels[6]. Urinary beta2-microglobulin will not increases in glomerular diseases.

Due to lack of studies about post-ESWL urinary beta2-microglobulin changes and the affecting factors, we designed the current study in our country to determine extracorporeal shock wave lithotripsy induced renal tubular damage and the affecting factors by measuring the urinary beta2-microglobulin.

MATERIALS AND METHODS

This is a cross-sectional study performed on 91 patients with urinary stones who underwent extracorporeal shock-wave lithotripsy at our center on an outpatient basis during 2012. All patients underwent lithotripsy procedure once with the power level of 3 and frequency of 2500 shock waves. Patients having any of the following conditions were excluded from the study: age under 14, using of nephrotoxic drugs, autoimmune diseases, polycystic kidney disease and congenital renal malformations. Besides, none of our patients had obstruction below the stone level in the urinary tract, complete obstruction at the stone level or uremia status. The study design was approved by ethics committee of the Guilan University of Medical Sciences.

After obtaining informed consent for participation in the study, the following variables were recorded for each patient: age, gender, co-administration of drugs, Body Mass Index (BMI), GFR, serum creatinine level,

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Table 1. Patients' characteristics and demographic data

variable	
Age, year; Mean ± SD	48.93±14.03
Male/Female	53/38
Serum creatinine, mg/dL; Mean ± SD	0.90±0.12
GFR, mL/minute/1.73m2; Mean ± SD	99.53±23.07
History of previous ESWL, N(%)	50(54.9)
History of previous kidney surgery, N(%)	7(7.7)
Stone size, mm; Mean ± SD	10.33±4.40

the history of hypertension, diabetes mellitus, previous ESWL or kidney surgery and the number, size and location of the stones. The GFR level was measured based on Cockroft Gault formula as follows:
Clcr = (140 – Age) x Wt / 72 x Pcr (x 0.85 for female patients)[10]
Urinary beta2-microglobulin level was measured in two discharged urine samples (the first and second samples were collected just before and right after the procedure respectively). To check urinary beta2-microglobulin level, an immunoassay kit,which measures the amount of this protein in urine by an ELISA based method- was used (MININEPHTM human beta2-microglobulin kit; The Binding Site Ltd, Birmingham, UK).
The collected data was analyzed using SPSS software (the Statistical Package for the Social Sciences, Version 17.0, SPSS Inc., IL). Urinary beta2-microglobulin concentrations after ESWL were compared to baseline values. To assess the changes in urinary beta2-microglobulin values before and after ESWL, first, one-sample Kolmogorov-Smirnov test was utilized to determine the variables distribution. The results indicated that urinary concentrations of beta2-microglobulin did not follow a normal distribution. Therefore, to assess its changes in urine after ESWL according to different variables, Non-parametric Mann-Whitney *U* test, Wilcoxon Signed Ranks test and the Kruskal-Wallis test with Spearman's correlation coefficients were used. To obtain odds ratios for significant variables, a logistic regression was used. All parameters with P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 91 patients with the mean ± SD age of 48.93±14.03 years were studied. 53 patients (58.2%) were male and 38 (41.8%) were female. Some data regarding patients' demographic variables have been summarized in **Table 1**.
The number of stones was 1 in 56 patients (66.7%) and more than one in the others, with the highest number of 16. Stone location was the ureter in 8 patients (8.8%), the upper calyx in 18 (19.8%), the middle calyx in 21 (23.1%), the lower calyx in 28 (30.8%) and the pelvis in 10 (11%). Seven patients (7.7%) had a history of previous kidney surgery and 50 (54.9%) patients mentioned a history of previous ESWL. Ten patients (11%) were hypertensive, eleven (12.1%) had diabetes mellitus and 5 (5.5%) had ureteral stent.
Mean urinary beta2-microglobulin values before and after ESWL were 0.08 ± 0.07 and 0.22 ± 0.71 mg/dL respectively. The average changes in urinary β2M level were 0.14 ±0. 07, showing a 166.66% rise in its concentration after ESWL (more than 1.5 times) which was significant in the Wilcoxon Signed Ranks test ($P < .001$).
In univariate analysis, history of hypertension, history of ESWL, lower GFR level and having a ureteral stent caused a significant difference in the post-ESWL urinary beta2-microglobulin level. The average difference in urinary beta2-microglobulin concentrations before and after ESWL was higher in patients with hypertension ($P = .003$) and in patients with the history of previous ESWL ($P = .01$) than those without. Patients with lower GFR levels, manifested a greater increase in post-ESWL urinary beta2-microglobulin value ($P = .007$) while having ureteral stent, was associated with lower post-ESWL urinary beta2-microglobulin excretion ($P = .03$). **Table 2** shows some of the results of

Table 2. Urinary beta2-microglobulin concentrations percentiles according to different levels of studied variables in univariate analysis

Variable		Percentile 25	Median	Percentile 75	*P* Value
Gender	Male	0.01	0.02	0.07	0.26
	Female	0.02	0.04	0.07	
Hypertention	Yes	0.03	0.08	0.17	0.003
	No	0.01	0.03	0.06	
Diabetes Mellitus	Yes	0.01	0.02	0.07	0.76
	No	0.01	0.03	0.07	
Ureteral Stent	Yes	0.06	0.08	0.15	0.03
	No	0.01	0.03	0.06	
History of Previous	Yes	0.00	0.03	0.17	0.99
Kidney Surgery	No	0.01	0.03	0.07	
History of ESWL	Yes	0.01	0.03	0.09	0.01
	No	0.01	0.03	0.05	

Table 3. Variables included in the logistic regression analysi

		B	S.E.	Wald	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Step 1a	age	.000	.030	.000	.985	.999	.942	1.060
	height	-.045	.038	1.382	.240	.956	.888	1.030
	weight	-.029	.041	.501	.479	.972	.897	1.052
	HTN(1)	1.768	1.398	1.600	.206	5.860	.379	90.722
	Ureteral stent(1)	1.430	1.267	1.273	.259	4.180	.349	50.119
	GFR	-.009	.020	.217	.641	.991	.953	1.030
	History of previous ESWL	1.754	1.173	2.233	.135	5.775	.579	57.592
	Constant	9.486	5.618	2.851	.091	1.317E4		
Step 8a	HTN(1)	1.711	.895	3.650	.056	5.533	.957	31.999
	History of previous ESWL	.910	.417	4.758	.029	2.485	1.097	5.633
	Constant	10.359	5.159	4.032	.045	3.153E4		

a. Variable(s) entered on step 1: age, height, weight, HTN, Ureteral stent, GFR, History of previous ESWL.

univariate analysis.

Multivariate analysis using logistic regression showed that hypertension and history of ESWL were predictive factors for higher excretion of urinary beta2-microglobulin after ESWL. Patients with hypertension, were at increased risk of higher urinary β2M excretion after ESWL (Odds ratio=5.53, 95% CI=0.95-31.99, P = .05). Also, the history of previous ESWL, increased the risk of higher post-ESWL urinary beta2-microglobulin (Odds ratio=2.48, 95% CI=1.09-5.63, P = .02). **Table 3** shows the results of logistic regression analysis.

DISCUSSION

Although ESWL is considered a safe course of treatment for urinary stones, various studies have shown that it can be accompanied by some degree of kidney damage and lead to a range of complications.[3,11-13]

To determine ESWL-induced renal tubular injury, we measured the beta2-microglobulin concentration in the urine before and after the procedure. Urinary beta2-microglobulin is a low molecular weight protein known as a sensitive marker of renal tubular damage in various studies.[4,5,7] The results showed that urinary beta2-microglobulin concentration is significantly increased after ESWL. These findings suggest the occurrence of renal tubular damage and dysfunction after this treatment.[7,8] Sheng and colleagues study on patients with urinary stones treated with ESWL revealed that the urinary beta2-microglobulin level is increased significantly as a result of ESWL and peaked by 24 hours and immediately after the treatment.[13] Another study by Villany et al. showed a significant increase in post-ESWL urinary excretion of beta2-microglobulin as well.[8] In addition, there are several other studies confirming that the level of urinary beta2-microglobulin increases significantly after ESWL.[7,14-16]

The exact mechanism of renal damage after ESWL is still not fully understood. But the effects of temporary reduction in renal blood flow, formation of free radicals caused by ischemic damages and thermal and cavitation effects have been discussed.[17] According to previous studies, the primary effect of shock waves is to cause a traumatic vascular injury that leads to the rupture of blood vessels and pooling of blood in renal parenchyma.[18] On the other hand, renal vasoconstriction ensuing ESWL results in tissue hypoxia. Hence, both blood pooling and tissue hypoxia are observed simultaneously in the damaged kidneys after ESWL.[19] This causes an ischemic-reperfusion injury affecting the urinary excretion of beta2-microglobulin in 2 ways: First, through tubular cell damage due to ischemic-reperfusion injury and the resulting oxidative stress that reduces reabsorption capacity and leads to increased excretion of these low molecular weight proteins[19,20]; and second, through a possible transient impairment in glomerular filtration barrier leading to an increase in the concentration of urinary filtrated proteins after ESWL-induced reperfusion injury.[21] However, studies in this area are limited and the role of glomerular damage in reperfusion injury-induced proteinuria is not completely known yet.

The results of this study suggest that hypertension is an independent prognostic factor for higher post-ESWL urinary beta2-microglobulin excretion. Christensen et al. reported that the increased secretion of urinary beta2-microglobulin level in patients with hypertension is due to increased filtration of plasma proteins in these patients saturating their renal tubular reabsorption capacity.[22] In another study, Musialik and colleagues suggested that increased secretion of urinary beta2-microglobulin in patients with hypertension is due to an increase in glomerular filtration rate and decreased reabsorption capacity of proximal tubule.[16] On these grounds, there is a possibility that in patients with hypertension, a further tubular injury might follow ESWL. According to Palm et al. study, hypertension can cause renal arteriolar dysfunction and impair renal auto-regulation. The endothelium becomes dysfunctional and vasodilatation response is gradually impaired.[23] It was also shown that shock waves induce vasoconstriction in the kidneys.[24] As a result, it can be concluded that

patients with hypertension have lower ability to compensate ESWL induced damages and the treatment can exacerbate underlying pathological conditions associated with hypertension in these patients.

The history of previous ESWL was another factor associated with a significantly higher post-ESWL excretion of urinary beta2-microglobulin. The study by York and coworkers pointed out that the influence of the remaining stone particles and the tissue effects of ESWL can contribute to a more difficult percutaneous nephrolithotomy in patients with urinary stones.[25] This could be a possible explanation of why patients with previous history of ESWL had an increased urinary excretion of beta2-microglobulin in this study.

Variables such as stone size, number and location were not significantly associated with changes in post-ESWL urinary beta2-microglobulin concentration in this study. Lee and colleagues demonstrated that the stone size is a risk factor for renal hematoma formation after ESWL, while no such association was seen for stone location.[26] Kardakos et al. reported no relationship between the characteristics of the stone and the change in markers of kidney damage after ESWL.[27] Also Dhar and coworkers found no association between stone location and the risk of renal hematoma after ESWL.[28] It can be concluded from the literature that the complications of ESWL do not bear a significant relationship with stone features and the results of our study provide further evidence for it. Nonetheless, in some studies it has been shown that characteristics such as size, location and number of stones have a statistically significant relationship with ESWL success rate.[2] Drach et al. observed that by increasing the size and number of stones, the risk of obstruction and entrapment of stone particles after ESWL increases.[29] Madbouly et al. also disclosed that the size of the stone significantly increases the risk of Steinstrasse after ESWL.[30] These studies did not evaluate post-ESWL kidney damage and none of them used the markers of renal tubular damage, so it can be assumed that the different results of our study in this regard can be attributed to its different method. But on the other hand it is likely that lack of significant correlation between these variables and urinary beta2-microglobulin changes after ESWL, is the result of the rather small population sample size of our study. Therefore, further studies with larger population sample sizes can be useful in this regard.

Studies about the factors which affect ESWL-induced kidney damage are limited. However, our study shows that there is a possibility that certain groups of patients (hypertensive patients and patients with previous history of ESWL) may be susceptible to further kidney damage after ESWL according to their underlying conditions and identification of these risk groups can have a significant impact on choosing the best treatment for these patients. We did not repeat measurement of urinary beta2-microglobulin after the 1st postoperative day to document the length of its increase after ESWL to differentiate between transient shortlasting increase in urinary beta2-microglobulin versus long-lasting elevation. This was the main limitation of current study and was due to financial considerations.

CONCLUSIONS

The findings of this study demonstrate the occurrence of renal tubular injury after ESWL and it appears that the damage is more severe in patients with hypertension and patients with a previous history of ESWL. ESWL should be used only when it is best indicated .

CONFLICT OF INTEREST

None declared.

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