Review

Current Status of Protein Biomarkers in Urolithiasis – a Review of the Recent Literature

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Current Status of Protein Biomarkers in Urolithiasis—A Review of the Recent Literature

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Abstract: Urolithiasis is an increasingly common clinical problem worldwide. The formation of stones is a combination of metabolic status, environmental factors, family history and many other aspects. It's important to find new ways to quickly detect and assess urolithiasis because it causes sudden, severe pain and often comes back. One way to do this is by exploring new biomarkers. Current advances in proteomic studies provide a great opportunity for breakthroughs in this field. The study focuses on protein biomarkers and their connection to kidney damage and inflammation during urolithiasis.

Keywords: urolthiasis; children; protein biomarkers

1. Introduction

Urolithiasis (i.e., kidney stone disease) remains a global public health problem with increasing prevalence [1,2]. This disease is spreading in developed countries and affecting both adults and children, becoming a problem for society.

Women have a higher risk of early onset lithiasis, with a tendency to have recurrences. Late stone formation occurs more frequently in those with a BMI >30 [3].

Urolithiasis is a disease in which deposits are formed in different parts of the urinary tract: the pyelocalyceal system, the ureter, or even the bladder. The pathogenesis of the disease is complex and multifactorial. Imbalance between promoters (like calcium, oxalic acid, uric acid, cystine, cell fragments) and inhibitors (like magnesium, citrates, zinc, glycosaminoglycans, uromodulin, osteopontin, osteocalcin, bicunin) concentrations, along with specific physicochemical conditions, increase the risk of lithiasis. The formation of stones is also influenced by antibiotic therapy and the reduction of intestinal colonisation with the bacterium Oxalobacter formigenes. Indeed, this organism uses oxalic acid as an energy source, reducing its absorption in the gastrointestinal tract [4]. Also, a sedentary lifestyle, high animal - based protein diet with a high intake of salt and low of water and presence of obesity can increase the risk of stone crystallisation. The chance of urolithiasis is 2-16 times higher in patients with a family history of stone disease [5]. We categorize urolithiasis into different types based on deposit composition and metabolic abnormalities. The most common type is calcium oxalate (CaOx) representing 70-80% of cases. Uric acid - caused by excessive excretion of uric acid as a metabolite of purine metabolism. Cystine is associated with cystinuria. Magnesium ammonium phosphate (struvite), on the other hand, accompany urinary tract infection. Other less common types include calcium phosphate, xanthine and 2,8-dihydroxyadenine [6]. On suspicion of urolithiasis, a comprehensive metabolic diagnosis is required to identify risk factors. The most common include hypercalciuria, hypocitraturia, hyperuricosuria and hyperoxaluria [5,7]. Most cases of deposits in the urinary tract are diagnosed during renal colic episode or incidentally during abdominal ultrasound performed because of non-specific symptoms, such as abdominal pain. Ultrasonography is the most important imaging study for diagnosing urolithiasis. It is widely available, sensitive, and does not involve radiation doses. In case of diagnostic problems, such as difficult localisation or size of the deposit, spiral computed tomography without contrast should be performed [8,9]. Metabolic assessment is important after stone expulsion and should be repeated multiple times. It includes blood tests, urine samples, and a 24-hour urine collection to test for

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crystallisation promoters and inhibitors. To get an accurate assessment, you need to have a healthy diet, lifestyle, and avoid urinary tract infections. Analysis of the composition of the expelled stone is also an extremely important aspect. We currently have three methods: infrared spectroscopy, polarisation microscopy and X-ray diffraction [8,10]. Based on the collected results, mainly from the metabolic assessment, targeted prophylaxis and conservative treatment can be implemented. Up to 80% of the deposits are expelled spontaneously, mainly those with a small diameter of up to 5mm. The treatment of urolithiasis can be divided into conservative and invasive. Medical expulsion therapy (MET) relies on analgesics (NSAIDs) and agents that facilitate expulsion: alpha-blockers (doxazosin, tamsulosin, alfuzosin), calcium channel blockers (nifedipine), corticosteroids. When conservative therapy is unsuccessful, procedures that are as minimally invasive as possible should be implemented. These include extracorporeal shock wave lithotripsy (ESWL), lithotripsy during ureteroscopy (URSL), percutaneous nephrolithotripsy (PCNL) and retrograde intrarenal surgery (RIRS). Because of the efficacy and prevalence of the above methods, classical surgical treatment is a rare choice [8,9].

Even though there are traditional diagnostic methods available, researchers are searching for new biomarkers to understand the risk of kidney stone formation and possible complications like AKI, CKD or urosepsis.

The goal of this study is to gather evidence from literature about protein biomarkers in urolithiasis patients and present it as a systematic review.

2. Materials and Methods

Search Protocol

This review follows the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [11]. We have searched PubMed and Web of Science databases. All records between January 2016 and September 2023 were checked with the strategy using MeSH (Medical Subject Heading) terms and keywords for the description of population and intervention with the help of the Boolean operators ”or”, “and”. We use the combination of: “urolithiasis” OR “kidney stones” AND “protein markers” AND “ blood” OR “urine”. The inclusion criteria were: 1/ human research 2/ clinical diagnosis of urolithiasis, 3/ protein marker obtained in blood or urine, with the use of ELISA method 4/ cohort and case-control investigations, 5/ articles published in English in peer-reviewed journal. The exclusion criteria were: 1/ animal research, 2/ no specific diagnosis of urolithiasis, 3/ other markers like: DNA/RNA molecules, bacterial, metabolome 4/ presence of factors like severe diseases or treatment that might influence on the results of obtained results, 5/ no control group or it was not precisely chosen, 6/ studies not in English, 7/ full text not available.

213 records in the period of last 7 years (2016-2023) were found but only 25 were taken into further review. The excluded studies were duplications or did not meet inclusion criteria, for instance: there was no obvious diagnosis of urolithiasis, research was performed on animals, “in vitro” studies, markers were not proteins or obtained in material other than blood or urine. There were also 10 case- and 9 review studies excluded, 3 were not available as a full-size text and 2 was not in English (Figure 1).

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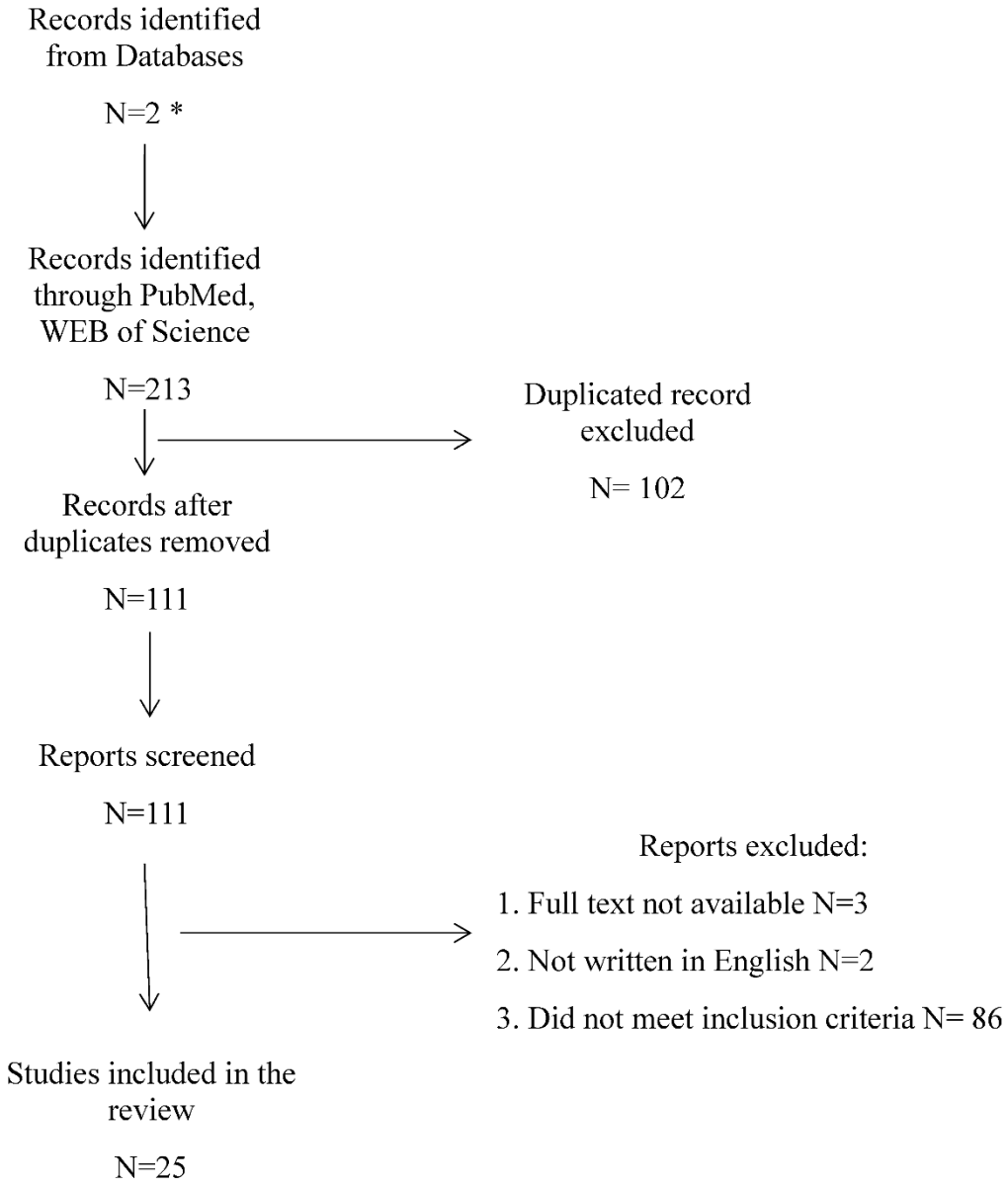

Figure 1. Studies of the last 7 years (2016-2023) included in this review—PRISMA 2020 flow diagram.* Web of Science, PubMed/Medline.

[https://pubmed.ncbi.nlm.nih.gov/?term=%28urolithiasis%29+AND+%28protein+markers%29&filter=years.2016-2023

https://pubmed.ncbi.nlm.nih.gov/?term=kidney+stones+AND+%28protein+markers%29&filter=years.2016-2023

https://www-1webofscience-1com-1bcnm7wwo0394.han.umb.edu.pl/wos/woscc/summary/663d75be-acc2-4ee8-b12c-07d315b2de09-a7460548/relevance/1]

3. Results

The review of protein biomarkers in urolithiasis patients detected a wide range of molecules in their urine and blood.

Detailed results of studies from the years 2016-2023 are organized in the Table 1.

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Table 1. Analysis of the research from the last seven years on new protein kidney biomarkers in urolithiasis.

Year of publication	Author and title	Study design	Results
2016	**Kandur Y. et al.**[12] Evaluation of urinary KIM-1, NGAL, and IL-18 levels in determining early renal injury in pediatric cases with hypercalciuria and/or renal calculi.	40 children with nephrolithiasis (NL), 23 patients with hypercalciuria (HC) and 20 healthy controls were included to measure Urinary concentrations of **NGAL, KIM-1** and **IL-18.**	In regard to the urinary **NGAL/cr** ratio ($p < 0.001$), a statistically significant difference was found between the patient groups (NL and HC) and the control group. No significant differences between patient groups and healthy children in terms of urinary **IL-18/cr** and **KIM-1/cr** ratio.
2016	**Amini E. et al**. [13] The role of serum and urinary carbohydrate antigen 19-9 in predicting renal injury associated with ureteral stone.	This study was designed to evaluate the role of urinary and serum **carbohydrate antigen 19-9** (**uCA19-9 and sCA19-9**) as a biomarker in the assessment of patients with ureteral stone. A total of 38 patients with ureteral stone and hydronephrosis who underwent transurethral lithotripsy (TUL) (Group A) and 24 age-matched healthy peers (Group B) were evaluated in this study. Urinary and serum **CA19-9** concentrations were measured in group A before TUL and 4 and then 8 weeks following the operation; **sCA-19-9** and **uCA19-9** concentrations were also measured in group B participants.	Median concentration of **uCA19-9** and **sCA19-9** was 34.0 and 15.0 kU/L in group A patients and 16.1 and 5.3 kU/L in group B, respectively ($p < 0.001$). Medians of **CA19-9** concentration in urine and serum reduced to 12.5 and 4.5 kU/L 8 weeks after TUL ($p < 0.001$). Following successful TUL and hydronephrosis resolution, a significant decline was detected in serum and urinary **CA19-9**. The duration of ureteral obstruction was associated with serum and urinary **CA19-9** concentrations, suggesting the potential role of this marker in predicting renal damage associated with urinary tract obstruction and determining the timing of interventions.

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2017	**Venkatesan, S et al.** [14] Association between vitamin D, parathyroid hormone and inflammatory markers in urolithiasis patients	It was a cross-sectional study. About 41 confirmed renal calculi patients and 41 age and sex matched controls were recruited. Patients with malignancies, hyperparathyroidism, chronic disease, and patients taking vitamin D supplementations were excluded. Serum levels of 25(OH) vitamin D, **i-PTH**, **hs-CRP**, **IL-6**, calcium and phosphorous, 24 hours urine levels of calcium and phosphorus were estimated.	There was a significant difference in the serum levels of 25(OH) vitamin D (12.26 vs 19.61 ng/mL), **i-PTH** (75.5 vs. 33.5 pg/mL), **hsCRP** (5117.05 vs. 1721.87 ng/mL), **IL-6** (13.49 vs. 1.47 pg/mL) calcium (11.5 vs. 9.4 mg/dL) and urinary calcium (370.5 vs. 342 mg/d) and phosphorous levels (1172 vs. 1432 mg/d) between the cases and the control. There was negative correlation between the levels of **i-PTH** and vitamin D (r = -0.765) and positive correlation between **i-PTH** and **hsCRP, IL-6**, Serum calcium and urine calcium (r = 0.353, 0.340, 0.522, 0.501 respectively)
2018	**Taşdemir M. et al**. [15] Urinary biomarkers in the early detection and follow-up of tubular injury in childhood urolithiasis.	Seventy children [36 girls, mean age: 7.3 ± 5.0 years (0.5-18.2)] with urolithiasis/microlithiasis were included. Anthropometric data, urinary symptoms, family history and diagnostic studies were recorded. Urine samples were analysed for metabolic risk factors (urinary calcium, uric acid, oxalate, citrate, cystine, magnesium, and creatinine excretion), and the **urinary KIM-1 (uKIM-1), NAG (uNAG)**, and **NGAL (uNGAL)** levels were	**UKIM-1/Cr**, **uNAG/Cr** and **uNGAL/Cr** ratios were not significantly different between patients and controls. Furthermore, no significant changes in their excretion were shown during follow-up. Only **uNAG/Cr** and **uNGAL/Cr** ratios were significantly increased in patients with hydronephrosis (n = 6, p = 0.031 and 0.023, respectively).

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		measured 3 times in 6-months intervals.	
2018	**Icer M. A. et al.**[16] Can urine osteopontin levels, which may be correlated with nutrition intake and body composition, be used as a new biomarker in the diagnosis of nephrolithiasis?	A total of 88 subjects participated in the study, including 44 affected patients with kidney stones, aged between 20 and 65 years and 44 healthy peers. Several serum parameters and urinary osteopontin (**uOPN**) levels were examined. In addition, anthropometric measurements were assessed, body mass index was calculated, 24-hour diet and water intake were registered, and participants completed an eating frequency questionnaire to assess their dietary status.	Among patients, **uOPN** levels (ng/ml) were significantly lower than in controls ($p<0.05$). A positive correlation ($p<0.05$) was also observed between **uOPN** levels in male patients and dietary intake of energy, carbohydrates, polyunsaturated fatty acids (PUFAs) and n-6 fatty acids. In contrast, in female patients, there was a negative correlation between uOPN level (ng/ml) and serum creatinine concentration (mg/dl) ($p<0.05$). The **uOPN** level was positively correlated with body weight, waist circumference, hip circumference and muscle mass in healthy men ($p<0.05$).
2018	**Jung K. et al.** [17] Assessment of cross-correlations between selected macromolecules in urine of children with idiopathic hypercalciuria.	In the study, uromodulin, osteopontin, calgranulin and bicunin were measured in a fresh morning urine sample in a group of children diagnosed with nephrolithiasis in the course of idiopathic hypercalciuria. The study included 57 patients between the ages of 12 and 18 years; 33 healthy children were the control group. The study included 57 patients aged 12 months to	Significantly reduced excretion of osteopontin and significantly increased excretion of bicunin were found in the urine of people with urinary tract stones. A significant positive correlation between uromodulin and bicunin was found in both groups. Calgranulin was excreted in higher amounts but without statistical significance.

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		18 years; the control group consisted of 33 healthy peers.	
2019	**Chirackal R.S. et al.** [18] Urinary extracellular vesicle-associated **MCP-1** and **NGAL** derived from specific nephron segments differ between calcium oxalate stone formers and controls.	The study was designed to test the hypothesis that extracellular vesicles (EV) containing potential biomarkers for inflammation (monocyte chemoattractant protein, **MCP-1**), kidney epithelium injury (neutrophil gelatinase-associated lipocalin, **NGAL**) and abnormal calcification (osteopontin, **OPN**) might reflect intrarenal stone formation process. 64 calcium formers (CF) and 40 age- and sex- matched healthy peers were included. Urolithiasis participants were divided into 2 subgroups: with low (<5%) and high papillary surface area that reflect the respective amount of Randall plaques (precursors of crystallisation). EV carrying **MCP-1**, **NGAL** and **OPN** were assessed in the urine.	The number of EV carrying **MCP-1** and **NGAL** were significantly lower in CF participants compared with healthy group but it did not differ between patients with low and high papillary surface area. The number of EV with **OPN** did not differ between any groups.
2019	**Shah T.T. et al.** [19] Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: results from the Multi-centre cohort	The research included 4170 patients with acute ureteral colic due to urolithiais. Presence of a single stone was showed in a CT scan. White blood cell (WBC) counts and other inflammatory indicators were studied, stone size and position were assessed as	The composite analysis did not detect that any of the measured parameters (WBC, neutrophil count, C-reactive protein (CRP)) did not predict SSP, with adjusted odds ratios (OR) of 0.97 (95% confidence interval [CI] 0.91-1.04, P = 0.38), 1.06 (95% CI 0.99-1.13, P = 0.1) and 1.00

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	study evaluating the role of Inflammatory Markers In patients presenting with acute ureteric Colic (MIMIC) study	well as use of medical excretory therapy (MET), with spontaneous stone passage (SSP). The main goal of the study was to measure spontaneous stone passage (SSP), with no need of intervention to facilitate stone passage (SP).	(95% CI 0.99-1.00, P = 0.17), respectively.
2019	**Okada A. et al.** [20] Identification of new urinary risk markers for urinary stones using a logistic model and multinomial logit model	The study included three groups of men (between 20 and 79 years of age): 48 healthy individuals without urolithiasis or history of renal colic, 22 individuals with calcium oxalate stones after one episode, 40 individuals also with calcium oxalate stones but with recurrent episodes of colic. The concentrations of 18 urinary proteins were measured in the urine samples using multiplex analysis on the MagPix (R) system.	The authors based on logistic regression models classifying control and first-time groups detected that interleukin **(IL)-1a** and **IL-4** were independent factors, with significantly high areas under the receiver operating characteristic curve (1.00 and 0.87, respectively, $P < 0.01$ for both). Multivariate models with **IL-4** and **granulocyte-macrophage colony-stimulating factor (GM-CSF)** showed higher areas under the receiver operating characteristic curve (0.93) compared with the univariate model with **IL-4**. In the classification of control, first-time and relapse groups, accuracy was highest for the multinomial logit model with **IL-4, GM-CSF, IL-1b, IL-10** and urinary magnesium (concordance rate 82.6%).
2019	**Kusumi K. et al.** [21] Adolescents with urinary stones have elevated urine	The main objective of this study was to compare urinary inflammatory markers in stone forming children versus healthy	Among others **MIP1β** and **IL13** were significantly increased in affected participants. Interleukin **17A**

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	levels of inflammatory mediators.	matched controls. The urine samples were collected from 12 adolescents with urolithiasis and 15 controls. The levels of 30 urinary cytokines were assessed with the use of a Mesoscale 3-0-Plex Human Cytokine panel and normalized to urine creatinine.	was elevated in the urine of controls.
2020	**Wang X. et al.** [22] Urinary monocyte chemoattractant protein 1 associated with calcium oxalate crystallization in patients with primary hyperoxaluria.	30 patients with primary hyperoxaluria and CaOx crystals and 47 healthy peers were included. In the urine samples of study participants a panel of biomarkers reflecting different nephron sites and potential mechanism of injury was assessed: **clusterin**, **neutrophil gelatinase-associated lipocalin (NGAL)**, **8-isoprostane (8-IP)**, **Monocyte Chemoattractant Protein -1 (MCP-1)**, **Liver-fatty acid binding protein (L-FABP)**, **heart-type fatty acid binding protein (H-FABP)** and **osteopontin (OPN).**	After adjustment for age-, sex-, and eGFR, a higher urinary **MCP-1** concentration and **MCP-1/creatinine** ratio was positively correlated with CaOx supersaturation. Higher **urinary NGAL** and **NGAL/creatinine** as well as **urinary OPN** and **OPN/creatinine,** were related to higher eGFR. IT seems that higher **urinary MCP-1** might reflect ongoing collecting tubule crystallisation, while greater **urinary NGAL** and **OPN** may reflect preservation of kidney mass and function.
2020	**Hughes S.F. et al.** [23] The role of specific biomarkers, as predictors of post-operative complications following flexible ureterorenoscopy	37 patients (24 men, 13 women) participated in the research, after FURS because of nephrolithiasis. Venous blood samples were taken from all patients in time intervals: before intervention and then after 30 minutes, 2 hours and 4 hours post	In the study, postoperative complications were observed in 4 patients (3 - URI with urinary retention, 1 - urosepsis). **NGAL** concentrations increased significantly after FURS ($p = 0.034$). In contrast, no significant differences were

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	(FURS), for the treatment of kidney stones: a single-centre observational clinical pilot-study in 37 patients.	surgery. Changes in the quantities of specified molecules were assessed: **NGAL, Cystatin-C, MPO, PCT** with the use of ELISA method.	observed in **cystatin C, MPO and PCT** concentrations . It should be noted that the study involved a small group of subjects and a sampling interval.
2020	**Castiglione V. et al.** [24] Evaluation of inactive Matrix-Gla-Protein (MGP) as a biomarker for incident and recurrent kidney stones.	The study assessed serum dpucMGP levels in subjects with symptomatic urolithiasis and individuals without stones at the initial visit. Symptomatic recurrence of stones was assessed in stone-forming patients over a 5-year period. The association of **dpucMGP** with incident or recurrent kidney stones was evaluated with and without adjustment for clinical, blood and urine characteristics.	There was no statistically significant difference in levels of serum dpucMGP between 498 stone-formers and 395 non-stone-formers (510 vs 501 pmol/L; $p = 0.66$). The higher the MGP level, the lower the risk of stone formation (OR = 0.674, 95% CI 0.522-0.870). Recurrence of renal colic occurred in 21% (79) of subjects (375) observed for 5 years. When comparing patients with recurrent and non-recurrent stones, there was no difference in serum dpucMGP levels (482 vs 502 pmol/l; $p = 0.26$). There was a correlation between serum dpucMGP and cystatin C levels in subjects without lithiasis and in subjects with incident and recurrent lithiasis ($r > 0.3$, $p < 0.0001$).
2020	**Hughes S.F. et al.**[25] Shock wave lithotripsy, for the treatment of kidney stones, results in changes to routine	Patients with unilateral kidney stones after SWL (n=12) were collected for the study. Venous blood samples were collected from patients (8 men and 4 women) aged between 31	After SWL surgery, a significant increase in NGAL concentration was observed at a maximum of 30 minutes after surgery ($p = 0.033$). IL-6 showed a significant increase from the preoperative period

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	blood tests and novel biomarkers: a prospective clinical pilot-study.	and 72 years (median 43 years) at different time intervals (preoperative-baseline, 30, 120 and 240 minutes postoperatively). A Sysmex XE-5000 and Beckman Coulter AU5800 and AU680 analyser were used. Concentrations of **NGAL, IL-18, IL-6, TNF-α, IL-10** and **IL-8** were determined by ELISA.	to 4 hours after surgery ($p < 0.001$), while TNF-α increased significantly, peaking at 30 min after SWL ($p = 0.05$). IL-18 increased, but not statistically significantly ($p = 0.116$). IL-10 and IL-8 concentrations did not change significantly after SWL ($p > 0.05$).
2020	**Cilesiz N.C. et al.**[26] Can serum procalcitonin levels be useful in predicting spontaneous ureteral stone passage? [21]	The study was carried out in patients with a single distal ureteral stone between 5 and 10 mm in diameter and without indications for interventional treatment and healthy subjects. Blood and urine samples were collected and analysed from all participants. Patients were followed up every 2 weeks for 1 month. Patients who did not pass stones at follow-up were considered to have complete stone passage [SP(+)] and failure [SP(-)] was defined if the patient did not pass stones by the end of the study. Levels of WBC (white blood cells), c-reactive protein (CRP), SED (sedimentation), MPV (mean platelet volume), NLR (neutrophil-to-lymphocyte ratio) and serum procalcitonin (PCT) were analysed. All patients received diclofenac sodium	The SP(+) and SP(-) groups were compared. PCT and leucocyturia levels were significantly higher in the SP(-) group than in the SP(+) group ($p = 0.000$; $p = 0.004$). Based on ROC curve analysis, 160 pg/ml (sensitivity 86.7%, specificity 70.8%, $p < 0.001$; AUC: 0.788 95% CI (0.658-0.917) was identified as the optimal cut-off value for PCT. In logistic regression analysis, significant efficacy was observed for PCT and leukocyturia in univariate analysis for spontaneous transition. In multivariate analysis, significant independent PCT activity was observed ($p < 0.05$).

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		75 mg/day, tamsulosin 0.4 mg/day and at least 3 l of fluids daily. Patients were followed up for one month using a variety of imaging techniques: plain films of the kidney, ureter, bladder (KUB), ultrasonography (USG) and unenhanced abdominal CT during MET treatment.	
2020	**Kovacevic L. et al**.[27] Cystatin C, Neutrophil Gelatinase-associated Lipocalin, and Lysozyme C: Urinary Biomarkers for Detection of Early Kidney Dysfunction in Children With Urolithiasis.	This was a prospective, controlled, pilot study where children with urolithiasis (RS) and a control group (HC) were assessed. Quantitative proteomic evaluation was the screening test for the RS and HC group liquid chromatography-mass spectrometry was used.	Three promising proteins, cystatin C (CYTC), neutrophil gelatinase-associated lipocalin (NGAL) and lysozyme C, were detected. These were significantly over-represented in the RS group compared with HC. Urinary CYTC and NGAL were significantly elevated and urinary lysozyme C levels were almost significantly elevated in the RS group (N = 24) compared with the control group (N = 13). In both hypercalciuria (N = 14) and hypocitraturia (N = 10), subgroup analysis showed significantly higher urinary CYTC levels compared to HC ($P < 0.05$).
2021	**Taiguo Q. et al**.[28] The predictive and diagnostic ability of IL-6 for postoperative urosepsis in patients	The aim of this study was assessment of the predictive and diagnostic role of **IL-6** for postoperative urosepsis in patients undergoing percutaneous nephrolithotomy (PCNL). 90	Compared with CON group, EXP1 group showed: higher serum levels of **IL-6** ($p < 0.001$) and neutrophil ($p < 0.001$) at postoperative hour two; higher serum levels **of IL-6** ($p < 0.001$),

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	undergoing percutaneous nephrolithotomy.	patients undergoing PCNL between April 2019 and September 2019 were studied. 16 patients progressed to urosepsis (EXP1 group, n = 16) and 74 patients did not (CON group, n = 74); 25 patients who progressed to postoperative urosepsis without receiving the test of **IL-6** between March 2018 and March 2019 were also enrolled (EXP2 group, n = 25); demographic and perioperative data were compared between all groups.	procalcitonin (**PCT**) ($p < 0.05$), white blood cell (WBC) ($p < 0.05$), and neutrophil ($p < 0.001$) on postoperative day one; higher serum levels of **PCT** ($p < 0.05$) and WBC ($p < 0.05$) on postoperative day three. ROC curves showed **IL-6** (AUC = 1.000) at postoperative hour two and **PCT** (AUC = 0.954) on postoperative day three. Compared with EXP2 group, EXP1 group showed shorter time to intervene ($p < 0.001$), a shorter postoperative hospital stay ($p < 0.001$), and a lower incidence rate of severe urosepsis ($p < 0.05$). The main conclusion was the possible predictive values of **IL6** as a early diagnostic marker for postoperative urosepsis in patients after PCNL at postoperative hour two and postoperative day one.
2021	**Ramasamy V. et al.** [29] Role of inflammatory markers and their trends in predicting the outcome of medical expulsive therapy for distal ureteric calculus.	The study assessed C-reactive protein (CRP), white blood cell (WBC) count and neutrophil percentage (NP) in relation to predicting the outcome of medical excretory therapy (MET). Nineteen hundred and two patients with distal ureteral stones >5 mm in size were included in the study. CRP, WBC and NP were	On days 1, 7, 14 stone size and mean CRP, WBC and NP values in patients who had not undergone stones were significantly higher compared to those who had undergone stones. ROC analysis showed an area under the curve of 0.798 (p=0.001) for CRP, and the cut-off value was 1.35 mg/dl. Multivariate analysis showed

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		measured on days: 1, 7, 14 MET and then analysed.	a significant association of higher CRP levels >1.35 mg/dl and stone size >7 mm with MET failure. A downward trend in CRP was observed in both groups, but values were higher in those who had not undergone stones. Only in those with stones did WBC and NP decrease.
2021	**Milisic E. et al.**[30] Urinary neutrophil gelatinase – associated lipocalin level as a biomarker of acute kidney injury following extracorporeal shock lithotripsy.	The aim of this research was to evaluate the severity of the kidney tissue response to extracorporeal shock wave lithotripsy (ESWL) injury by measuring the **urinary neutrophil gelatinase-associated lipocalin** (**uNGAL**) as an indicator of acute kidney injury (AKI) in the early phase. The study included 62 patients with nephrolithiasis undergoing single ESWL therapy**. UNGAL** level was measured before the procedure and 6 h and 12 h after it.	The median **uNGAL** level increased by 126% 6 h post ESWL ($p<0,001$) with the further growth up to 583,7% after 12 h when compared to pre-treatment level. The median estimated glomerular filtration rate (eGFR) dropped by 15,3% 12 h post intervention but increased by 5 % in the period of 7 days to 3 months after. **uNGAL** level was significantly negatively correlated with eGFR 12 h, 7 days, and 3 months after ESWL. The sensitivity of uNGAL 12 h after ESWL was 60,6% and specifity 5% with a positive predictive value of 74% and negative predictive value of 61,7%. **UNGAL** had the highest predictive value of AKI 12 h after the ESWL treatment.
2021	**Wymer, KM et al.** [31] A Serum C-Reactive Protein and Procalcitonin-	Retrospectively, more than 30 clinical parameters were assessed in patients presenting to the emergency room after upper urinary	There were 98 patients included in the study in which true UTI was identified in 50 (51%). The standard model of serum

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	Based Risk Score to Predict Urinary Infection in Patients with Obstructive Urolithiasis Undergoing Decompression	tract decompression for fear of recurrent urolithiasis and a composite risk score was created. The aim was also to identify predictors of a true urinary tract infection (UTI).	white blood cell count >15 or temperature >38 degrees C had an area under the curve (AUC) of only 0.67 to predict UTI. A multivariable regression-based 4-point risk score (1 point for each of the following: positive urine Gram stain, perinephric fatty bands on CT scan, serum CRP >21.95 and serum procalcitonin >0.36) had an AUC of 0.91 to predict UTI. Individually, these components had AUCs of 0.68, 0.68, 0.80 and 0.77, respectively. The chances of confirming ZUM were 8%, 11%, 68% and 100% for risk scores of 0, 1, 2 and 3 to 4, respectively ($p < 0.001$).
2022	**Xiaohong F. et al.**[32] Metabolic Differences between Unilateral and Bilateral Renal Stones and Their Association with Markers of Kidney Injury.	The study included 10,281 participants. All subjects had a renal ultrasound examination to detect urinary stones; stone-formers were divided into groups with unilateral or bilateral kidney stones based on ultrasound. CKD was defined according to reduced estimated glomerular filtration rate (eGFR, <60 ml/minute/1.73 m2) and/or albuminuria (albumin/creatinine ratio ≥30 mg/gm). Elevated urinary NAG and α1-MG levels were defined as their values	4.9% (507) of participants had unilateral nephrolithiasis and 0.7% (75) had bilateral nephrolithiasis. The percentage of CKD in those without stones, with unilateral and bilateral kidney stones was 11.0%, 19.2% and 29.7%, respectively (p for trend <0.001). Those with bilateral nephrolithiasis had the highest proportion of metabolic components, such as elevated blood pressure and serum glucose levels. Bilateral nephrolithiasis was significantly associated with an increased risk of lower

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		above the 75th percentile of the sample distribution.	eGFR (OR 3.38; 95% CI 1.05-10.90), albuminuria (OR 3. 01; 95% CI 1.76-5.13), CKD (OR 3.18; 95% CI 1.88-5.36), increased urinary NAG/creatinine ratio (OR 1.95; 95% CI 1.21-3.16) and α1-MG/creatinine (OR 2.54; 95% CI 1.56-4.12) compared with no stones.
2022	**Noonin et al.**[33] Systematic analysis of modulating activities of native human urinary Tamm-Horsfall protein on calcium oxalate crystallization, growth, aggregation, crystal-cell adhesion and invasion through extracellular matrix.	This research was planned to clarify the roles of native urinary **Tamm Horsfall Protein** (**THP**) in CaOx monohydrate stones formation. In the study 24 h urine specimens from 10 male patients with idiopathic nephrolithiasis without no well-known metabolic risk factors were collected. At least 50% of stones were composed of CaOx. As controls 10 men and 10 women were assessed without personal or family history of kidney stones. **THP** was purified from the urine by adsorption methods and its effects on stone formation, crystal growth, aggregation, cell adhesion and further invasion through extracellular matrix were examined.	Analyses revealed that **THP** concentration-dependently (0,4-40 μg/ml) reduced CaOx monohydrate crystals size but without effect on their mass during initial crystallization. What is more THP concentration-dependently inhibited CaOx crystals growth, aggregation and further adhesion but it did not prevent crystals invasion through the extracellular matrix. It occurred that **THP** has two large calcium binding domains and three small oxalate binding domains, however in immunofluorescence it appeared that THP binds only calcium ions with high affinity.
2022	**Kovacevic L. et al**.[34]	A prospective, controlled, pilot study in which urine collected from RS (N = 30, 24	67 proteins were decreased in the RS group and 17 were significantly different

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	Proteomic analysis of inhibitory protein profiles in the urine of children with nephrolithiasis: implication for disease prevention.	women, mean age 12.95 ± 4.03 years) was examined and compared with HC using liquid chromatography-mass spectrometry. Criteria for protein selection were: (1) patient/control ratio < 0.5; and (2) p-value ≤ 0.05 for Fisher's exact test. Results were confirmed by ELISA.	compared to the control group. 5 proteins (2 actin, annexin A5, keratin 6B and serpin B4) were completely absent in the urine of patients with lithiasis, but were present in the control group. The 12 other proteins were significantly less frequent in the urine of patients compared to the control group. Modelling of protein-protein interactions of significant proteins identified syndecan-1 as a key node, a protein associated with adhesion pathways. There was a statistically significant difference in urinary osteopontin excretion (5.1 ± 3.22 ng/mg creatinine vs. 14.1 ± 9.5 ng/mg creatinine, p = 0.046) between patients with hypocyturic stones and controls. A positive correlation was also detected between urinary osteopontin levels and urinary citrate excretion (r = 0.417, p = 0.03).
2023	**Memmos D. et al.**[35] The effect of standard percutaneous nephrolithotomy, miniaturized percutaneous nephrolithotomy and retrograde intrarenal surgery	The study was designed to compare the effect of standard percutaneous nephrolithotomy (sPCNL) with miniaturized PCNL (mPCNL) and retrograde intrarenal surgery (RIRS) as a nephrolithiasis treatment and measure urinary ratios: **NGAL/creatinine (uNGAL/cr), KIM-**	No significant differences were shown in **uNGAL/cr** changes between sPGNL and mPGNL and RIRS. Similarly no-between group changes were observed for urinary ratio **KIM-1** and **IL-18** at 2 h and all biomarkers at any time point post operatively. Within particular groups increases from baseline were

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	on biomarkers of renal injury: a randomized clinical trial.	**1/creatinine (uKIM-1/cr)** and **Interleukin-18/creatinine (uIL-18/cr)** at baseline and 2- , 6-, 24- and 48 h postoperatively.	noted only for **uNGAL/cr**, **uKIM-1/cr** and **uIL-18/cr** at 2 h and progressively lower rises from time zero were in all participants for **uKIM-1/cr** and **uIL-18/cr** at 6- , 24- and 48 h post procedure. No significant differences in these indicators were noticed in AKI or other complications.
2023	**Savin Z. et al.** [36] The role of serum and urinary markers in predicting obstructing ureteral stones and reducing unjustified non-contrast computerized tomographic scans in emergency departments.	The study evaluated all patients admitted to the ED between December 2019 and February 2020 with symptoms of renal colic (acute flank pain) and assessed by non-contrast computed tomography (NCCT). Serum white blood cell (WBC), C-reactive protein (CRP) and creatinine (Cr) levels and urine findings were measured. Rates of unreasonable NCCT scans were also calculated.	The NCCT method diagnosed obstructive urolithiasis (OU) in 108 of the 200 patients studied (54%). The median WBC, CRP and Cr values were 9 100/mu L, 4.3 mg/L and 1 mg/dL, respectively. The most accurate thresholds for predicting OU were WBC = 10 000/mu L and Cr = 0.95 mg/dL. Only WBC >= 10 000/mu L (OR = 3.7, 95% CI 1.6-8.3, p = 0.002) and Cr >= 0.95 mg/dL (OR = 5, 95% CI 2.3-11, p < 0.001) were associated with OU. The positive predictive value and specificity for detecting OU in patients with a total WBC count >= 10 000 and Cr >= 0.95 were 83% and 89%, respectively. Significantly more unsubstantiated NCCTs (p = 0.03) were performed in patients with negative serum marker criteria. The negative predictive value of serum

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			criteria for a justified NCCT test was 81%.

Discussion

I. Biomarkers of tubular injury

There is a strong link between urolithiasis and renal tubular injury. On the one hand there are evidences that oxalate and CaOx crystals injure tubular epithelium.

Research using animals found that having CaOx crystals in the kidney can cause tubular cell damage and result in enzymes and debris in urine [37–39].

On the other hand there are studies suggesting that tubular cells injury may stimulate crystallisation. The report of Wiessner et al. revealed that both individual cells and total tubular monolayer injury exposed cells surfaces resulting in increased affinity for crystal adhesion and their further retention in collecting duct [40].

Bigger stones, during passage down the ureter, may obstruct renal outflow, causing acute or chronic kidney injury. In patients with renal colic because of urolithiasis, elevation in creatinine serum concentration is often observed. Nevertheless, this classical kidney function indicator lacks specificity in detection the underlying cause of renal damage and rises late in the process of acute injury. There are various biomarkers proposed to identify and monitor the process of kidney injury. Few of them may apply to urolithiasis as well.

Cystatin – C

Cystatin C has definitely gained importance in the diagnosing AKI and CKD. It is a low molecule (13.3 KD) removed from the bloodstream by the kidneys and its serum levels are a more precise test of kidney function than serum creatinine levels [41]. Most studies proof that cystatin C levels are less dependent on age, gender, ethnicity, diet or muscle mass when compared to creatinine [42]. Cystatin C is a good kidney biomarker in a range of different conditions including diabetic patients, CKD and after kidney transplant [43].

We have analysed more recent researches on cystatin C in urolithiasis however, got conflicting results.

In the study of Hughes at al. who compared pre ureterorenoscopy (URS) and post URS cystatin C levels in urolithiasis patients, no significant difference was found [23]. In 2020, Kovacevic et al. found significant Cystatin C elevation in patients with urolithiasis [27]. We should wait for new studies on larger groups of affected participants to make a reliable conclusion on cystatin C role in urolithiasis.

Neutrophil gelatinase associated lipocalin (NGAL)

Neutrophil gelatinase associated lipocalin NGAL is a 25 kDa protein bound to gelatinase from neutrophils. Its expression was shown in the proximal and distant tubular cells of the kidney [44]. NGAL is upregulated during the inflammatory process because it meditates cellular proliferation and differentiation and has a bacteriostatic effect [45]. It is a marker of great interest in acute tubular damage, as the expression is up-regulated 2-4 hours post nephrotoxic and ischaemic kidney injury [46–48]. Evidence of several studies point that NGAL is useful in detection or monitoring kidney disorders where tubules are affected [49]. In the report of Bolgeri et al. not only patients with obstructive uropathy but also those, who had urolithiasis without blockade in urine flow had higher sNGAL and uNGAL when compared to healthy peers [50]. Some reports give evidence that highest uNGAL levels are observed in patients with urolithiasis combined with urinary tract infection [51], what seems to be understood as this marker rises in inflammatory conditions. In the more recent study of Tasdemir M. et al. who compared, among others, uNGAL levels in patients with nephrolithiasis, it was shown that only those who had hydronephrosis (HN) had also elevation in uNGAL [15]. This observation may bring a very careful hypothesis that in patients with nephrolithiasis without HN markers of tubular injury are not increased because urine flow is not interrupted and tubular injury is not present in contrast with those where dilation of renal pelvis was

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observed together with a rise in uNGAL/cr and uNAG/cr. The biggest limitation of this observation is a tiny number of patients with HD that were included. Other recent findings on NGAL in stone formers are presented in the Table.

Kidney Injury Molecule 1

Kidney Injury Molecule 1 **(**KIM-1) is a transmembrane protein produced by proximal tubules and present in plasma and urine after renal injury [52]. It was detected 12-24 hours post AKI and higher urinary values were observed in patients with ischemic acute tubular necrosis than in other conditions including CKD, diabetic nephropathy or steroid resistant nephrotic syndrome [53]. Several studies assessed KIM-1 in nephrolithiasis giving conflicting results. Some researchers found that uKIM-1 was increased in patients with obstructive nephropathy [54,55]. Similarly, in the study of Fahmy et al. elevation of uKIM-1 was clear in patients who underwent retrograde intrarenal surgery and shockwave lithotripsy because of kidney stones compared to healthy controls [56]. These findings are in contrast to Urbschat et al. who found no difference in uKIM-1 between participants with obstructive nephropathy and controls [57]. Reviewed results of the recent researches on KIM-1 as a marker of urolithiasis are gathered in the Table 1.

Carbohydrate Antigen 19.9

Carbohydrate Antigen 19-9 (CA 19-9) is a 36-kD glycoprotein normally expressed in different tissues starting from gastrointestinal tract, through bronchi or endometrium and ending on prostate. It is best known as a marker of pancreatic and other gastrointestinal cancers [58–60]. Nevertheless, some investigators revealed its higher urinary levels in urinary tract obstruction [61–64]. Suzuki K. and Kajbafzadeh A.M. found that CA 19-9 could be a marker for kidney injury related to urinary obstruction in their research on patients with hydronephrosis [62,63]. Amini et al. conducted a study on people with urolithiasis and HN before and after a procedure called transurethral lithotripsy [13]. The affected group had a significant elevation before the operation, which decreased in the following measurements.

It was also noted that duration of ureteral obstruction was correlated with serum and urinary CA 19-9 levels what may suggest its potential as a predictive molecule for renal damage. CA 19-9 may seem to be sensitive in detection of urine flow blockade, but it is not specific to urinary tract and this significantly limits its use as a marker.

N-acetyl-B-D-glucosaminidase

N-acetyl-B-D-glucosaminidase (NAG) is also one marker of tubular damage however, in vivo studies on urolithiasis, its urinary levels were not elevated in stone formers [10z1]. Nevertheless, in the recent study of Xiaohong F. et al. it occurred that bilateral stone formers were more endangered with CKD and had, among others, increased urine NAG/creatinine ratio (OR 1.95; 95% CI 1.21-3.16) when compared with healthy peers [32].

Myeloperoxidase

Myeloperoxidase (MPO) is involved in the generation of oxygen radicals by neutrophils in the inflammatory conditions [65]. It may rise in the kidney formers however it was not proved in 'in vivo' study. Hughes et al. compared pre- and post- URS MPO values in stone forming participants and no differences were observed between these two groups [23].

II. Markers of inflammation

Interleukines

Interleukins are cytokines involved mainly in inflammatory response. Most studied in the kidney disorders are listed below. Different tissues like macrophages, osteoblasts, and smooth muscles in vessels produce IL-6, which can cause inflammation. It is also a myokine released by muscles in response to excessive contractions and, in this role, has mainly anti-inflammatory effect by inhibition of TNF-alpha [66]. Its importance was shown in many diseases, including different cancer, obesity or severe COVID-19 infection [67]. In sepsis with AKI elevation of IL-6 was also noticed [68,69]. IL-8 is another potent cytokine accelerating inflammation. It induces chemotaxis in target cells (neutrophils and other granulocytes) to make them migrate to the site of infection and then stimulates phagocytosis [67]. As a marker of inflammation urinary IL-8 increase was noticed

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in the course of pyelonephritis [70]. IL-18 can modulate innate and adaptive immunity and dysregulation of its distribution can lead to autoimmune or inflammatory diseases. Primary site of IL-18 production are macrophages in various organs. It was found in the proximal tubular cells of kidney as well. IL-18 seems to be the most involved cytokine in kidney disorders. It was even proposed to be the marker of early AKI as it increases after 6-24 hours post starting factor. In the kidney IL-18 is also associated with excessive urinary protein excretion and can be a marker of the progression of diabetic nephropathy [71,72]. Researches on inflammatory cytokines in urolithiasis are not consistent. In the study of Memmos et al. who compared the effect of standard percutaneous nephrolithotomy (sPCNL) with miniaturized PCNL (mPCNL) and retrograde intrarenal surgery (RIRS) as a nephrolithiasis treatment and measured, among others, uIL-18/cr ratios at baseline and 2-, 6-, 24- and 48 h postoperatively in above patients, no significant differences in its level were shown. Similarly, no-between group changes were observed for urinary IL-18/cr at 2 h and point post operatively. Within particular groups increases for IL-18/cr from baseline were noted at 2 h and progressively lower rises from time zero in all participants at 6- , 24- and 48 h post procedure. No significant difference in this marker level was noticed in AKI or other complications [35]. Similarly in the study of Kandur Y. et al. who assessed urinary IL-18/cr in 40 pediatric patients diagnosed with nephrolithiasis (NL), 23 patients with hypercalciuria (HC) and 20 healthy controls, no significant differences between patient and control groups regarding urinary IL-18/cr were observed [12]. Kusumi K. et al. observed that uIL-13 was significantly increased in lithiasis participants, while IL-17A was elevated in the urine of controls [21]. More results of the most recent researches on urinary interleukins as markers of urolithiasis are in the Table 1. They seem to be conflicting and need further observations on larger and homogenous groups of subjects.

Tumor necrosis factor – α

Tumor necrosis factor – α (TNF- α) is both adipokine and cytokine. As a cytokine, it is used for cell signalling. Macrophages detecting an infection release TNF to alert other immune system cells and start an inflammatory response. TNF-α regulates cell proliferation, differentiation and apoptotic death and may be used in detection of various renal disorders [73]. Hughes et al. observed that TNF-α levels significantly increased in lithiasis patients undergoing SWL, peaking at 30 minutes post-SWL [25].

Monocyte chemoattractant protein 1

Monocyte chemoattractant protein 1 (MCP-1) is an inflammatory chemokine produced by mononuclears and intrinsic cells in the kidney to activate and recruit monocytes [74]. It's up-regulation is the response to various damaging factors. Studies on several kidney disorders demonstrated its potential as a biomarker. Lupus nephritis severity correlated with urinary MCP-1 (uMCP-1) levels in paediatric patients. Similarly MCP-1 was higher in patients with chronic kidney disease (CKD) or autosomal recessive polycystic kidney disease (ARPKD) when compared to healthy controls [75]. In urolithiasis MCP-1 may find its place as well. In the research of Umekawa T. et al. exposure of cultured renal epithelial cells (from a rat renal proximal tubular cell line) to CaOx crystals resulted in higher expression of MCP-1 mRNA and increased level of the protein [76]. A recent study by Wang X. et al. found that primary hyperoxaluria patients who form stones have high levels of MCP-1 in their urine, which may indicate ongoing crystallization. Other studies on MCP-1 are gathered in the Table 1.

C-reactive protein, Procalcitonin

CRP was first identified by Tillet and Francis in 1930. They found that it can make streptococcus pneumoniae C-polysaccharide precipitate. CRP is synthesised in liver as a fast response to inflammation and decreases rapidly after its resolution [77]. Similarly, procalcitonin (PCT) concentration rises as a reaction to a pro-inflammatory stimulus, especially of bacterial origin. Both CRP and PCT are commercially used in blood laboratory tests to detect severe inflammatory diseases. In several studies on urolithiasis it was shown that elevation in CRP and PCT occurs, especially when stones cause obstruction leading to inflammation of the surrounding tissue [78]. The size of the deposit and its location are some of the most important factors influencing the choice of treatment options for ureteral obstruction. According to The European Association of Urology medical

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expulsive therapy (MET) with the use of alpha blocker should be started in patients with renal colic, distal ureteric stones less than 5mm, whose symptoms are controlled [79]. Classical inflammatory markers can also support the decision-making process. Observations of Cilesiz et al. show that stone formers who failed MET had higher values of serum PCT than those who spontaneously passed the stone [26]. Similar observations considering serum CRP were demonstrated earlier by Ockan et al. [80] as well as Aldaqadossi et al. [81] and Jain with colleges [82]. They gave cut-off values of CRP as a predictor of spontaneous stone passage ranging from 0.506 to 21.9 and 4,1 mg/L, respectively. Further research is needed to determine the optimal cut-off level for classical inflammatory indicators in urolithiasis resulting in ureteral obstruction, despite the certainty of their role.

Macrophage Inflammatory Protein 1beta

Macrophage Inflammatory Protein 1beta (MIP1β) is a chemokine starting recruitment of the immune cells responsible for innate and adaptive immune activity. It is involved in the process of inflammatory response during infection [83]. As another inflammatory molecule it may be present in the stone induced kidney injury. In the study of Kusumi K. et al. urinary MIP1β levels were significantly elevated in stone forming adolescents compared to healthy controls [21].

III. Other urinary proteins

Osteopontin

Osteopontin (OPN) is a phosphorylated protein playing an essential role in bone mineralisation [84]. Most probably, it is also involved in the process of inflammation, cell survival and leukocyte recruitment [85]. It has a wide tissue distribution associated with abnormal calcification including an organic matrix of the kidney stones. OPN is produced in the kidney and found in human urine. It probably acts as one of the urolithiasis inhibitors by preventing the formation of CaOx and further adhesion of crystals to renal epithelial cells [86,87]. Nevertheless, some researches on animals give exactly opposite conclusions [88,89]. Some authors observed that OPN may increase risk of CaOx urolithiasis by progression of renal tubular cell damage [88,89].

In the recent study by Icer et al. who compared urinary excretion of OPN between patients with urolithiasis and healthy controls, was shown that affected participants had significantly lower levels of OPN than unaffected peers [16]. They concluded that low urinary OPN levels were correlated with a higher risk of urolithiasis. More studies on OPN are presented in the Table 1.

Nephrocalcin

Nephrocalcin (NC) is one of the most studied molecules taking part in the process of stone formation as an inhibitor of calcium oxalate (CaOx) crystallization. It was first described in 1978 by Nakagawa et al. as an unidentified acidic polypeptide [90]. During the next ten years, several studies showed its inhibitory effect on CaOx crystallization and in 1987 it was isolated from the urine and named nephrocalcin [90–94]. This glycoprotein is in the proximal tubule and thick ascending limb of the Henle's loop [95]. It has many polymeric forms and at least four isoforms: NC-A, NC-B, NC-C and NC-D. The risk of CaOx crystallization and nephrolithiasis depends on the proportion of the isoforms in the urine [96]. Those who are more likely to develop kidney stones excrete greater proportions of NC-C and-D than NC-A and -B [97]. Noyan et al. assessed NC-PreA/cr ratio in the urine of 41 stone forming children and 25 matched healthy controls. It appeared to be significantly higher in affected participants [98].

Bikunin

Another protein that slows CaOx crystallization is bikunin. It is a small chondroitin sulfate proteoglycan joined with a single glycosaminoglycan chain localized in the proximal tubule and the thin descending part of Henle loop [99]. It is a potent inhibitor of CaOx crystal nucleation and aggregation mostly in healthy human, whereas in the presence of urolithiasis it's preventing role is limited [95, 96]. Existing literature on bikunin role gives conflicting results. Higher levels of bikunin were found in children with urolithiasis while in an other study on adults, those affected with kidney stones had 50% lower urinary concentration when compared to healthy peers [102,103].

Calgranulins

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Calgranulins, otherwise S100 proteins, are a family of calcium-binding molecules present in cytosol. Some of them, including S100A8 (calgranulin A) and S100A9 (calgranulin B) have been classified as danger-associated molecular patterns of endogenous origin – alarmins, a group of molecules released as an inflammatory signal mediators after cell death [104]. Normally calgranulin A and B are produced mainly by neutrophils and monocytes as well as dendritic cells while in other cells types the appear after activating signal [105,106]. Momohara et al. found calgranulins inhibit crystallization, aggregation, and adhesion of CaOx monocrystals to endothelium, while Mushtaq et al. found they promoted crystal aggregation [107,108].

In the more recent study of Jung K. et al. in children with urolithiasis no significant differences where observed between study and control group [17].

Matrix Gla protein

Matrix Gla protein (MGP) was identified in the bone matrix and then in other tissues, including vascular [109]. Although it is suspected to have an inhibitory effect on calcification the recent study on stone formers do not confirm this hypothesis [24,109].

Tamm-Horsfall protein

Tamm-Horsfall protein (THP) known as uromodulin is one of the most extensively investigated macromolecules in nephrolithiasis. It is found in urine of all placental invertebrates as a polymer with molecular weight up to several million Da [110,111]. It is involved in the pathogenesis of nephrolithiasis and tubule interstitial nephritis[112]. The studies on the particular role of THP in the stone formation give conflicting answers. Some point that it is an inhibitor of crystallisation [113–116]whereas other point its promoting role [113–116] [117–119]. Perhaps its action depends on the concentration of this protein and other solutes [120]. In a recent study by Nonnan et al., THP was found to inhibit crystallization by binding calcium ions in a concentration-dependent manner [121].

Urinary prothrombin fragment – 1

Urinary prothrombin fragment -1 (UPTF-1) is a part of thrombin. There are both 'in vitro' and 'in vivo' studies indicating its inhibitory effect on crystallization. Epidemiological observations confirm bigger incidence of stones formation in people who had lower UPTF – 1 [122,123].

4. Conclusions

In this review we have tried to explore the most discussed proteins that contribute in the process of stone formation. Recent studies on proteins involved in stone formation are conflicting and inconclusive, making it difficult for clinicians to choose the best treatment.

Above might have few explanations. First, urolithiasis, although in about 70% - 80% related to idiopathic hypercalciuria, is not one homogenous disorder. Kidney stones may be composed of different minerals. What is more, there are various co- factors promoting their formation. The patients studied were different in age, kidney function, urinary tract defects, and other health issues including medications.

What is more, the numbers of participants were usually low, below 100. There is one more important matter that should be taken into consideration while reviewing existing literature and projecting future research. In the findings of Sheng X. et al. who noticed that CaOx monohydrate adhesion to epithelium depended on the presence of protein carboxyl groups was pointed that inhibitory effect of macromolecules was related not only on their urinary levels but also the histochemical features[124]. It is important to examine not only their quantity but also quality, what is usually missed in the recent researches.

Nevertheless, some proteins like NGAL, KIM-1, OPN or THP seem to be more attractive as proposed biomarkers. More reliable conclusions can be drawn in the future by conducting research on larger, similar populations with urolithiasis and using validated proteomic methods.

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List of Abbreviations

AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
CaOx	Calcium Oxalate
eGFR	Estimated Glomerular Filtration Rate
HN	Hydronephrosis
hs-CRP	Highly sensitive C-reactive protein
IL	Interleukin
KIM-1	Kidney Injury Molecule – 1
L-FABP	Liver-type Fatty Acid-Binding Protein
MCP-1	Monocyte Chemotactic Protein – 1
MET	Medical expulsion therapy
MGP	Matrix Gla protein
MPO	Myeloperoxidase
NAG	N-Acetyl-β-d-amino Glycosidase
NC	Nephrocalcin
NGAL	Neutrophil Gelatinase-Associated Lipocalin
OPN	Osteopontin
PCNL	Nephrolithotripsy
PTH	Parathyroid hormone
RIRS	Retrograde intrarenal surgery
SSP	Spontaneous stone passage
UPTF-1	Urinary prothrombin fragment -1
URS	Ureterorenoscopy
THP	Tamm – Horsfall Protein
TNF – α	Tumor Necrosis Factor alpha

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