REVIEW ARTICLE

KIDNEY STONE DISEASE WITH SPECIAL REGARD TO DRUG-INDUCED KIDNEY STONES – A CONTEMPORARY SYNOPSIS

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ABSTRACT

Kidney stone disease (nephrolithiasis; urolithiasis) is a clinical entity with long-term course and recurrence, primarily affecting mature and ageing men, involving the formation and presence of urinary stones in the kidneys and urinary tract. The pathogenesis of this disorder is complex and still not fully understood. A rare, potentially modifiable, form of kidney stone disease takes the form of drug-induced urinary stones.

The aim of the review was a brief description of the classification and pathophysiology of kidney stone disease, along with the short characteristics of drug-induced urinary stones. This type of stones is formed as a result of crystallisation in the kidneys and urinary tract of sparingly soluble drugs and their metabolites, or as a result of metabolic changes caused by drugs, predestinating the development of stones containing endogenous compounds.

Conclusion: Therefore, during treatment with the use of drugs with high lithogenic potential, the safety of pharmacotherapy should be monitored in the context of its increased risk of developing urinary stones.

KEY WORDS: kidney stones, urolithiasis, nephrolithiasis, drugs, adverse drug reaction

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INTRODUCTION

Urinary lithiasis is as old as humanity – the first mention of urinary stones comes from the ancient times and the first stones were identified in Egyptian mummies. In 1901, the English archaeologist E. Smith, who performed his excavation works in El Amrah in Egypt, found a bladder stone from a 4500–5000-year-old mummy [1]. Documented written notes regarding urolithiasis and its management date back to 3200–1200 BC [2]. The first surgical descriptions of "cutting for the stone" were given by a surgeon who lived in ancient India – Sushruta, around 600 BC. He was the author of the book Sushruta Samhita, in which he characterised about 300 surgical procedures, including perineal lithotomy [1]. Thus, mankind has known kidney stone disease since its inception and the disorder invariably accompanies our civilization through the centuries.

Nowadays, kidney stone disease (also referred to as nephrolithiasis or urolithiasis) is a relatively common clinical entity and the estimates indicate that the general prevalence of the disease vary between 1 and even 20% [3]. The overall incidence of kidney stone formation, however, ranges in different parts of the world. In an adult population, the risk of kidney stone development seems to be lower in Asia (1–5%; mostly Pakistan, India, Thailand, Indonesia, the Philippines) than in Europe (5–9%; especially the British Isles, Scandinavian countries, Central Europe, Mediterranean countries), Canada (12%) and USA (13%). The highest number of patients suffering from renal stones is reported in Middle Eastern countries (e.g. about 20% in Saudi Arabia and in Sudan, Egypt, the United Arab Emirates, Iran) [4,5], probably because of the hot climate and increased risk of dehydration, which is an important environmental factor of kidney stone development. Kidney stone disease affects all ages, sexes and races but its incidence rate is higher in ageing men (male/female ratio is 2/1) and only 1–2% of urinary lithiasis patients are children [4].

A characteristic feature of kidney stone disease is its chronicity. The disease is characterised by high recurrence. Without any management, in about half of all patients, the next episode of the disturbance is observed over the course of ten years. Moreover, the recurrence rate is approximately 10% at 1 year and 33%–40% at 5 years [5,6].

When untreated or incorrectly treated, recurrent kidney stone disease is associated with progressive kidney damage and increased risk of chronic kidney disease development. Renal stones account for 2–3% of end-stage renal cases, mostly if nephrolithiasis is associated with nephrocalcinosis [7]. Other data estimate that this disease is even the cause of terminal chronic kidney disease requiring renal replacement therapy in 5% of European patients [8].

To sum up, kidney stone disease is a significant health problem. One of the causes of the disease, although rare, are drugs used in the pharmacotherapy of multiple diseases.

THE AIM

The aim of this paper was to discuss the basic issues of drug-induced kidney stones against the background of the general pathophysiological premises of nephrolithiasis.

Table I. The basic characteristic of urinary stones [3,10].

Chemical name	Common mineral name	Chemical formula	Shape of crystals in light microscopy	General etiology	X-ray feature
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4*H_2O$	Dumbbell-like; Biconcave disks	Non-infectious	Radiopaque
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4*2H_2O$	Bipyramids; Envelope-like	Non-infectious	Radiopaque
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6*(OH)_2$		Non-infectious	Radiopaque
Tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$		Non-infectious	Radiopaque
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$		Non-infectious	Poor radiopacity
Calcium carbonate	Aragonite	$CaCO_3$	Large spheroids with radial striations or smaller crystals with round to ovoid shapes	Non-infectious	Poor radiopacity
Uric acid	Uricite	$C_5H_4N_4O_3$	Rectangular or rhomboidal	Non-infectious	Radiolucent
Ammonium urate		$NH_4C_5H_3N_4O_3$	Spherical bodies with irregular protrusions ("thorn-apples")	Infectious	Radiolucent
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4*6H_2O$	Coffin-lid	Infectious	Poor radiopacity
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4PO_4*H_2O$		Infectious	Poor radiopacity
Cystine		C6H12N2O4S2	Hexagonal	Genetic	Poor radiopacity
Xanthine		C5H4N4O2		Genetic	Radiolucent
2,8-Dihydroxyadenine		C5H5N5O2		Genetic	Radiolucent
Other rare calculi (e.g. proteins, cholesterol, bilirubin, melamine, drug stones, foreign body calculi)			e.g. bilirubin - needle-like to granular crystals that are yellow in color	Other, complex mechanisms	Radiolucent (mostly)

MATERIALS AND METHODS

Narrative full-text reviews published in the English language were search in PubMed-NCBI and Google Scholar databases. The various applied search terms included: "kidney stone disease", "nephrolithiasis", "urolithiasis", "kidney stone", "renal stone", "drug-induced kidney stones", "drug-induced renal stones", "drug-induced nephrolithiasis", "drug-induced urolithiasis".

Published articles on or after 2000, which were available as free full texts on the public domain were selected during the performed query.

REVIEW AND DISCUSSION

TYPES OF KIDNEY STONES

Urinary stones can be classified according to chemical composition (mineralogy), the overall aetiology of formation, size, location or X-ray features [3]. The stone composition indirectly determines the size and shape of urinary stones and is an important premise for management decisions. A brief summary of individual stone types is given in Table I.

Based on the above-mentioned chemical composition, five main types of stones can be classified: calcium, struvite or magnesium ammonium phosphate, uric acid or urate, cystine and rare stones (including drug-induced ones). The above-listed stones contain mineral or small organic compounds, which form crystals, while the matrix as a non-crystalline phase acts as a template participating in the assembly of urinary deposits. The organic matrix is composed of glycosaminoglycans, cell membrane lipids, carbohydrates and some proteins [7].

Calcium stones account for about 80% of all urinary stones (70% of all urinary stones are composed of calcium oxalate and 10% include calcium phosphate or other calcium-containing deposits). The factors responsible for calcium stone formation are complex and mainly involve: low urine volume, hypercalcuria (due to enhanced renal resorption, intestinal absorption or metabolic calcium turnover disorders), hyperoxaluria, hypocitraturia, hypomagnesuria, hyperuricosuria or hipercystinuria. Urinary pH of 5.0–6.5 favours calcium oxalate stone development, whereas pH greater than 7.5 is a causative agent of calcium

Table II. Inhibitors and promoters of urinary stones development [7].

Stage of lithogenesis	Inhibitors	Promoters
Nucleation	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin glycosaminoglycans	Tamm-Horsfall protein (uromodulin) albumin collagen
Crystal growth	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin histone-lysine N methyltransferase alpha – 2HS glycoprotein chondroitin sulphate heparin sulphate human urinary trefoil factor 1 glycosaminoglycans citrate pyrophosphate magnesium	alpha-defensin myeloperoxidase histone H1B
Aggregation	nephrocalcin osteopontin albumin urinary prothrombin fragment-1 alpha-1-microglobulin bikunin fibronectin	alpha-defensin myeloperoxidase
Retention	osteopontin bikunin crytal adhesion inhibitor fibronectin glycosaminoglycans	nucleolin hyaluronic acid monocyte chemoattractant protein-1 annexin II antigen CD44

phosphate deposit growth [5, 7, 10, 11]. As a side note, it should be mentioned that, although calcium stones, contrary to struvite ones, are regarded as non-infectious, there are some reports suggesting that nanobacteria may contribute to the formation of a calcium phosphate shell, serving as a crystallisation centre for those stones [11].

Struvite stones form about 10–15% of all cases of kidney stone disease and their development is highly associated with chronic urinary tract infection caused by urease-producing bacteria (*Proteus mirabilis, Klebsiella pneumonia, Pseudomonas aeruginosa, Ureoplasma urealyticum, Escherichia coli* and *Enterobacter*). In more than half of all urease-producing infections, Proteus mirabilis was found to be a causative factor. Bacterial urease splits urea into ammonia and carbon dioxide with subsequent elevation of urinary pH. Alkaline urine decreases the solubility of phosphates that precipitate to insoluble ammonium products and usually take the form of large "staghorn" stones [5, 7, 8, 10, 11].

Uric acid stones or urate constitute about 5–10% of all urinary stones. They develop mostly as a result of hyperuricosuria due to the elevation in endogenous uric acid production and its excretion into urine. This occurs in high purines intake (diet rich in meat and fish containing animal proteins) and the precipitation of uric acid occurs in low urinary pH (uric acid is poorly soluble in acidic urine with pH about 5.5 or less). Those stones contain uric acid only or additional calcium [5, 7, 8, 10].

Cystine stones account for less than 1–2% of all cases. They are conditioned by genetic disturbances manifesting by hypercystinuria. This is associated with an autosomal recessive disorder due to the rBAT gene attributed to chromosome 2 deficiency, resulting in abnormal renal tubular reabsorption of cystine, ornithine, lysine and arginine. These types of stone are usually large and bilateral [5, 7, 8, 10].

According to the general aetiology, one can distinguish infectious and non-infectious stones, those caused by genetic defects and those induced as a result of adverse drug reactions [3].

In terms of size, urinary stones can measure up to 5, 10, 20 or above 20 mm, at their largest [3]. Deposits smaller than 5mm, after several weeks of conservative treatment most often pass spontaneously through the urinary tract and are excreted. Larger stones require specialist treatment and urological procedures for removal, while stones above 10 mm are unlikely to be expulsed unaided [6]. In terms of the general location of urinary stones, these may be located inside the kidney (in the upper, middle or lower calyxes or in the renal pelvis) and/or in the urinary tract (in the upper, middle or distal urether, in the urinary bladder or the urethra) [3]. The special term "staghorn renal stones"

Table III. The most common drug-induced urinary stones [25-28].

Class of drugs	Drugs examples	Primary stone composition	Rationale for stone development
Drug-containing stones			
Sulfonamides	sulfadiazine	sulfadiazine, N-acetylsulfadiazine	The basic premises for these types of stones development are: (1) The long-term treatment involving the administration of high doses of drug excreted by the kidney; (2) The administered drug and its metabolites are poorly soluble in urine; (3) There is the co-existence of the patient-dependent risk factors for the development of urinary stones.
	sulfaguanidine	N,N-diacetylsulfaguanidine	
	sulfamethoxazole	N-acetylsulfamethoxazole	
	sulfasalazine	N-acetylsulfapyridinine	
Antibiotics	aminopenicillins	ampicillin trihydrate amoxicillin trihydrate	
	cephalosporins	calcium ceftriaxonate	
Quinolones	pipemidic acid	pipemidic acid	
	ciprofloxacin	ciprofloxacin magnesium salt	
	norfloxacin	norfloxacin magnesium salt	
Other antibacterial drugs	nitrofurantoin	nitrofurantoin	
Protease inhibitors	indinavir	indinavir monohydrate	
	nelfinavir	nelfinavir	
	atazanavir	atazanavir	
Antacids	magnesium trisilicate	amorphous silica	
	aluminium hydroxide	aluminium magnesium potassium urate	
Various drugs	triamterene	triamterene, hydroxytriamterene sulfate	
	allopurinol	oxypurinol	
	ephedrine	ephedrine, norephedrine, pseudoephedrine	
	acyclovir	acyclovir	
	methotrexate	methotrexate, 7-hydroxymethotrexate	
Drug-induced "metabolic stones"			
Calcium-containing supplements	many commercially available	calcium oxalate, calcium phosphate	These drugs enhance an intestinal calcium absorption, leading to the hypercalcemia and the hypercalciuric state.
Vitamin D-containing supplements	many commercially available		
Loop diuretics	furosemide		
Anhydrase inhibitors	acetazolamide	calcium phosphates, mainly carbapatite	These drugs inhibit bicarbonate reabsorption and hydrogen ion excretion in proximal tubules, leading to systemic metabolic acidosis, an increase in urinary pH and decrease of urinary citrates.
	zonisamide		
	topiramate		
Laxative drugs (when abused)	hyperosmotic or stimulant agents	ammonium urate, uric acid, calcium oxalate	These drugs, when abused, cause an increased gastrointestinal fluid and potassium loss and low urinary output. The potassium depletion contributes to intracellular acidosis compensated by renal ammoniagenesis enhancement in kidney proximal tubules and increased citrate reabsorption, potentiated by increased expression of the H+/K+ activity in the distal tubules.
Corticosteroids	cortisol	calcium oxalate, calcium phosphate	These drugs promote the release of calcium from bones and lead to the hypercalcuria and hyperphosphaturia state.
Ascorbic acid (vitamin C)	many commercially available of dietary supplements	calcium oxalate	The excess of vitamin C is metabolized to oxalates and it increases the urinary oxalates excretion. Moreover, high doses of vitamin C also contribute to urinary acidification.
Xanthine oxidase inhibitors	allopurinol	xanthine, oxypurinol	The drug inhibits the biotransformation of hypoxanthine into xanthine and final synthesis of uric acid, leading to the formation of xanthine-containing purine stones.
Uricosuric drugs	benzbromarone probenecid	uric acid	These drugs reduce hyperuricemia by enhancing urinary uric acid excretion, leading to the formation of uric acid-containing purine stones.

refers to the massive kidney stones that fill the renal pelvis and at least one of the renal calyces [9]. The comparison of urinary stones depends on their chemical composition. In kidney-urether-bladder radiography, radiopaque (calcium oxalate, calcium phosphates), those characterised by poor radiopacity (magnesium ammonium phosphate, apatite, cysteine) and radiolucent (uric acid, ammonium urate, drug-induced) urinary stones can be distinguished [3].

THE RISK FACTORS OF URINARY STONE FORMATION

The main factors determining urinary stone development can be divided into individual and environmental. The first group includes sex, race, age, inheritance, genetic features and individual predisposing diseases. As already mentioned above, kidney stone disease is more common in ageing men, usually manifesting itself for the first time in patients aged 20–50 [7]. Genetic predisposition must be taken into account in a patient with a family history of stones and in the diagnosis of renal tubular acidosis, cystinuria, Barret's syndrome or genetic monogenic diseases. Among the diseases predisposing to the development of urinary stones, both metabolic (hypercalcuria, hypocitraturia, hyperoxaluria, hyperuricosuria and a history of gout) and anatomical (medullary sponge kidney, ureteropelvic junction stenosis, pyeloureteral duplication, polycystic renal disease and horseshoe kidney) disorders should be listed. Other diseases contributing to urinary stone development are: hyperparathyroidism, hypertension, obesity, inflammatory bowel diseases or other intestinal malabsorption states and recurrent urinary tract infections. Environmental factors involve climate change (global warming) and seasonal variations (higher prevalence of urinary stones in summer rather than winter), socio-economic conditions and associated lifestyle, and dietary habits or low water intake causing dehydration and subsequent low urine output [4, 7, 10]. Diet is a very important risk factor of kidney stone disease. Lack of drinking water with an excessive intake of animal proteins, salt and vitamin D with reduced content of citrate, fibre and potassium in the diet are considered to be the main abnormalities leading to urinary stone formation. Studies also suggest that high intake of carbohydrate-rich food and less physical activity are directly proportional to kidney stone disease development. Conversely, regular consumption of water (up to 2.5–3 litres per day, unless otherwise indicated), fruit and vegetables (except green leafy ones containing a higher amount of oxalates) and maintaining proper physical activity are the most important preventive factors [12].

THE PATHOPHYSIOLOGY OF KIDNEY STONES. MECHANISMS OF URINARY STONE FORMATION

The pathophysiology of kidney stone disease (nephrolithiasis, urolithiasis) is complex and still not fully understood. The general pathophysiological premises of urinary stone formation assume three main disturbances: (1) an excessive urinary concentration of some compounds, exceeding their solubility in the urine, (2) an imbalance between promoters and inhibitors of precipitation, and (3) urothelial abnormalities allowing an attachment and subsequent growth of the rising urinary deposits [5]. There are a few "milestone" points in the complex pathophysiological cascade of urinary stone development.

The initiation phase of the process is nucleation, followed by a stage of crystal growth with their subsequent aggregation and retention on the surface of the renal tubules. Nucleation can be described as a phase change of dissolved mineral compounds into a solid, with the formation of a nucleus, also termed nidus [7]. This phenomenon is observed in a super-saturation solution that contains more of the compounds that can be dissolved in the solvent under normal circumstances. Nucleation can be either homogeneous (occurring spontaneously in an unstable zone of supersaturation when the concentration of two ions exceeds their saturation point in the solution) or heterogeneous (taking place at a lower degree of saturation in the presence of nucleating agents in urine – promoters of nucleation, such as exfoliated epithelial cells, urinary casts, red blood cells, mucopolysaccharides etc.). The promoters form a surface on which precipitation may take place, which reduces the energy necessary for crystallisation [5, 11]. The homogeneous nucleation mechanism is consistent with the general hypothesis of the "free particles", while the heterogeneous one meets the criteria of the "fixed particles" concept, which is also often mentioned in the literature [13].

In the second step, the microcrystals continue the oriented overgrowth on to a substrate crystalline lattice ("epitaxy"). Stone growth is accomplished through aggregation of the preformed crystals or secondary nucleation of the crystal on the matrix [7]. The process depends on urinary pH, the physicochemical properties of the crystallisation base material or the molecular size and shape of the precipitated compounds [5].

Aggregation is a process of binding the adjacent crystal nuclei to each other and forming larger particles due to the existence of small interparticle attractive forces conducive to aggregation [5].

The final step is the association and fixation of the crystals in the renal tubules cell lining. Thus, the retention phase consists in the interactions between the developing crystals and epithelial cells. Those interactions result in the movement of the formed and growing nidus from the basolateral cellular region and its anchoring into the basement membrane. Some of the crystals are digested and phagocytosed by locally resident macrophages or they are subjected to endocytosis with subsequent lysosomal degradation. This also leads to an increase in oxidative stress, and ultimately to damage of the renal tubules [5, 7]. This phenomenon impairs the possibility of the cellular elimination of developing crystals and allows their further growth. Finally, the formed deposits may detach from the kidney tissue and may be passed through the urinary tract, although the factors determining the passage of the stone to the urinary tract remain unknown.

At each of stage of the formation of urinary stones, the urinary stone matrix protein modulators play an important role, acting as inhibitors or promoters of a given phenomenon. Some are listed in Table II. Hence, it can also be concluded that the pathogenesis of urinary stones is the result of the deficiency of inhibitor action accompanied by the over-expression of the promoters.

KIDNEY STONES SYMPTOMS, DIAGNOSIS AND MANAGEMENT

The symptomatology and management of kidney stone disease is dependent mainly on the size and location of the urinary stones and the presence of a possible associated urinary tract infection. Stones smaller than 5 mm are likely to pass spontaneously through the urinary tract and patients require careful observation, hydration and pain treatment. Analgesics exerting additional anti-inflammatory effect used in renal colic include metamizole or, alternatively, depending on gastrointestinal and cardiovascular risk factors, diclofenac, indomethacin or ibuprofen. Opiates – morphine, pethidine, pentazocine, tramadol are regarded base drugs of second choice or they are administered to patients suffering from severe pain, uncontrolled by non-opioid analgesics [3]. During the passage of the stone through the urinary tract, renal colic symptoms present themselves. Renal colic is a severe, cramping pain evoked by the movement of a stone through the urinary tract, which is augmented by the ureteral spasm and the possible obstruction; thus, it is also treated with spasmolytic agents, such as papaverine, drotaverine, hyoscine or oxyphenonium, administered in addition to analgesics. Pain originates in the flank area and spreads downward into the genital region when the stone reaches the distal ureter. It is usually not related to body position and is accompanied by nausea, vomiting and macro- or at least micro-hematuria and often bladder overactivity symptoms (sensation of urinary frequency and urgency) [6].

Stones larger than 5 mm are mostly treated with interventional procedures. A medical expulsive therapy (MET) seems to be effective in patients who are amenable to conservative management, with distal ureteral stones > 5 mm. MET includes the administration of alpha-1-blockers (tamsulosin), calcium channel inhibitors (nifedipine) or phosphodiesterase-5-inhibitors (tadalafil). Patients treated with those agents (with the superiority of tamsulosin) exhibit fewer colic episodes compared to untreated ones [3]. Massive stones that bilaterally block the flow of urine can be a pathophysiological cause of the development of acute kidney injury and failure, with anuria and hypercreatinemia. Long-term consequences of the urinary stones involve the development of several complications, e.g. hydronephrosis or obstructive nephropathy even leading to chronic kidney disease.

The chronic treatment of kidney stone disease includes preventive methods and pharmacological agents with/or without surgical treatment. Regardless of the aetiology, the most important preventive treatment consists of hydration to reduce urine supersaturation and to maintain a urinary output of at least 2 L/day. The patient is also advised to restrict daily intake of animal proteins [14]. Pharmacological intervention involves the administration of herbal medicine containing terpenes and essential oils (e.g. Rowatinex), potassium citrate (causing a significant urinary pH increase) or thiazide diuretics, which are considered to be effective hypocalciuric agents due to their contribution to enhanced calcium reabsorption in the distal tubules. Acetohydroxamic acid reversely inhibits bacterial urease; thus, it is administrated in patients with urea-splitting bacterial infections. Urinary tract infections require treatment with antibacterial chemotherapeutics. In cystine stones, tiopronin is used to reduce urinary cystine concentration by forming a water soluble mixed disulfide complex. Surgical procedures include extracorporeal shockwave lithotripsy (ESWL), ureteroscopy or percutaneous nephrolithotomy [3, 10, 15]. There are also reports of the beneficial effects of using herbs that seems to be the safest and most inexpensive treatment; however, this requires time for the beneficial therapeutic effects to become apparent. In many countries, there are different experiences with the use of various species of herbs, including those that are often endemic only in given areas and, for this reason, they are part of traditional Chinese or Indian medicine. One can also list here, however, some plants more widely available in Europe, such as *Trigonella foenum-graecum, Origanum vulgare, Berberis vulgaris, Ammi visnaga, Oenothera biennis, Rubia tinctorum, Rosa canina, Punica granatum* and others [16, 17].

The diagnosis of urinary stones is based on both laboratory testing and imaging studies. Blood tests usually measure creatinine, urea, uric acid and electrolytes. In urine samples, the presence of red and white blood cells, nitrates and pH are determined. The microscopic assessment of urinary sediments and casts is also performed. The evaluation of chemical composition is crucial for further medical treatment and the patient is instructed to collect urine and excreted deposits for examination during stone evacuation [3, 10]. There are also precise physical methods – X-ray diffraction and Fourier transform infrared spectroscopy – enabling the identification of each chemical constituent of the urinary stone with semi-quantitative evaluation of their proportions [18]. Imaging studies for urinary stones include: ultrasonography, radiography of the kidneys, ureters and bladder (KUB), computerised tomography (CT) and magnetic resonance imaging (MRI). Ultrasound is often the first-line imaging modality due to its advantages – it is not expensive, it is portable and ubiquitous, and does not expose patients to any radiation. Moreover, it is able to detect some complications of kidney stone disease, such as ureteral dilation, peri-renal fluid or hydronephrosis. Conversely, ultrasonography is not suitable for obese patients. It is also inaccurate for determining stone size and is regarded to have decreased sensitivity and specificity compared to CT. Radiography is still useful for the evaluation of urinary stone patients, especially when

paired with ultrasonography. KUB enables the visualisation of calcium-containing stones and assesses their radio-opaqueness and density. The sensitivity of this study is only 45–58%, mostly due to overlying bowel gas, and extra-renal or extra-ureteral calcification outbreaks. KUB is also based on the necessity of contrast administration, which may produce some adverse reactions and exposure of a patient to X-ray radiation. MRI is a non-radiation study enabling the complex evaluation of all soft tissues of the abdomen and pelvis, including the anatomical details of the kidneys and urinary tract. This examination is often suggested to pregnant women or children when radiation is contra-indicated or it is performed in patients presenting symptoms of nephropathy, who must avoid contrast administration and possible additional kidney injury. CT scans are regarded as ideal, requiring no intravenous contrast administration, and are a first-line imaging study, especially for patients with acute symptomatology of kidney stone disease, diagnosed in emergency departments. The main advantage of the study is that all stones (with small exceptions for drug-induced ones) are detectable in CT. CT reveals stone size, its location and its overall density with skin-to-stone distance, which are predictors of successful fragmentation during ESWL [19, 20].

DRUG-INDUCED URINARY STONES

The excretory system is susceptible to potential damage also caused by xenobiotics – drugs, whose adverse reactions may be present as renal or urological disorders. Adverse drug reaction (ADR) is defined as the noxious and unintended response to a drug, which occurs at doses usually administered for prophylactic, diagnostic or therapeutic purposes, or to evoke the desired modification of the physiological functions. Examples of the most common ADR developing in the kidneys and urinary tract are: intratubular crystallisation or formation of urinary stones, urinary tract infections (including cystitis), erectile dysfunction in men, urinary retention and incontinence. The possible, most dramatic consequence of ARD may be the development of acute kidney injury (AKI). Overall estimates indicate that about 14–26% of all adults and 16% of pediatric AKI cases are drug-induced. Some cases of chronic kidney disease also result from chronic drug-induced nephrotoxicity [21, 22].

In general, crystal nephropathy takes on a wide spectrum of kidney damage caused by precipitated crystals, consisting of endogenous mineral salts, end waste metabolites, proteins and/or exogenous nutrients or xenobiotics, including drugs. Crystal-induced kidney damage caused by crystals, depending on the location of the crystallisation centres and the dynamics of this process, may be divided into three basic types. In the first type, the crystals are deposited in the vascular wall, with subsequent vascular calcification, which results in renal ischemia. Type 2 crystal-induced kidney damage involves extra- and intra-tubular crystal deposition that initiates tubular cell injury, kidney interstitial inflammation development and possible tubular lumen obstruction. In the third type of the proposed classification of crystal-induced kidney injuries, a stone formation in the kidney and urinary tract, with possible obstructive nephropathy, occurs. Therefore, it can be concluded that drug-induced kidney stone disease is a special ADR, which can be categorised as a sub-type of crystal nephropathy [23].

Drug-induced stones are a rare type of stones, similarly to melamine ones or those associated with rare congenital metabolic defects, such as xanthine oxidase deficiency or alkaptonuria [24]. The urinary stones account for about 2% of renal calculi cases, although the incidence of these types of stones seems to be underestimated. First, most drug-containing stones are radiolucent in radiography (although these stones are detectable in an ultrasound study). This is the reason behind the diagnostic difficulties of this type of stones. Secondly, careful anamnesis is necessary, since the patient's detailed medical history together with establishing a detailed list of medications and dietary supplements are the basis for revealing the potential relationship between urinary stone formation and pharmacotherapy. The demonstration of the pathophysiological relationship between the drugs taken by a patient and the development of urinary stones is difficult, taking into account the possibility of recognising this clinical entity, even many years after the cessation of the given, "suspected" treatment. Moreover, the diagnosis of drug-induced kidney stone disease must take into account the problematic fact that the patient can be treated with several potentially lithogenic drugs, which makes it difficult to identify a specific one as the main aetiological factor of urolithiasis. This is very important in the context of the prevention of the development of drug-induced kidney stone disease; only precise determination of the drug that is most likely to cause urinary stone formation and its withdrawal reduces the risk of the development of the disorder. Conversely, there are also strong indications when a patient may be suspected of suffering from drug-induced urinary stones. The disease can be initially diagnosed in a patient without a history of urolithiasis, who is treated with a drug with high lithogenic potential, and when the conditions mentioned below have been fulfilled [25].

The risk factors for drug-induced urinary calculi involve both patient- and drug-specific issues. Among the factors associated with the patient, the following points should be mentioned: personal and family history of nephrolithiasis, low 24-hour urine output, aberrant low or high urinary pH, recurrent urinary tract infection episodes, malformation predisposing to urinary stasis and stone formation (e.g. pre-existing calculi, prostatic hypertrophy), metabolic disorders associated with biochemical lithogenic abnormalities (e.g. hypercalcuria), environmental factors (e.g. hot temperatures causing excessive sweating). One can also distinguish several attributes of the drug itself, predisposing to the development of urinary stones: the administration of high doses of the compound, long-term treatment, low aqueous solubility of high urinary excretion of the drug and/or

its metabolites and polytherapy, as well as co-administration of other drugs that may cause pharmacokinetic interactions, interfering with the excretion of lithogenic substances and xenobiotics [25].

Two main types of drug-induced urinary stones can be distinguished, taking into account the main pathomechanism of their formation. The first group includes stones composed principally of the drug and/or its metabolites. These stones are mostly formed by poorly soluble compounds, for which the kidneys are the main route of elimination. Therefore, in accordance with the general, aforementioned pathophysiological premises, when the solubility equilibrium is exceeded, these drugs may undergo nucleation and crystallisation (both homogeneous and heterogeneous) in supersaturated urine. The second group of drug-induced urinary stones are those classified as a sub-type of "metabolic stones", due to the evoked metabolic effects of a drug, primarily on calcium or purine metabolism [25, 26]. Many drugs may induce urinary stone development by affecting the pH of urine (in such a way that the solubility of many endogenous substances decreases), alternation of the glomerular filtration and tubular secretion/reabsorption of the endogenous substances, or impairing the balance and action of crystallisation promoters/inhibitors (while enhancing the effects of the promoters of the phenomenon) [27]. To sum up, the physiological and biochemical disturbances, which form the basis for urinary stone development (nucleation, crystal growth, crystal aggregation) may be also drug-evoked. Since the chemical composition of drug-induced metabolic stones does not contain the drug itself, but appears identical to the non-drug dependent counterparts, the differential diagnosis of those drugs is particularly difficult and requires careful assessment [25–28].

The characteristics of both types of drug-induced urinary stones are given in Table III.

CONCLUSIONS

Kidney stone disease is an important disorder that can periodically manifest itself with painful ailments, and in the long-term may even lead to serious complications. The disease can also develop as adverse nephrological and urological drug reactions. Drugs that are considered to have high lithogenicity potential may cause metabolic abnormalities predisposing to the crystallisation and precipitation of the physiological components of urine or they may crystallise themselves in the urine. Therefore, treatment based on the use of drugs perceived as highly lithogenic, especially in patients with other risk factors for the development of urinary stones, must be carefully monitored for the safety of the implemented pharmacotherapy. Due to the fact that drugs that may cause the formation of urinary stones belong to different pharmacological groups, the possibility of drug-induced kidney stones should be taken into account by practitioners of various specialties in planning pharmacotherapies and assessing their risk.

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Conflict of interest
Author declare no conflict of interest.

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