

# Evaluation and physiopathology of minor transient shock wave lithotripsy – induced renal injury based on urinary biomarkers levels

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**Introduction** Extracorporeal shock wave lithotripsy (ESWL) is one of the most useful methods available for the treatment of urolithiasis. However, despite its significant benefits, adverse effects can occur. Oxidative stress mediated by ischemia-reperfusion might contribute to kidney injury after ESWL. Moreover, an acute kidney injury (AKI) may develop. AKI is typically diagnosed by measuring serum creatinine level, yet serum creatinine does not allow for early detection of sub-clinical AKI. The latest report has investigated multiple ways to determine ESWL – induced renal damage through the evaluation of various urine biomarkers of renal injury.

**Materials and methods** The Medline and Web of Science databases were searched without a time limit in November 2017 using the terms ‘ESWL’ in conjunction with ‘kidney failure’, ‘kidney damage’, ‘renal injury’ and ‘inflammation markers’, ‘biomarkers’. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. In this review, we described all the up-to-date reported urine markers of ESWL-induced renal damage.

**Results** In recent years, several studies demonstrated evaluation of ESWL – induced renal injury based on urinary biomarkers levels and its utility in clinical practice. They have a beneficial role in the early detection of AKI, as well as in observation of a transition of this acute illness into chronic kidney disease.

**Conclusions** Different markers have been evaluated in the urine before and after the ESWL treatment, but their number is still limited and results remain inconclusive. Further investigations are mandatory.

**Key Words:** extracorporeal shock wave lithotripsy ↔ acute kidney injury ↔ renal damage ↔ urine markers

## INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is one of the most useful methods available for the urolithiasis management, and it has been the first treatment option for many patients for more than three decades. However, despite its significant benefits, adverse effects such as reduced renal function, perirenal hematomas, hypertension, urinary obstruction or sepsis can occur [1]. Bubble cavitation and shear stress have been demonstrated to play an essential role in the mechanical trauma induced by the shock wave [2]. Unfortunately, kid-

ney injury occurs during every ESWL session, and what is more – this process does not end when the treatment is finished. Consequently, the effects of shock waves on renal function and morphological structure must be elucidated.

Two major types of effects of shock waves on renal tissue can be distinguished: traumatic vascular injury and ischemic injury [3, 4]. Both of them have a different pathophysiological background. The ischemic (hypoxic) injury is caused by renal vasoconstriction together with intraparenchymal bleeding, and it appears in both kidneys, whereas traumatic injury is induced by the physical force of waves and occurs only

in the treated one. Furthermore, oxidative stress mediated by ischemia-reperfusion might contribute to kidney injury after ESWL [5]. As a result, an acute kidney injury (AKI) may develop [6]. AKI is typically diagnosed by measuring serum creatinine concentration, yet serum creatinine does not allow for early detection of sub-clinical AKI. A significant aim in the past few years has been to find a biomarker sensitive enough to detect kidney injury, independently of serum creatinine level and urine output. The fact that AKI in subclinical form is not clinically determined does not mean that the kidney is undisturbed with normal glomerular filtration rate (GFR).

Therefore, there is a need to develop accurate and sensitive biomarker-based tests for post ESWL renal transient injury recognition to determine the actual degree of organ damage during treatment. The latest report has investigated multiple ways to determine ESWL-induced renal damage through the evaluation of various biomarkers of renal injury [7, 8].

## MATERIAL AND METHODS

The Medline and Web of Science databases were searched without a time limit in May 2017 using the terms 'ESWL' in conjunction with 'kidney failure', 'kidney damage', 'renal injury' and 'inflammation markers', 'biomarkers'. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Auto alerts in Medline were also run, and reference lists of original articles, review articles and book chapters were searched for further eligible articles.

The search was limited to the English and Polish language. Articles that did not address the topics were excluded, and the full text of the remaining articles was reviewed.

## RESULTS

In this review, we described all the up-to-date reported urine markers of ESWL-induced renal damage.

### $\beta$ 2-microglobulin

Urinary  $\beta$ 2-microglobulin has been demonstrated to be a sensitive marker of renal tubular injury [9, 10], and its increased excretion after ESWL procedure represents the proximal tubule cell damage together with kidney dysfunction following the treatment [11]. This protein has low molecular mass and is easily filtrated and reabsorbed nearly by 100% in proximal tubules under physiological conditions. Its reuptake process is very efficient, hence any disturbance

in its reabsorption results in increased amount in urine, representing subtle changes in renal tubular function [12]. Therefore, the measurement of serum  $\beta$ 2-microglobulin level can be helpful in revealing the slight decline in GFR levels [13]. The ischemic-reperfusion injury caused by ESWL influences the urinary excretion of  $\beta$ 2-microglobulin in two ways. The first one occurs through tubular cell damage due to ischemic-reperfusion injury and the resulting oxidative stress that reduces reabsorption capacity, what leads to its high excretion [4, 14]. The second one results in a transient impairment in the glomerular filtration barrier, what leads to the increase of urinary filtrated proteins after ESWL-induced reperfusion injury [15].

Only a few studies demonstrate the link between urine  $\beta$ 2-microglobulin excretion and ESWL-induced renal tubular damage. Nasseh et al. showed in a cross-sectional study conducted on 91 patients with kidney stones, who underwent ESWL in 2012 (with the power level of 3 and frequency of 2500 shock waves) that the urinary excretion of  $\beta$ 2-microglobulin increased by 167% immediately after the ESWL procedure [16]. Hypertension and previous ESWL sessions have been recognized as independent predictive factors for elevated excretion of urinary  $\beta$ 2-microglobulin after treatment. These findings suggest the presence of renal tubular damage and kidney dysfunction after ESWL. It was also shown, that variables such as stone size, stone location, and a number of concrements in the kidney were not significantly associated with changes in post-ESWL urinary  $\beta$ 2-microglobulin concentration. Another study, carried out by Sheng et al. [17], (60 patients with renal stones, 2,000 shock waves during 30–45 min in an MZ-V lithotripter with an electromagnetic wave generator at 16 kV) demonstrated an increased urinary  $\beta$ 2-microglobulin level immediately following the ESWL procedure. Similarly, Villany et al. [11] showed a significant transient increase in post-ESWL urinary excretion of  $\beta$ 2-microglobulin in the group of 65 pediatric patients as well (Dornier Compact Lithotripter, 2360 shock waves, shock wave energy 11–13 kV). Studies performed by Li et al. [2] on animal model of rats with a single kidney revealed significantly elevated values of urinary  $\beta$ 2-microglobulin than those in the control group at three days post-shock wave. Shock wave induced a significant increase of urinary  $\beta$ 2-microglobulin at 105 days post-shock wave as well.

### TNF- $\alpha$

Some agents, including bacteria, viruses, immune complexes, and reactive oxygen intermediates in-

crease the tumor-necrosis-factor- $\alpha$  (TNF- $\alpha$ ) level [18, 19]. TNF- $\alpha$  is an inflammatory cytokine, which plays an essential role in many different kidney disease pathomechanisms [20, 21]. Its presence is postulated to be in shock-wave induced renal damage. Clark et al. [22] demonstrated in the animal model study on female farm pigs a significant urinary TNF- $\alpha$  excretion increase one hour after ESWL (2000 SWs at 24kV, HM3), that declined within four hours toward baseline values.

In another study, the same authors did not detect a significant change in the urinary excretion of TNF- $\alpha$  in pigs that received either 500 or 1,000 shockwaves (120 SWs/min and 24 kV, HM3 lithotripter) [23]. However, when they increased the number of shockwaves, they found that the urinary TNF- $\alpha$  secretion level was increased significantly in pigs receiving 2,000 shock-waves at one hour after ESWL, and declined after that. Another study showed a significantly increased level of urine TNF- $\alpha$  on the animal rat model after ESWL (HK MZ-V lithotripter, 500 shocks at the voltage of 18 kV) [24]. These results also demonstrated that shock wave treatment significantly increased the serum TNF- $\alpha$  level three days post-procedure. Contrary, Goktas et al. [6] (2,500 shockwaves at 100 shockwaves/min and 0.039 J, Dornier Compact Sigma) did not detect any elevated amount of TNF- $\alpha$  in the urine of treated patients nor in the control group. However, authors underlined that the detection limit of their methods was too low and it could be not sensitive enough to prove the difference. They also suggested, that in the clinical practice, more accurate methods, with lower detection limits to measure urine TNF- $\alpha$ , are needed. Dundar et al. [24] measured urine TNF- $\alpha$  level before and after two hours following ESWL and found no significant changes as well (3000–4000 shock waves at the range of 8–20 kV, Elmed). In the light of the literature, urine TNF- $\alpha$  seems to not be a useful tool in the evaluation of the ESWL-induced renal injury.

## Interleukins

Interleukins are a broad group of cytokines, multifunctional peptides used by cells for intracellular communication and controlling the environment they operate in. Interleukins participate in the regulation of immune responses and inflammatory reactions. Interleukin-1 (IL-1) and interleukin-6 (IL-6) promote inflammation [25], and their increased serum level is a marker of an inflammatory process. The relationship between the high amount of inflammatory cytokines in urine was found by Rhee et al. [26], who measured the urinary IL-1a, IL-1b, and IL-6 levels and

found a significant elevation in the IL-6 level in the group of 56 patients with symptomatic stone disease. Opposite results showed Rieder et al. [27], but their study was limited by the small number of patients. Goktas et al. [6] evaluated the severity of the inflammatory response to ESWL by measuring the urinary excretion of IL-1a and IL-6. The study involved the entire group of 35 patients. Median IL-1a levels measured before and 24 h after ESWL treatment were not significantly different from the results obtained in the control group; however, after 14 days IL-1a concentration increased, and the difference was statistically significant. These results demonstrate that IL-1a could be used as a useful marker of renal damage in the late phase, but not in the early stage of ESWL treatment. In contrast to IL-1a, a meaningful difference in the IL-6 level before and after the ESWL procedure was observed, demonstrating a strong inflammatory response to ESWL in this period. After 14 days, IL-6 concentration decreased rapidly. By contrast, Dundar [24] suggested no inflammatory response to ESWL, detecting no IL-6 in urine samples after the procedure. However, his measurements were done only 2 hours after treatment.

Clark et al. [23] measured the IL-6 level in pig kidney tissue and found its amount high, 4 hours after ESWL in the renal medulla within the focal zone of the lithotripter. They also found a significant positive correlation between the IL-6 level and the number of shockwaves. However, no positive detach was found in urine.

Li et al. [2] aimed to investigate the potential mechanism of renal inflammatory damage induced by shock wave on 48 rats with solitary kidney. The level of urine IL-6 and IL-18 were increased significantly after procedure. At 105 days post-shock wave, the expression of IL-18 was increased significantly, as well as urine  $\beta$ 2-microglobulin.

Opposite results were demonstrated by Jobs et al. [28]. Their aim was to assess the safety of ESWL using the albumin to creatinine ratio, serum cystatin C levels and concentration of IL-18 and neutrophil gelatinase-associated lipocalin (NGAL). In 30 children aged from 7 months to 17 years, treated with lithotripsy, serum NGAL and cystatin C concentrations, albuminuria and urinary IL-18 and NGAL levels were measured: 48 hours before, 2–4 hours after and 48 hours after the procedure. IL-18 and NGAL levels pre- and post- ESWL did not show any statistically significant differences.

## Other urine markers

Urinary enzyme levels have been evaluated in various clinical settings including AKI caused

by chemotherapy, antibiotics, heavy metals, analgesics or graft rejection. N-acetyl- $\beta$ -D-glucosaminidase (NAG) is a lysosomal enzyme highly abundant in the renal proximal tubular cells. It is also present in the serum, but its molecular weight does not permit glomerular filtration; that is why an increased urinary NAG activity is one of the most sensible markers of renal tubular injury [29]. Ceylan et al. [30] aimed to demonstrate renal parenchymal injury depending on two sessions of ESWL (1500–2500 shock waves, 70–90 kW/h, electrohydraulic lithotripter) on 20 ESWL naïve patients, who had ureteropelvic junction (UPJ) stone in one kidney, and whose stone load was under 2 cm. Their 24-h urine samples were collected just before and after the ESWL treatment to evaluate the urine excretion of citrate, uric acid, retinol-binding protein (RBP), NAG, creatinine, sodium, potassium, phosphorus, calcium, and chlorine metabolites. They found that RBP, NAG, Cr, and Na may be useful urine markers that can indicate renal parenchymal injury within the ESWL session number. The other finding was that all of these substances, except NAG and creatinine, may be used as excellent indicators of the kidney recovery process in order to give information about the recovery period of the kidney.

Carvalho et al. [31] aimed to show the effect of repeated ESWL on urinary biochemical markers on the animal model study. Twenty rats were assigned for ESWL to one of the two groups: single ESW and double ESW in a 14-day interval. Within the 24-hour period before and after the application of shock waves, the animals were placed in metabolic cages for a 24-hour urine collection. The pH, sodium, potassium, creatinine, chlorides, magnesium, calcium, phosphorus, oxalates, alkaline phosphatase and citrates were determined. A significant increase in urinary alkaline phosphatase was found in both studied groups, suggesting a proximal tubule lesion. Rodriguez Vela et al. [32] gave into considering another study of the renal lesions produced during ESWL. The following variation (pre- and post-ESWL) of various biochemical parameters of the 24-hour urine was analyzed in 50 patients. A significant increase in urinary NAG, urinary NAG/urinary creatinine quotient, serum creatinine, proteinuria, and potassium was detected during the 24 hours following ESWL. A significant decrease in urinary osmolality, creatinine, and uric acid clearance was also exposed. Authors observed a positive correlation between these alterations, the number of shocks and the kilovoltage used. Sheng et al. [17] also confirmed the impact of ESWL on renal tubular damage by measuring the urine NAG,  $\gamma$ -glutamyltransferase ( $\gamma$ -GT) and

creatinine in 60 patients. Every patient received 2,000 shock waves during 30–45 min in an MZ-V lithotripter, 16 kV.  $\gamma$ -GT and NAG activities reached the highest levels at 24 h in the control group and decreased to baseline by 72 h and 1 week. Since NAG and  $\gamma$ -GT are in particular markers of the proximal tubule damage, an increase in these indices is representative of shock-induced impairment of the cell membrane integrity. Other studies concerned 28 kDa calbindin-D, a vitamin D-dependent calcium-binding protein, found mainly in the distal renal tubules [33]. 28 kDa calbindin-D was measured in the serum and urine samples just before and after 2 or 24 hours after ESWL in 83 consecutive patients. The serum 28 kDa calbindin-D level was below the degree of detection whereas urinary 28 kDa calbindin-D could be measured in every sample, with a significant increase at 2 hours after ESWL, decreasing to the baseline level within 24 hours. These results prove calbindin-D to be excreted from damaged distal renal tubule cells into the serum and urine during ESWL and to be an accurate marker for renal damage caused by ESWL.

A similar examination was performed by Takashi et al. [34]. To make clear whether proximal or distal renal tubules are affected by ESWL treatment, urinary 28-kD calbindin-D and NAG was measured before, 2 and 24 hours after the procedure, in 17 renal urolithiasis patients. Levels of urinary calbindin-D, as well as NAG, were elevated considerably immediately and 2 hours after ESWL, decreasing after 24 hours. These results exhibit that ESWL damages both in proximal and distal renal tubules.

## DISCUSSION

Despite broad use of ESWL in patients and its consideration as a safe course of treatment for urinary stones, this method of treatment has many side effects on the renal and surrounding tissues, leading to numerous complications [35]. Questions about the safety of this method of treatment have come up after recently published studies, demonstrating an implication between ESWL-induced tissue injury and chronic diseases occurrence, such as diabetes, hypertension or urolithiasis exacerbation [36]. Therefore, a better understanding of the mechanism of ESWL-induced renal injury and conditions in which ESWL may cause such effects is mandatory for new treatment protocols development to protect kidneys during the treatment. The primary effect of shock waves is to cause vascular injury in renal tissue, leading to the blood vessels rupture and pooling of blood in the parenchyma [14]. The renal papilla and medulla are the most sensi-



tive to injury [37]. Additionally, renal vasoconstriction results in hypoxia in particular areas of renal tissue, which become liable to free-radical production as reperfusion occurs. These phenomena are observed simultaneously in the damaged kidneys after ESWL [4]. ESWL-induced injury leads to urinary excretion of low molecular weight proteins, such as  $\beta$ 2-microglobulin in two molecular pathways: through tubular cell damage resulting in oxidative stress that diminishes reabsorption capacity, affecting increased biomarkers excretion [38]; and through temporary attenuation in glomerular filtration barrier. However, findings in this area are limited and the role of glomerular impair in reperfusion injury-induced proteinuria is not completely proved.

Oxygen-free radicals are to be an indispensable element in ESWL-induced renal injury through an indirect mechanism. Free-radical formation and following organ impairment may be assigned to shock wave lithotripsy in the same manner as in the ischemia-reperfusion model [17, 39]. Hence, administration of antioxidants around procedure has a protective effect on renal function [17, 19, 40, 41], which was proved, measuring differences in some urine biomarkers pre- and post-ESWL treatment. Stones located in soft tissues are crushed by the physical effects of shockwaves, which exert adverse effects on the surrounding tissues. As a consequence, an inflammatory response to ESWL appears with possible kidney damage at an early stage after procedure and induction of chronic fibrosis, resulting in long-term renal insufficiency [2, 42]. Post-ESWL inflammatory response can be measured using individual biochemical markers. However, this is a complicated metabolic process that may take a long time. Consequently, the use of a single marker is not sufficient to evaluate the entire response and measurements over short periods.

Moreover, the specificity and sensitivity of each marker may be unique and might not demonstrate the complete response adequately. Therefore, more studies involving urinary excretion of a broad panel of markers, like pro-inflammatory cytokines, over an extended period are needed. Most of the pub-

lications, who consider adverse effects of ESWL treatment, evaluate complications with the use of imaging examinations and clinical symptoms, such as pain, fever, urinary retention, infection, renal hematoma, urine abnormalities (proteinuria, hematuria) or skin changes in the area of shock-wave pass. A lot of crucial information are obtained given by radiological examination – ultrasound and scintigraphy. Contrary, only a few works discuss the problem of postoperative assessment of renal function at the molecular level.

New biomarkers of kidney function were tested in estimating the episodes of AKI, such as serum and urine NGAL [43], kidney injury molecule 1 (KIM-1) [44] and specific cytokines, like urine IL-18 [45]. They have a beneficial role in early detection of AKI, as well as in observation of a transition of this acute illness into chronic kidney disease. While an estimation of ESWL effectiveness regarding stones location, number, chemical composition, and size remains relatively easy effortless, it is much more challenging to perform studies evaluating the safety of this method of treatment. It is due to small amount of specific and sensitive markers of kidney injury, which appears right after the harmful effect and allows to predict and monitor potential long-term side effects. It is of great importance to find the universal and accurate marker of renal injury, so the effortless and reliable estimation of the actual organ damage could be possible, in each of the popular urolithiasis methods of treatment.

## CONCLUSIONS

In recent years, several studies demonstrated evaluation of extracorporeal shock wave lithotripsy – induced renal injury based on urinary biomarkers levels. Different markers have been evaluated in the urine before and after the procedure, but their number, as well as population sample size, are still limited. Further investigations with larger population sample sizes can be useful in this regard.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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