The significance of calcium metabolism in uric acid stone formers

Königsberger, Sebastian Tobias

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Sebastian Königsberger

THE SIGNIFICANCE OF CALCIUM METABOLISM IN URIC ACID STONE FORMERS

Diploma thesis

Academic year
2022/2023

Mentor:
Prof. Walter Ludwig Strohmaier, MD, PhD

Coburg, August 2023

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Sebastian Königsberger

THE SIGNIFICANCE OF CALCIUM METABOLISM IN URIC ACID STONE FORMERS

Diploma thesis

Academic year
2022/2023

Mentor:
Prof. Walter Ludwig Strohmaier, MD, PhD

Coburg, August 2023

ACKNOWLEDGEMENT

I am immensely grateful to my mentor, Prof. Walter Ludwig Strohmaier, MD, PhD, whose guidance and expertise have been crucial in shaping the direction of my diploma thesis. Your unwavering support, constructive feedback, and dedication to my academic growth have been invaluable.

To my family, my sister Isabella Königsberger, who I will always be looking up to, and my parents Rainer and Alexandra Königsberger, words cannot express the depth of my gratitude. Your constant encouragement, belief in my abilities, and sacrifices have been the pillars of my journey. Thank you for being my foundation and for always being there, no matter the challenges.

I would also like to extend my thanks to my friends, Silvio Heinig and Timm-Frederik Lemcke. Your companionship, laughter, and support during both the challenging and joyous moments of this journey have made it truly memorable.

Last, but not least, I thank all my professors, mentors, doctors, and the student offices of the University of Split - School of Medicine and the Medical School REGIOMED, for their support throughout all these years.

LIST OF ABBREVIATIONS:

ADH – Anti-Diuretic Hormone

ALARA – As Low As Reasonably Achievable

ASIR – Age-Standardized Incidence Rate

AUA – American Urological Association

BMI – Body Mass Index

CT – Computed Tomography

DASH – Dietary Approach to Stop Hypertension

ESWL - Extracorporeal Shock-Wave Lithotripsy

HIV – Human Immunodeficiency Virus

IVU – Intravenous Urography

KUB – Kidney-Ureter-Bladder

MAP – Magnesium-Ammonium-Phosphate

MET – Medical Expulsive Therapy

MRI – Magnet Resonance Imaging

NHANES – National Health And Nutrition Examination Survey

NSAIDS – Nonsteroidal Anti-inflammatory Drugs

PNL – Percutaneous Nephrolithotomy

ROKS – Recurrence Of Kidney Stones

RRd – Diastolic Blood Pressure

RRs – Systolic Blood Pressure

S-Ammon. – Serum Ammonia

S-Ca – Serum Calcium

S-Crea – Serum Creatinine

S-Gluc – Serum Glucose

S-K – Serum Potassium

S-Na – Serum Sodium

S-UA – Serum Uric Acid

U-Ammon. – Urine Ammonia

U-Ca – Urine Calcium

U-Citrate – Urine Citrate

U-Crea – Urine Creatinine

U-pH – Urinary pH

U-UA – Urine Uric Acid

U-Urea – Urine Urea

U-Vol – Urine Volume

URS – Ureterorenoscopy

US – Ultrasound

UTI – Urinary Tract Infection

1. INTRODUCTION

1.1. Urolithiasis

The medical term “Urolithiasis” (from Greek: o*uron:* urine and *líthos*: stone) describes a medical condition, characterized by formation of calculi along the urinary tract, comprising the renal pelvis, ureter, urinary bladder and urethra (1).

1.2. History of urolithiasis and treatment

Urolithiasis has been recognized in human history for numerous millennia. Besides being discussed in many historic medical texts, one of the first indicators, that this disease was already present in ancient times is the finding of urinary stone remnants in an approximately 7000-year-old Egyptian mummy (2). The history of the treatment of urinary stone disease dates back to the time of the civilizations of ancient Egypt, Mesopotamia, India, Greece, and the Roman Empire. The earliest Egyptian medical texts, from approximately 1500 before Christ (BC), described dietary modifications and conservative treatments of urinary diseases. Archaeological findings of treatment instructions on stone tablets from Mesopotamia included surgical and conservative approaches. While non-surgical remedies included different recipes and dietary recommendations, surgical treatment was reserved for stones of hard consistency (3).

The Indian surgeon Sashruta (approximately 600 BC) was one of the first authors to describe the formation of urinary bladder stones in detail, including the process of precipitation and the association with an unhealthy diet in his book *Sashruta Samhita.* In addition to these early explanations of the pathophysiology of the disease, he formulated treatments like dietary recommendations, urethral milk injections, and surgical procedures in detail (4).

The significance and complexity of the stone disease were also well known by the ancient Greeks. Their knowledge of the severe risks associated with surgical procedures, especially the perineal approach of urinary stone surgery, can be easily recognized when citing the Hippocratic Oath. An early acknowledgement of the need for specialist care can be appreciated in the following statement of the oath: “I will not use the knife, not even on sufferers from stone, but will withdraw in favour of such men as are engaged in this work” (5).

In the third century BC, Ammonius of Alexandria revolutionized the surgical technique, as he was the first person to describe crushing of the uroliths before their removal. Therefore he was known as "Ammonius Lithotomus" – Ammonius the Stein-Schneider (= stone cutter), although his work wasn´t immediately accepted – in part because of the prohibition of such technique by the Hippocratic Oath (3). Another method, the perineal lithotomy, was first introduced by the Roman physician Cornelius Celsus (25 BC – 40 AD) in his *Encyclopaedia de Medicina,* for which it received the name "Celsian Method". This operative technique, also called *apparatus minor,* required only a small number of instruments and was almost exclusively used in young male patients. It included preoperative measures, such as diet and physical activity, in attempt to move the urinary stone to the neck of the bladder. It furthermore gave perioperative instructions, especially the fixation of the patient by his guardian to expose the site of incision. The physician then was instructed to perform digital rectal manipulation in such a manner, that the urolith is pulled inferiorly with the index finger and positioned closer to the incision site. Specific instruments to cut or extract the stones were additionally described. In fact, his procedure had such a big impact, that it was used until the eighteenth century (3, 4, 6).

Throughout the Middle Ages, the negative stance of the church on surgery and its influence on the medical profession led to a stagnation of the scientific progress in the treatment of urolithiasis. Especially the pontifical edict in the twelfth century AD, which prohibited surgical procedures being performed by physicians, induced a change of paradigm. Instead of being performed by academically trained professionals, surgery was demoted to a craft, conducted by barbers and other, often less educated, practitioners (4, 7). With the end of the Middle Ages and the new era of Renaissance the surgical development rose again. The gradual reconciliation of surgeons and physicians ultimately resulted in the return of surgery to the medical profession. Advancements in anatomy, instrumentation, professional regulations, and operative techniques led to more effective interventions. A new way of operating on patients, the Marian operation, or *apparatus major* (indicating a bigger variety of instruments used in this operation), which was recommended for adult patients, was developed (4, 7).

The seventeenth to the nineteenth century was the time of many technological and scientific milestones. It was now possible to analyse the composition of urinary stones for the first time, leading to the discovery of uric acid as the main constituent of a specific type of urolith by Karl Wilheim Scheele (1742 – 1786 AD). The invention of the *Lithotritor* by John Civiale in the early nineteenth century enabled physicians a completely novel approach to the treatment of stone disease. In contrast to lithotomy, this device allowed to access the stone endoscopically via the urethra. Together with the evolution of anaesthesia and further modification of the technique, this minimally-invasive procedure resulted in a strong reduction in mortality (3, 4, 7).

The introduction of X-ray into medicine during the twentieth century facilitated the detection and localization of urinary stones. Continued innovations and advancements in the field, like ESWL (extracorporeal shock-wave lithotripsy), have led to the emergence of modern, less invasive, treatment modalities, resulting in a reduction in the utilization of open surgery for patients with urinary stones to less than 4% of cases (4, 7).

1.3. Epidemiology and economic aspects

In order to be able to create effective prevention strategies and distribute healthcare resources, understanding the epidemiology of urolithiasis is crucial. The economic impact of the disease is significant and includes the direct costs of diagnosis and treatment, as well as indirect costs with diminished productivity and quality of life. A better insight into epidemiological patterns and associated financial expenditures, potentially allow further development of targeted therapy and improved patient outcomes.

1.3.1. Prevalence

Determining the prevalence (the percentage of individuals having a disease at a given point in time) of Urolithiasis is not an easy task. Significant challenges in determining the percentage of the global population suffering from the disease don´t only include factors like climate, gender and ethnicity, geography and diet causing major variations in prevalence, but also the lack of information about large groups of the global population, allowing only rough estimates of the global disease occurrence. However, population-based studies indicate a range of 4-20% of the population of industrialized countries to be affected by urolithiasis, showcasing how widespread the disease is. Additionally, by taking the existing data into account, a further increase in prevalence is expected in future years (7–9).

1.3.2. Incidence

Similar to prevalence, an overall increase in the incidence of urinary stone disease has been reported, even though specific numbers vary across the literature. Recent studies suggest a global incidence range from 5% to 40% depending on geographic location (10).

A study by Qian et al. displayed a significant increase in new urolithiasis cases from approximately 77.78 million in 1990 to 115.5 million cases in 2019. Paradoxically, this study found that the age-standardized incidence rate (ASIR) declined by 0.83% every year. By using the ASIR, the influence of age, and therefore the demographic change, on the global incidence is removed (8, 11).

Further studies are necessary to determine whether the rise in incidence is only attributable to ageing and growth of the global population and changing diagnostic possibilities, or if other possible factors contribute to this development (12).

1.3.3. Recurrence

Stone recurrence, describing the state of having one or more episodes of urolithiasis after an initial episode, is very common. The recurrence rates of urolithiasis in a population of urinary stone formers in Minnesota, USA, were 11%, 20%, 31% and 39% in a period of two, five, ten and fifteen years after the initial stone episode (13, 14). This high probability for patients to experience two or more stone episodes has a significant impact on the quality of life and the economic burden associated with the stone disease (15–17).

Even though stone recurrence, in general, has a high probability, many risk factors have been identified, individually as well as collectively contributing to the likelihood of experiencing two or more stone episodes. Stone composition, just representing one of these factors, has been shown to influence recurrence rates significantly. While other types of stones exhibit lower recurrence rates, cystine stones have a 90-100% probability to recur, if not treated appropriately (7, 17).

Because of the large number of risk factors and the individual contribution to a cumulative risk, the recurrence of kidney stones (ROKS) nomogram has been established by Rule et. al (14). This easily accessible tool (https://qxmd.com/calculate/calculator_438/roks-recurrence-of-kidney-stone-2018) gives physicians reasonable prediction estimates for the recurrence rates of urinary stones in a particular patient. While having its limitations, such a tool has the potential to help with treatment-decision, resource allocation, improvement of targeted preventive measures and ultimately reducing the burden of the disease (14, 18, 19).

1.3.4. Geographic distribution

Geography plays a significant role in the epidemiology of urolithiasis. Although the literature is limited in terms of data on a global level, studies of specific geographic regions allow an insight into the differences in kidney stone disease around the world (11).

While urolithiasis is shown to be more prevalent in the western parts of the world, than in the eastern hemisphere, some countries like Saudi Arabia represent an exception to this trend (3, 20).

The geographic variation not only contributes to differences in epidemiological patterns of urinary stone disease worldwide but also within specific countries. A study, using data from over 200.000 stone analyses, showed geographical variations in stone composition, gender distribution and other population-based factors within Germany, a country without extremes in climate or geography (21). Strohmaier and Seilnacht reported an exceptionally high percentage of uric acid stone formers in the region of Upper Franconia. With 28% of all stones, this value is significantly higher than the average percentage of uric acid stone formers in Germany, where uric acid stones were the main component in 8.7% of patients (22, 23).

When comparing differences between countries and regions, it becomes apparent, that geography can´t be just seen as a single entity, contributing to the variance in urolithiasis. It instead represents a unique cluster and complex interplay of different factors that affect the disease (9).

1.3.5. Climate and season

A wide array of studies, describing the connection between variations in climate and urolithiasis, have been published (3, 7, 9, 24–41). Areas with higher mean annual temperatures have been shown to inherit a higher risk for urinary stone development (9). Furthermore, higher incidence and prevalence rates throughout the season of summer, specifically during the month of July through September in the northern hemisphere and January through March in the southern hemisphere, have been reported (27).

In contrast to that, Strohmaier and Öszi found a higher incidence of renal colic due to uric acid stones in Upper Franconia (Germany), during the third and fourth quarters of the year, representing the season of summer – a warm temperature season, and the season of autumn and early winter, with cooler temperature (42). For calcium oxalate stones, no seasonal variation was found by the German research group (43).

A Korean study by Park et al. investigated approximately 1.7 million cases of urolithiasis in the period from 2006-2010. Besides confirming the higher ratio of urinary stones during the summer season, the study has identified a threshold temperature of 18.4 °C. For every degree of temperature exceeding this threshold point, the risk for a stone episode rose by about 1.71% in the Korean population. Park et al. have defined the ambient temperature to be the single major contributor to the monthly variation in their research (34). In contrast to that, other studies have identified further climate elements potentially affecting the disease, such as the amount of sunlight, rainfall, atmospheric pressure, and humidity (39, 40). One study, which analysed urolithiasis in major US cities, reported higher numbers of stone episodes when the ambient temperature was 30 °C versus 10 °C, suggesting the number of hot days (30 °C) to be a better predictor for the prevalence of urolithiasis (28).

The pathophysiological mechanisms behind the increased risk for stone formation with higher ambient temperatures are not completely clear. It is assumed that a higher surrounding temperature induces, an often discrete, fluid loss over the surface of the skin. The consequence is a rise in the osmolality of the extracellular fluid. When this increased osmolality is sensed by the osmoreceptors, the neurohypophysis releases ADH (anti-diuretic hormone) causing increased renal fluid reabsorption and consequently a concentration of urine. Stone-forming substances may become supersaturated which consequently leads to the formation of crystals and urinary stones (7, 25).

The rise in greenhouse gases and overall environmental contamination is projected to lead to a global-mean surface temperature increase, ranging from 1.5 to 4.5 per cent, by the year 2100 (44). Such a trend would likely have a significant impact on the health economy. A computer-based cost prediction estimates an increase in direct treatment costs of 0.9 million - 1.3 billion US-Dollars in the United States alone (26).

1.3.6. Gender

It is well-documented that gender influences the risk for urolithiasis.
While the disease incidence is significantly higher in the male population, the male-to-female ratio in the U.S. declined from 3:1 in 1970 to 1.3:1 in 2000 (45). Male prevalence remained relatively stable, the prevalence among the female population, on the other hand, increased continuously (39). The reason behind this reduction of the so-called gender gap remains a subject of discussion (46). One possibility could simply be a higher detection rate of asymptomatic kidney stones. Some studies suggest that environmental factors are responsible for the increase in female prevalence, while heritable risk factors are having a bigger influence in urolithiasis among the male population (47, 48).

Other studies reported differences in male and female hormone balance to be causing the variation in epidemiological data on the stone disease. In a study population of urinary stone formers, the number of renal androgen receptors was significantly increased (47, 49).

Furthermore, it has been hypothesized that oestrogen, one of the female sex hormones, inherits a protective role in stone formation. Proteomic investigation of renal tubular cells, responding to an oestrogen stimulus, revealed an in vitro downregulation of the cellular potential to bind calcium oxalate, suggesting a possible role in physiologic and even therapeutic disease prevention (50). In support of this protective role of oestrogen, it has been shown that deactivation of the oestrogen receptor in knockout mice has caused an increase in renal calcium oxalate deposition (51).

The stone composition is also subject to gender variation. While women are more likely to develop struvite or infection stones, in addition to carbonate apatite stones, male patients are more likely to suffer from calcium oxalate and uric acid stones (48, 52).

Pregnancy in general is not considered to be a direct risk factor for urolithiasis. Contrarily, the number of pregnancies is shown to raise the probability of stone development with every pregnancy (48).

1.3.7. Ethnicity

Studies have reported variations in stone composition and formation rates in relation to different ethnicities. Among the defined ethnic groups, individuals of black, non-Hispanic descent had the lowest prevalence of stone episodes. Results from the 2007-2010 National Health and Nutrition Examination Survey (NHANES) have been analysed and concluded a prevalence of just 4.3% in black, non-Hispanic individuals, compared to 6.4% in Hispanic and 10.3% in non-Hispanic, white individuals (53–55). While different studies report a similar trend, a 2013 review of the scientific literature, regarding the influence of race and ethnicity on urolithiasis, revealed that a majority of scientific articles and studies lack in explanation and theories on the mechanisms behind the difference in epidemiology data on the urinary stone disease. 48.5% of the reviewed material presented only the fact that several factors, like socio-economic status, environment, diet, genetics and sex hormones exist, rather than describing how these factors influence the pathophysiology of the disease (3, 54, 56).

Stamatelou and Goldfarb suggested that cultural, behavioural and socioeconomic variables, rather than solely inborn differences could explain the prevalence range in urolithiasis (39). Supporting this statement, another study reported a rise in stone occurrence among black Americans, after they adopted to Caucasian diet and nutrition (3).

1.3.8. Diet

Diet plays a significant role in the development and management of urolithiasis. Many dietary factors have been investigated and identified to either contribute to urinary stone formation or to reduce the risk of lithogenesis (57).

1.3.8.1. Fluid

Fluid balance is of major importance in the therapy, as well as in the pathogenesis of urolithiasis. Inadequate fluid intake significantly increases the likelihood of developing kidney stones, while on the other hand, increased fluid intake can effectively lower the risk of stone formation by increasing the urine volume and therefore reducing the concentration of lithogenic substances (9, 58). A comparison of daily fluid intakes showed an almost 50% lower risk for incident kidney stones with a total fluid consumption of up to 2 L/d, compared to an intake of less than 1 L/d (59). Recent guidelines, including the American Urological Association (AUA) guideline on the medical management of kidney stones, as well as the German S2k guideline on the diagnosis, therapy and metaphylaxis of urolithiasis, defined a target urine volume of 2.0-2.5 L daily. Taking different routes of fluid loss into account, a daily fluid intake of up to 3 L is recommended (60, 61). A systematic review and meta-analysis, evaluating over 50 articles and 1.3 million individuals, compared different types of beverages regarding their risk for stone formation. Significant risk reduction was reported for tea, coffee, and water. Beer and other alcoholic beverages reduced the lithogenic risk by 40% and 31%, respectively (59). A higher risk for kidney stones was associated with sugar-sweetened cola and non-cola beverages, which therefore should not be recommended for metaphylaxis (39, 60).

1.3.8.2. Dietary salt

Increased sodium intake has been linked to elevated urinary calcium concentrations and a 38% increase in lithogenic risk (59). Sodium-rich diets can raise urinary pH levels, promoting the formation of certain stone types, and reduce citrate levels in the urine (3). A maximum amount of 6 g sodium chloride is recommended by recent guidelines (61). When reviewing the literature, differences in nomenclature and definitions of “salt” can be identified, and caution in interpreting the provided values has to be exerted (60, 61). Common descriptions include NaCl (sodium chloride) or table salt, and Na (sodium) where 6 g table salt / NaCl are equivalent to 2.4 g Na (9).

1.3.8.3. Protein

A diet, rich in meat and animal protein, has been shown to affect the prevalence of urinary stones significantly. A high protein diet increases the risk for urinary stones, while a low protein intake, combined with low salt, low-fat dairy and high fruit and vegetable consumption has been proposed to reduce the risk for urolithiasis (62). Several mechanisms are suggested to be responsible for the increase in lithogenic risk of high protein diets. Animal proteins, especially those that include sulphur-rich amino acids like cystine and methionine, can raise the body's acid load, which in turn causes bone resorption and calcium excretion. The abundance of purines in animal protein, may stimulate uric acid excretion and contribute to the development of uric acid stones. A high protein diet can also cause persistent metabolic acidosis, which impairs the kidneys' ability to reabsorb calcium and can accelerate stone formation. Increased proton excretion by the kidneys further promotes uric acid urolithiasis and decreases urinary concentration of citrate, a potent inhibitor of stone formation (3).

In summary, the available evidence indicates that it is crucial to regulate the consumption of dietary protein to effectively manage the risk of urolithiasis.

1.3.8.4. Diet regimen

Because our meals consist of a variety of nutrients in different quantities and the overall effect on health is likely to be depending on the interaction between each dietary element, it is more practical to provide recommendations on dietary patterns rather than focusing solely on individual nutrients (59).

While individual variations and dietary requirements should be the focus of attention in formulating dietary recommendations, general trends on the risk of urolithiasis can be seen with popular diet regimens. A ketogenic diet, which is commonly used in the treatment of therapy-refractory paediatric epilepsy, is suggested to cause hypercalciuria and therefore potentially contribute to stone development (62). In contrast to this, evidence indicates that several diets, especially the Mediterranean Diet and the DASH-style (Dietary Approach to Stop Hypertension) Diet, can reduce the risk of urolithiasis by up to 36% and 31%, respectively (59, 63). These diets contain a high proportion of dietary fibre, fruits and vegetables, all sources of the crystallisation inhibitor phytate (59, 64).

1.4. Classification

Urinary stones consist of a wide spectrum of inorganic and organic crystals combined with proteins (65). Depending on the urinary abnormalities present, they can vary in size, morphology, and chemical composition (66). Having a comprehensive understanding of the configuration of urinary stones, particularly non-calcium stones such as oxalate and uric acid stones, can provide insights into underlying medical conditions (67). By conducting a precise chemical analysis of the stones, valuable information about the factors that contribute to stone formation can be obtained.

While imaging modalities often allow a limited estimation of stone composition, more detailed information can be obtained by various methods of calculi analysis, including chemical analysis, different types of spectroscopy, X-ray diffraction, X-ray crystallography and scanning electron microscopy (68). The more comprehensive analysis of urinary calculi, provided by these methods, can help physicians predict and potentially prevent recurrence, guide therapeutic management and create an individualized treatment approach (69, 70).

Since physical properties differ among stones, specific therapeutic methods are less likely to be successful in one stone type compared to the other. Stone fragility, for example, can influence the susceptibility of different stone types to ESWL (Extracorporeal shock wave lithotripsy) (70).

1.4.1. Calcium stones

The majority of urinary stones are calcium stones, accounting for 70-90% of all stones (7). Principal subtypes of calcium stones include calcium oxalate and calcium phosphate stones. Depending on their crystalline structure, calcium oxalate stones can be further subdivided into calcium oxalate monohydrate or whewellite and calcium oxalate dihydrate, also known as weddellite. Calcium phosphate calculi include the subtypes of brushite and carbon apatite (71).

Hypercalciuria, hyperuricosuria, hyperoxaluria and hypocitraturia are the most common conditions associated with calcium stone formation (72).

Elevated urinary calcium levels can be caused by various mechanisms, such as elevated intestinal calcium absorption, increased activity or level of parathyroid hormone, defective renal calcium handling, disorders in Vitamin D metabolism, excessive bone resorption and other pathophysiologic mechanisms that are not fully understood yet (72, 73).

Hyperuricosuria is found in 40% of calcium stone formers. Elevated urinary uric acid concentrations increase the risk for calcium oxalate stones in particular (73). Caused mainly by increased dietary intake of purine-rich food, endogenous uric acid production or increased renal excretion, hyperuricosuria is contributing to calcium oxalate precipitation by the following mechanisms: 1) Monosodium urate crystals, acting as nucleation sites, allow calcium oxalate crystals to grow and aggregate on their surface, in a process known as heterogenous nucleation. 2) The colloidal effect of urate can eliminate the inhibitory effect of other urinary substances on calcium oxalate crystallisation. 3) Increased urate levels can reduce the solubility of calcium oxalate, leading to precipitation at lower concentrations of calcium oxalate in the urine (73–76).

Urinary oxalate levels over 45mg per day is called hyperoxaluria. Elevated production, increased absorption and dietary excess of oxalate contribute to this condition. Hyperoxaluria predisposes to calcium oxalate supersaturation in the urine and therefore increases the lithogenous risk in these patient groups (73, 77).

Citrate is known to decrease the likelihood of crystallization in calcium urolithiasis. Calcium phosphate and calcium oxalate supersaturation are less likely in the presence of urinary citrate. Regulated endogenously, citrate metabolism is subject to physiological and pathological variation. Systemic acid – base disturbances have been shown to influence renal citrate handling. The high intracellular or extracellular acid load can lead to a rise in renal citrate absorption and therefore reduced urinary citrate levels (73).

1.4.2. Struvite stones

Struvite urolithiasis often develops as a result of urinary tract infections (UTIs) with urease-positive microorganisms (7, 71–73). It is also known as infection-related stone disease or magnesium-ammonium-phosphate (MAP) urolithiasis, describing the major constituents of these stones (72, 78). Stone development occurs because of the ability of various bacteria, like the species Proteus, Klebsiella and Pseudomonas, to produce an enzyme that breaks up urea and generates ammonia (NH_4+) in turn. The high levels of ammonia, produced by these urease-positive organisms, result in urinary alkalisation (71). If the urinary pH levels rise above a value of about 7.2, struvite crystals, that are soluble at normal pH levels, can precipitate, leading to the formation of magnesium-ammonium-phosphate calculi (72).

There is a large tendency of infection stones to form staghorn calculi, which can rapidly grow in the renal pelvis and calyces, creating their distinct appearance. In fact, these types of stones rather remain in the kidneys, than present as ureteral stones or spontaneously pass in the urine. They often cause haematuria, renal obstruction or impaired kidney function (72, 73).

Women are more commonly affected than men, possibly due to the higher rates of urinary tract infections (72, 79). While struvite stones make up between 10% and 20% of all urinary stones, some of these calculi are initially of different compositions and become secondarily infected by urea-splitting bacteria, forming MAP stones (73). Surgical treatment of struvite stones requires special care because any stone remnants or persistent infection can lead to a rapid recurrence of the stones. In fact, recurrence rates can be up to 70% in infection stone formers (7).

1.4.3. Cystine stones

Cystine stones are rare types of urinary stones, representing around 1-2% of all stones (7). Cystine urolithiasis is caused by an inherited defect of renal tubular amino acid transporters, known as cystinuria (73). While the disease is most often passed on in an autosomal recessive pattern, autosomal dominant inheritance with incomplete penetrance is possible (71). In healthy individuals, the renal tubular transport proteins function to reabsorb dibasic amino acids, including cystine, lysine, arginine and ornithine (78). In cystinuric individuals, mutations in the two genes SLC3A1 and SLC7A9, responsible for impaired transport protein function and consequently elevated levels of amino acids in the urine, have been identified (80). Among these amino acids, cystine has the lowest solubility and therefore has the highest probability to crystallize (71). In the normal population, urinary cystine is only present in small concentrations and therefore dissolved in the urine (71, 73). Increased levels in cystinuria patients, can exceed the solubility of cystine and allow the precipitation of this substance into cystine calculi (71, 73). Cystine stones are likely to present at young age, can form large staghorn calculi and recur up to 90-100% (7, 73).

1.4.4. Uric acid stones

Uric acid lithiasis comprises a significant percentage of urinary stones. While exact numbers vary across different geographic areas, countries and populations, it is estimated that uric acid stones are responsible for 5-15% of all urolithiasis cases (7). In specific regions of the world, the percentage is even higher, as it is the case in Upper Franconia, the region in Germany, where the population of this study is based. Here it is estimated that uric acid stones make up 25-28% of all urinary stones (22, 81, 82).

Three main risk factors contributing to uric acid stone formation have been identified (73).

The first and most important factor is abnormally decreased pH levels of the urine. Uric acid exists in two chemical states, depending on the surrounding acidity. In a medium of higher pH values, the majority of uric acid becomes ionized, forming the relatively more soluble urate ion. In more acidic environments, uric acid predominantly exists in its nonionized form, which is less soluble and more likely to precipitate (73, 83, 84). If the urinary pH levels decrease from 6.0 to 5.0, the concentration of uric acid multiplies by six, demonstrating the significant role of urine acidity in uric acid urolithiasis (73).

The second factor for uric acid urolithiasis is hyperuricosuria. High levels of uric acid in the urine can be caused by elevated production, reduced excretion, or a combination of the two. Hyperuricosuria is associated with various conditions, like gout, inborn errors of metabolism, myeloproliferative diseases and medications (85, 86).

Low urinary volume is the third risk factor for the development of uric acid urolithiasis. In fact, the urinary volume contributes to supersaturation and precipitation of substances in all types of urinary stones (86).

1.5. Pathogenesis

The pathogenesis and pathomechanism of urolithiasis are multifaceted and further research is required to elude the intricacies of disease development. However, several factors and mechanisms have been shown to contribute to lithogenesis.

While exact sequences of stone formation vary among different stone types, some general concepts have been identified as contributing to urinary stone formation (66, 87).

1.5.1. Supersaturation

Supersaturation describes a physicochemical state, in which the concentration of a given substance exceeds its solubility threshold. Causative factors include low urine volume, changes in urinary pH levels, and hyperexcretion of stone-forming substances. As a consequence, aggregation and crystallization can occur (66, 87). The saturation of urine is calculated by the quotient of the concentration of a particular substance to its solubility. At a ratio of 1, urine is saturated and the activity product of substances in a saturated solution neither leads to crystallization nor to dissolution of precipitates. If the ratio falls below 1, urine is undersaturated and the substance can dissolve in its environment. If the activity product of a substance exceeds its solubility, the solution is supersaturated (7, 66, 87, 88). However, supersaturation does not necessarily lead to crystal formation. When substance concentration rises above its solubility, the solution firstly enters the state of metastable supersaturation, where a catalytic factor is required for crystal formation (7). With further rise in concentration, the fluid reaches the maximum level of metastability. Beyond this point, also known as the formation product, it is suggested that spontaneous crystallisation can occur. The solution is now in the state of unstable supersaturation (87).

1.5.2. Nucleation

Crystal nucleation is a process, in which previously soluble atoms, ions and molecules combine to form microscopic clusters, termed nuclei (66). In a supersaturated solution, these clusters can precipitate and initiate stone formation (78). Nucleation can be divided into heterogenous and homogenous nucleation. Heterogeneous nucleation describes the crystal formation and building of clusters on pre-existing particles or surfaces, including protein, cellular components and other crystals (89). In a metastable solution, nucleation can only occur heterogeneously (7). With higher levels of supersaturation, spontaneous homogenous nucleation can occur. In this process, solute molecules form clusters directly, independent of pre-existing structures and particles (87, 89).

1.5.3. Crystal and stone growth

Crystals increase in size as ions are deposited onto their surfaces. While crystal growth can happen through the movement of ions from the solution, it is suggested that the processes of aggregation or secondary nucleation inherit a more significant role in stone growth (87).

Different theories of crystal formation and growth have been investigated (78). According to the free particle theory, crystals can form independently in a solution, without the influence of pre-existing surfaces or particles. In this theory, crystal nucleation and growth occur directly from the supersaturated solution. It is suggested that solute molecules come together and form nuclei through the process of homogenous nucleation (73, 90). Nuclei further grow into crystals, through the deposition of additional solute molecules from the surrounding solution. The rapid growth of these crystals eventually leads to the formation of so-called plugs, which can block the openings of collecting ducts. When these plugs extend out of the collecting ducts, they can further promote stone formation and even unattached stones can develop (89, 91, 92).

Another concept, the fixed particle theory, suggests that pre-existing surfaces like cellular components, debris, or Randall´s plaques can initiate crystallisation and promote stone growth (66, 78, 89, 93). By heterogenous nucleation, crystals can adhere to these surfaces and form the nuclei responsible for kidney stone formation (91). Randall´s plaque formation, commonly seen in calcium urolithiasis, starts with calcium phosphate crystallization in the renal tubular basement membrane and the renal interstitium. Interstitial supersaturation and possible inflammatory processes are proposed to play a key role in this crystallization process. With further calcification, these crystals can grow into the base of the superficial papillary urothelium. Erosion of this covering urothelium exposes the plaque to the urinary environment. This allows urinary substances to heterogeneously nucleate, grow in size and ultimately form urinary stones (88, 90, 94).

1.5.4. Crystal aggregation

Some scientists suggest that the main step in the formation of calcium oxalate renal stones is the aggregation of crystals. While crystal growth is indeed involved in the process, it has been discussed that growth occurs at such a slow rate that the crystals could not grow sufficiently to block the renal tubules and be retained exclusively through this mechanism (87, 93). Conversely, aggregation is thought to have the capacity to promote the retention of crystals within the kidneys, by forming large particles, sufficient in size to cause obstruction (93).

1.5.5. Crystal retention and adhesion

Two concepts, namely crystal retention and crystal adhesion are of further importance in urinary stone formation. Crystal retention refers to the relatively slower movement of urinary crystals through the urinary system, compared to urine flow. This may be caused by several factors, including large crystal size and injury to the urothelial surface.

The adhesion of crystals to tubular cells is another example of crystal-cell interaction. This interaction can be influenced by several substances, which either promote adhesion or inhibit it (95).

1.5.6. Modulators of stone formation

Modulators, which can be divided into promoters and inhibitors of stone formation, affect the pathogenesis of urolithiasis (66). Inhibitors are substances or factors that counteract supersaturation, nucleation, crystal and stone growth, aggregation, crystal retention, adhesion and any other mechanism that contributes to stone formation (66). Inhibitory modulators include: 1) citrate, a small organic anion, that can bind calcium and prevent crystal formation and potentially inhibit aggregation and cell-crystal interactions, 2) pyrophosphate, which prevents calcium crystal formation and growth, 3) phytate, a plant-derived substance showing the ability to inhibit crystal formation, 4) magnesium, as an inhibitor of crystal aggregation and growth, 5) Osteopontin and its potential to prevent crystal growth and nucleation, 6) Tamm-Horsfall protein, which has been shown to act as a strong opposing agent on crystal aggregation, 7) urinary prothrombin fragment 1, an inhibitor in calcium oxalate stone formation (87, 96).

A variety of other substances have been identified to inherit an inhibitory role in stone formation (66, 93). It must be noted that although these substances have been categorized as inhibitors of stone formation, their effect on lithogenesis can vary among stone types and individual patients. Furthermore, some inhibitors can even act as promoters in certain circumstances and the exact role of specific inhibitors is still subject of discussion (7, 93).

Similar to inhibitors, promoters can act on several mechanisms of stone formation. High urinary concentrations of stone-forming substances like calcium, oxalate, uric acid or cystine promote stone formation. Lipids of the cell membrane, including phospholipids, glycolipids and cholesterol are suggested to have a similar effect on lithogenesis (66).

It is suggested that the imbalance of promoters and inhibitors, rather than the influence of a single modulator, is responsible for the formation of urinary stones (96, 97).

1.6. Clinical picture

The clinical presentation of urolithiasis can vary among individual patients depending on stone size, location, severity of obstruction, anatomy and other individual factors (72). Stone development and deposition in the kidney usually happen without the appearance of clinical symptoms. In most occasions, symptoms appear as the stones translocate from the kidney into the ureters and can include pain, haematuria, nausea, vomiting, disorders in micturition and bowel function and other less specific symptoms (7, 72).

Many patients experience severe pain as the disease becomes symptomatic. Depending on the characteristics, this pain can be described either as colicky or non-colicky pain or a combination of both (72). While non-colicky pain is caused by stretching of the renal capsule, colicky pain develops, when eccentric forces act on the walls of the ureters (7, 72). If a stone obstructs the ureteric lumen, smooth muscle contraction in the walls of the ureter follows. This contraction can become tonic in nature and lead to spastic contraction of the ureteric wall. Nerves, excited by this spasticity, send signals to the spinal cord and lead to pain perception (7). In contrast to intestinal colic, renal colic doesn´t necessarily exhibit the classic undulating pattern of pain (72).

The location of obstruction and tissue irritation influences pain localization and character. Calculi, located in the renal calyces often cause dull flank or back pain with varying severity. Large stones in the renal pelvis can cause obstruction, at the site where ureters originate from the kidneys, and lead to severe pain at the costovertebral angle. Sharp pain in the costovertebral angle or flank is experienced in cases of proximal and mid-ureter calculi. Its severity depends on the level of obstruction and movement along the ureter. Stones located in the middle section of the ureter can cause anteroinferior pain projection to the middle and lower aspects of the abdomen. If the lower section of the ureter is affected, pain is likely to radiate to the inguinal or genital region (72).
Caution has to be taken to not confuse the pain caused by the stone disease with other diseases that can cause symptoms at similar locations (72). Vegetative symptoms, such as nausea and vomiting, can accompany the pain caused by urinary stones and patients often appear restless while trying to alleviate the symptoms by movement and changes in position (7, 72). Haematuria can also occur with urolithiasis. This can present either as gross haematuria or microhaematuria, detected by urine analysis. As stated earlier, urolithiasis can develop through urinary tract infection, or infection can develop with pre-existing stones. In such cases, it is not surprising to detect signs of inflammation, like fever. If fever or other symptoms of urosepsis are found, urgent treatment is often indicated (72).

1.7. Diagnosis

Diagnostic evaluation of patients, suspected of urolithiasis, is required to confirm the presence of the disease and guide treatment decisions. Diagnostic work-up includes obtaining the patient history, physical examination, laboratory diagnostics and imaging.

Exact diagnostic guidelines vary across countries and specific investigations may be necessary for individual patients (7, 60, 98).

1.7.1. Patient history

Obtaining a thorough patient history is an important part of the diagnostic evaluation. By doing so, physicians can acquire information to potentially rule out any other disease, responsible for the patient´s condition. In addition, identification of predisposing conditions and risk factors can lead towards the correct diagnosis, whereas pain assessment can indicate possible sites of stone location (7, 60, 89, 98).

1.7.2. Physical examination

A physical examination is a valuable tool in patient assessment, as it can provide further insight into the patient´s physical status. Pain can be assessed in detail and specific findings can differentiate renal colic from other disorders, such as peritonitis. Examination of vital parameters or the finding of vegetative symptoms can help physicians to identify urgent or emergent situations, which would require prompt treatment. Results from the physical examination can additionally justify further diagnostic or therapeutic procedures (7, 72, 98, 99).

1.7.3. Laboratory diagnostics

Serum laboratory tests should encompass electrolytes, calcium, bicarbonate, creatinine, uric acid, and C-reactive protein, which can provide insights into potential underlying medical conditions linked to urolithiasis. A complete blood count can also be helpful in disease assessment. Urine dipstick analysis and microscopic examination are included in the comprehensive urine analysis. This allows for the measurement of urine pH, detection of indicators of infection, and identification of specific crystals that could be suggestive of the type of stone present. In patients with presumed urinary tract infections or those experiencing recurrent urinary tract infections, urine culture should be analysed to identify the causative bacteria and guide appropriate treatment (7, 98–100).

1.7.4. Imaging modalities

Different methods of diagnostic imaging can be useful in detection or exclusion of urinary stones and the determination of stone location, size, and characteristics. Based on these findings, therapeutic decision-making can be facilitated. The different imaging procedures vary in sensitivity and specificity, radiation exposure, associated costs, and other factors. The “Deutsche Gesellschaft für Urology” (German Society for Urology) provides recommendations on ultrasound (US), X-ray, computed tomography (CT), magnet resonance imaging (MRI) and ante- and retrograde pyelography.

Diagnostic guidelines include the so-called ALARA principle, which stands for "As Low As Reasonably Achievable". It is a fundamental concept in diagnostic imaging that aims to minimize radiation exposure to patients while still obtaining the necessary diagnostic information. This principle is especially important in diagnostics for urolithiasis, because repeated imaging studies may be necessary for diagnosis, treatment planning, and follow-up (7, 98).

1.7.4.1. Ultrasound

The German Society of Urology recommends ultrasonography as diagnostic method of choice. As a safe and efficient tool, ultrasound is also useful in emergency situations, where quick assessment is advantageous. Ultrasonography allows the visualisation of urinary stones in the bladder and kidneys. For aspects of the urinary tract that can´t be directly visualized, detection of dilated renal calyces can indicate the presence of obstruction. The sensitivity of sonography can reach up to 93% and the specificity is 95-100% (7, 98).

1.7.4.2. Plain radiography

Plain X-ray studies of the kidney ureter and bladder (KUB), to detect radiopaque urinary stones, were frequently used in the past. The advantages of this method are the broad availability and low costs. However, due to its low sensitivity and inability to detect radiolucent calculi, its role nowadays is limited (99, 101).

1.7.4.3. Intravenous urography

Historically, intravenous pyelography or urography was widely used for detection of urinary calculi. Intravenous Urography (IVU) involves the injection of a contrast agent followed by X-ray imaging and can help identify the presence, location, and size of stones. However, IVU has been largely replaced by superior diagnostic methods, such as the more accurate CT and less invasive ultrasound. IVU is indicated in case a CT is not available, for preoperative evaluation of anatomical structures and for detection of cancerous and necrotic lesions. Absolute contraindications include renal insufficiency, hyperthyroidism and contrast agent allergy, while renal colic is to be seen as a relative contraindication (7, 98, 102).

1.7.4.4. Computed tomography

Computed tomography (CT) has the highest specificity and sensitivity with values of 92-100% and 94-100% respectively. Alongside with US, CT is considered a standard diagnostic method in management of urolithiasis. Its ability to accurately detect radiopaque as well as radiolucent stones, with exception of indinavir and matrix stones makes it superior to other diagnostic methods, such as plain radiography. The stone composition can be estimated by evaluating the density of the stones, measured in Hounsfield – units. High radiation exposure is a known side effect of CT – imaging. Even low–dose CTs with only 0.97–1.9 mSv exposure, compared to native CT imaging with 4.5–5 mSv, cause a significantly higher radiation exposure than plain radiography (approximately 0.5 mSv) for example (7, 98).

1.7.4.5. Magnet resonance imaging

Magnet resonance imaging (MRI) mainly identifies urinary filling defects or dilatations along the urinary tract. It often fails to directly visualize urinary stones and is therefore only of minor importance in the diagnosis of urolithiasis. However, it can be used as imaging modality in cases where radiation exposure is contraindicated or undesirable, such as pregnancy or in paediatric patients. One particular advantage of MRI imaging is its capability to detect Indinavir stones. Therefore, it can be used in the diagnostic work-up of Human Immunodeficiency Virus (HIV) patients under Indinavir–therapy, who show symptoms of urinary obstruction or colic (98, 101).

1.7.4.6. Ante- and retrograde pyelography

In antegrade or retrograde pyelography a contrast agent is directly introduced into the urinary system by nephrostomy or via cystoscope. This method can be used in patients with contrast agent allergy and allows contrast-enhanced imaging independent of renal function (7, 98).

1.8. Therapy

The primary goal of therapy is to relieve symptoms, eliminate or fragment the stones, prevent complications, and reduce the risk of stone recurrence. Treatment depends largely on disease characteristics, including stone size, location, composition, and symptoms present, which makes an individualized approach inevitable. Based on individual findings, several treatment options are available (103, 104).

1.8.1. Conservative therapy

Most urinary calculi are small enough to pass spontaneously and the decision to treat the disease conservatively is based on the likelihood of a urinary stone to do so. Together with the location of stones, stone size influences this likelihood markedly. Calculi with a size of 4 mm or smaller have a probability of up to 95% to pass in the urine within 40 days. With an increase in stone size, this percentage decreases significantly and interventional treatment may be necessary (98).

1.8.1.1. Observation

Small stones with a size of up to 7 mm, that are asymptomatic or causing minimal discomfort, may be managed conservatively with close monitoring. Adequate hydration, pain management, and lifestyle modifications, such as dietary adaptions, may be recommended to promote stone passage (73, 98, 103).

1.8.1.2. Medical therapy

Pharmacotherapy can include analgesia, chemolysis and medical expulsive therapy (MET). Exact recommendations for analgesia can vary among countries and guidelines. In general, non-opioid analgesics and NSAIDs are first-line agents to reduce pain. Escalation in analgesia may include opioids, although the use of these agents is not undisputed due to their spasmogenic effect (7, 89, 98, 103).

Medical expulsive therapy may effectively promote stone passage and reduce the total analgesic dose required for pain relief by accelerating the process of stone excretion. Alpha-blockers are the mainstay of treatment in MET. Beneficial effects are also seen with calcium channel blockers, while the role of Phosphodiesterase 5 -inhibitors and corticosteroids remains disputed (98).

Under specific circumstances, pharmacologic dissolution of urinary stones can be attempted. This includes the oral chemolysis with sodium- or potassium bicarbonate and potassium citrate for uric acid urolithiasis in particular, which is mainly achieved by alkalisation of urine. Percutaneous chemolysis is generally possible, but due to the associated risks and long duration of treatment, this method is not used broadly anymore (72, 98, 103).

1.8.2. Interventional therapy

Active therapy includes interventional procedures, such as Extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PNL), Ureterorenoscopy (URS) and laparoscopic and open surgery. Indications depend on stone size, location-associated symptoms and grade of obstruction, and stone composition can direct physicians towards the intervention of choice (7, 89, 98).

1.8.2.1. Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) is a non-invasive method of stone fragmentation. Electrohydraulic, electromagnetic, and piezoelectric mechanisms create a high-energy acoustic wave which, when directed towards a stone, can break it apart. The small stone fragments, created by this procedure, can consecutively be excreted via the urine. ESWL can be used with most types of stones, but treatment success is influenced by the location of the calculus and stone density.

Side effects include renal and neighbouring organ damage, urinary tract infection and stone recurrence. The German Society of Urology recommends postinterventional imaging studies and adjunctive MET therapy to facilitate stone passage. For very large stones (over 10mm) ESWL can be less effective and other methods of stone removal may be indicated (7, 89, 98, 103).

1.8.2.2. Ureterorenoscopy

Ureterorenoscopy (URS) allows retrograde transurethral access of an endoscope to the kidneys and ureter, through which urinary stones can be visualized and further instruments can be introduced into the urinary system. The endoscope, also referred to as ureteroscope, can either be flexible or rigid, where the former is mainly used for distal stones and the latter is commonly used for proximal calculi. With the help of different devices for stone disintegration, such as the Ho: YAG laser, intracorporeal lithotripsy can be performed and stone fragments can be extracted. While some studies suggest a better stone-free rate for URS compared to ESWL, URS is also associated with higher complications and longer hospitalization (89).

1.8.2.3. Percutaneous nephrolithotomy

Percutaneous nephrolithotomy (PNL) is the method of choice for removal of large renal calculi, especially in the renal pelvis and lower renal calyces. After imaging-guided percutaneous access, a flexible or rigid endoscope is placed in the renal pelvis through which stone disintegration can be performed and fragments can be recovered. Intraoperative complications, like bleeding or other circumstances that limit intrarenal visibility, may make repetitive sessions necessary. Its higher efficacy (up to 80-90% stone-free rate), compared to ESWL or URS, is at the expense of higher invasiveness. Main contraindications include pregnancy, UTIs and bleeding diathesis (89, 101).

1.8.2.4. Laparoscopic and open surgery

Laparoscopic and especially open surgery procedures are less common methods of stone removal. Open surgery was often performed in the past, but modern, less invasive procedures widely replaced this approach, due to their better risk profile and lower costs. However, these invasive techniques still have their value in individual cases, where anatomical conditions complicate endoscopic methods or the success of other interventions is highly unlikely (98, 103).

1.8.3. Metaphylaxis

Metaphylaxis refers to the pharmacological, dietary and lifestyle adaptions in urinary stone formers, in order to prevent stone recurrence. Stone analysis and risk stratification are prerequisites for metaphylactic recommendations and successful recurrence prevention. Recommended methods of stone analysis include infrared spectroscopy and X-ray diffraction, as well as polarisation microscopy, which can produce similar results (98, 103).

After a stone episode, patients are categorized according to their risk of stone recurrence. Depending on the stone composition and basic evaluation, which includes patient history, physical examination, imaging and laboratory diagnostics, stone formers are either assigned to the high-risk group or the low-risk group. Patients with a low-risk profile receive recommendations for general metaphylaxis, while management of patients with high risk of stone recurrence should include specific diagnostic evaluation and extended metaphylactic measures (98, 103).

1.8.3.1. General metaphylaxis

General metaphylactic recommendations are made for both groups of stone formers. The most important general measure is the dilution of urine. A target volume of 2 – 2.5L of urine per day is recommended, to adequately reduce the concentration of stone-forming substances in the urinary system. Advice to consume a balanced diet, rich in fruit and vegetable and with limited amounts of salt, protein, calcium, and oxalate is further given. Physical activity, a normal BMI and stress avoidance are also included in the general metaphylactic recommendations (98, 103).

1.8.3.2. Specific metaphylaxis

Prevention of stone recurrence includes, besides general prophylactic measures, specific metaphylactic actions. Individualized stone prevention strategies not only involve the extended diagnostic evaluation of stone characteristics, risk factors, metabolic imbalances and underlying diseases, in order to identify causative conditions but also targets them with pharmacologic, dietary and behavioural measures (73, 98, 103).

1.8.3.3. Specific metaphylaxis in uric acid urolithiasis

This paragraph is aimed to further elude the principle of specific metaphylaxis, according to the guidelines of the German Society of Urology and the European Association of Urology, using uric acid stones as an example.

The presence of uric acid stones assigns a patient to the group of high-risk stone formers, hence further diagnostics and preventive measures are indicated.

Uric acid stones usually form when urine pH levels are low, in patients with hyperuricosuria, or both. Reduced urine volume can lead to solute concentration and can therefore also contribute to stone formation. Extended diagnostics aim to identify these conditions and the underlying disorders causing them. Hyperuricosuria can be detected by analysis of 24-hour urine samples. Increased levels of uric acid in the urine can be due to an unbalanced diet, gout, inborn errors of metabolism, myeloproliferative disorders, tumor lysis syndrome or drugs. Low urinary pH values can be caused by reduced ammonia excretion, increased endogenous acid production, increased dietary acid uptake or alkali loss. If such conditions are identified, the treating physician or urologist has then the opportunity to give specific dietary recommendations, such as reduced protein or increased fluid intake. Furthermore, pharmacologic treatment can be initiated, including alkaline citrate or sodium bicarbonate to correct urinary pH levels, or allopurinol to reduce uric acid levels (98, 103).

1.9. Potential influence of calcium

A study conducted by Strohmaier, Hörmann, and Schubert (2015) examined the relationship between renal papillary calcification and the recurrence of uric acid urolithiasis in a population sample of 30 patients with uric acid urolithiasis. Investigating papillary calcification as a potential prognostic factor for uric acid stone disease, the analysis did not result in significant evidence to support this role. However, their statistical investigation revealed a significant correlation between serum calcium levels and the number of stone episodes in the studied population (105). This finding prompted the current research, which aims to thoroughly assess the impact of calcium metabolism on the recurrence of uric acid stones by comprehensive statistical analysis. The study seeks to achieve valuable insights into the understanding of variables and factors that could contribute to the recurrence of uric acid urolithiasis.

2. OBJECTIVES OF RESEARCH

2.1. Aim of study

By analyzing historical data, the study aims to explore potential associations between calcium-related factors and urolithiasis recurrence. Furthermore, this study aims to identify any other variables, potentially contributing to the recurrence of uric acid urolithiasis.

2.2. Hypothesis

Imbalances in calcium metabolism contribute to a higher recurrence of uric acid urolithiasis.

3. PATIENTS AND METHODS

3.1. Study design

The present study uses a retrospective, observational study design to investigate the relationship between calcium metabolism and recurrence of uric acid urolithiasis. In this design, data is collected from pre-existing patient records, eliminating the need for prospective data collection or interventions. The study incorporated a diverse set of variables to investigate the influence of calcium metabolism on the recurrence of uric acid urolithiasis. The dependent variable considered is “stone episodes”. Independent variables included are age (years), gender (male/female), BMI (kg/m2), Diabetes (yes/no), systolic and diastolic blood pressure (mmHg), serum creatinine (mg/dL), serum sodium (mEq/L), serum potassium (mmol/L), serum uric acid (mg/dL), serum glucose (mg/dL), serum calcium (mEq/L), urinary calcium (mmol/24h) urinary pH, urine volume (L), urinary uric acid (mmol/24h), urinary citrate (g/24h), urinary urea (mmol/24h), urinary ammonia (mmol/d) and urine creatinine (mg/dL). Variables associated with calcium metabolism were defined, including serum calcium, urinary calcium, urinary citrate, and urinary pH.

3.2. Setting

The study was conducted in the Urology Department of the REGIOMED – Klinikum Coburg, in Upper Franconia, Germany. The region served by this department covers approximately 500,000 residents, accounting for half of the population of Upper Franconia.

3.3. Ethical approval

The present study was conducted in compliance with ethical guidelines and principles to ensure the protection of participants' rights, privacy, and well-being. Ethical approval for this research was obtained from the Institutional Review Board (IRB) of the Medical School Regiomed Coburg. The IRB thoroughly reviewed the research project and confirmed its adherence to ethical standards. By performing only retrospective analysis, no clinical intervention was performed, and further ethical approval was therefore not necessary.

3.4. Participants and patient data

The study used patient data from the uric acid stone register of the Urology department of the REGIOMED Hospital Coburg, encompassing 496 patient records from the period of 2008 to 2021. Patient data were coded and anonymized to ensure patient confidentiality. The database includes all patients with presence of pure uric acid urinary stones, which were treated at the REGIOMED hospital Coburg and underwent complete metabolic evaluation.

The stone composition was determined by polarization microscopy and X-ray diffraction. Metabolic assessment was performed within one month after spontaneous stone passage or surgical removal.

The uric acid stone register was then evaluated for missing values and errors in documentation and corresponding patients (n=115) were removed from the study. From the initial 496 patients, a total of 381 patients were included for further analysis.

3.5. Variables

Arterial blood pressure measurement was performed in accordance with the World Hypertension League with the patients having rested five minutes before measurement. Urinary pH analysis was done during a three-day assessment, with one measurement in the morning (fasting), at noon (post-prandial) and in the evening (postprandial), respectively. Urine dipsticks with a 0.1 pH scale were used (Madaus GmbH, Cologne, Germany). Blood analysis was performed for creatinine (Jaffé reaction, Dade Behring Marburg, Germany), calcium (indirect ion-sensitive electrode), potassium (atomic absorption), glucose (postprandial; hexokinase-glucose-6-phosphate dehydrogenase method, Flex™ Siemens Healthcare Diagnostics Newark, DE, USA) and uric acid (modified uricase method, Dade Behring Marburg, Germany).

To measure citrate excretion, 24h urine was collected (citrate lyase method, Boehringer Mannheim, Germany). Further 24h urine analysis included calcium (indirect ion-sensitive electrode), uric acid (modified uricase method, Dade Behring Marburg, Germany), ammonia (modified glutamate dehydrogenase method using NADPH, test kit Ammonia Flex™, Dade Int., Newark, DE, USA) and urea (urease-lutamate dehydrogenase, Dade Behring Marburg, Germany).

3.6. Statistics

In this study, the statistical analyses were performed using IBM SPSS Statistics software (Version 29.0.1.0, IBM Corp., Armonk, NY, USA). The significance level of $P<0.05$ was set.

A comprehensive set of statistical tests was employed to explore the relationship between calcium metabolism and the recurrence of uric acid urolithiasis. The data were initially subjected to descriptive statistics to gain insights into the characteristics of the variables.

For categorical variables, including gender and diabetes, frequencies and percentages were calculated to evaluate the distribution of these factors within the study sample. For numerical variables, mean, median and mode were calculated for further identification of characteristics and central tendencies.

To investigate the associations between the continuous numerical variable, stone episodes, and other variables, Spearman correlation analysis was conducted. This non-parametric test was chosen due to the non-normal distribution of stone episodes and the other variables.

To facilitate further assessment of the influence of various variables on the frequency of stone recurrence, stone episodes were categorized into three groups: non-recurrent stone formers (Group 1: one episode), recurrent stone formers (Group 2: two or three episodes), and frequent recurrent stone formers (Group 3: four or more episodes). Subsequently, an ordinal logistic regression was applied, including the categorized stone episodes and other correlating parameters. A stepwise approach was carried out to include significant variables and exclude non-significant ones, ensuring a robust regression model and reducing bias. The model was furthermore assessed for goodness of fit. For significant variables of the ordinal logistic regression model, we additionally conducted a Kruskall – Wallis test to investigate differences in the median values of the significant variables among the three groups and performed pairwise comparison tests for further insight. The test of Parallel Lines was conducted to assess the assumption of parallelism in the final ordinal logistic regression model. This test aimed to determine whether the effects of these predictors on the cumulative log odds of the different stone episode groups were consistent.

4. RESULTS

4.1. Demographic data

From the initial dataset, a total of 381 patients were included in the analysis. There were no missing values reported for the variables of interest.

Gender distribution was asymmetric, with 76.9% (n = 293) male patients and 23.1% (n = 88) female patients. A total of 138 patients were reported to have a history of diabetes without further classification of the disease, representing 36.2% of the study population, while the rest of the patients (63.8%) were reported to be diabetes-free. The mean age was 62.52 years with a median of 63.00 years and the most frequently observed age (mode) was 73 years. Further investigation of age distribution revealed a slightly negative skewness of -0.149, indicating a leftward tail. Frequencies of stone episodes ranged from 1 to 25 episodes with a mean of 2.34 episodes, a median of 2 episodes and a mode of 1 episode (Figure 1).

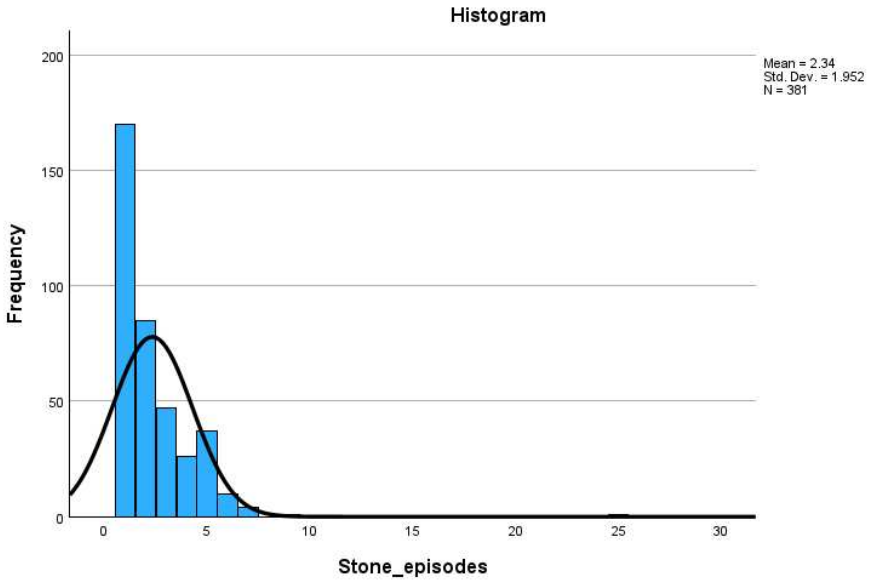

Figure 1. Distribution of stone episodes

As shown in Table 1, 170 patients with just one stone episode were identified, making up 44.6% of the study population. 22.3% of patients (n=85) had two episodes, while 12.3% had three episodes. 6.8% of all patients (n=26) had four episodes, 9.7% (n=37) had five episodes, and 2.6% (n=10) had 6 episodes. Only a few patients had seven or more episodes, with 1% (n=4) having experienced seven episodes, 0.3% (n=1) having nine episodes and 0.3% (n=1) having 25 episodes. The distribution of stone episodes furthermore showed highly positive skewness, with a skewness value of 4.710 and a kurtosis value of 47.054, indicating a leptokurtic distribution.

Table 1. Frequencies of stone episodes

c		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	170	44.6	44.6	44.6
	2	85	22.3	22.3	66.9
	3	47	12.3	12.3	79.3
	4	26	6.8	6.8	86.1
	5	37	9.7	9.7	95.8
	6	10	2.6	2.6	98.4
	7	4	1.0	1.0	99.5
	9	1	0.3	0.3	99.7
	25	1	0.3	0.3	100.0
	Total	381	100.0	100.0	

Further distributive statistics of body mass index (BMI), systolic and diastolic blood pressure (RRs & RRd), serum creatinine (S-Crea), serum sodium (S-Na), serum potassium (S-K), serum calcium (S-Ca), serum uric acid (S-UA), serum glucose (S-Gluc), urine pH (U-pH), urine volume (U-Vol), urine creatinine (U-Crea), urine calcium (U-Ca), urine uric acid (U-UA), urine citrate (U-Citrate), urine urea (U-Urea) and urine ammonia (U-Ammon.) can be found in Table 2. Except for age, diastolic blood pressure, serum potassium and urine pH, most variables had relatively high skewness values, indicating a non-symmetric distribution.

Table 2. Distribution of variables

	N					Std.		Kurtosis
	Valid	Missing	Mean	Median	Mode	Deviation	Skewness	
Age	381	0	62.52	63.00	73	12.380	-0.149	-0.493
BMI (kg/m^2)	381	0	31.510	30.200	30.0	6.1042	1.266	2.946
Stone_episodes	381	0	2.34	2.00	1	1.952	4.710	47.054
RRs (mmHg)	381	0	141.98	140.00	140	15.068	0.370	0.043
RRd (mmHg)	381	0	82.73	80.00	80	8.219	0.121	0.193
S-Crea (mg/dL)	381	0	1.234	1.200	1.1	0.3983	2.161	11.320
S-Na (mEq/L)	381	0	139.32	140.00	140	3.415	-0.592	1.330
S-K (mmol/L)	381	0	4.217	4.200	4.2	0.4152	-0.115	0.417
S-Ca (mEq/L)	381	0	4.647	4.700	4.7	0.2804	-0.378	1.413
S-UA (mg/dL)	381	0	6.827	6.900	7.0	1.7627	0.415	0.661
S-Gluc (mg/dL)	381	0	141.37	123.00	105[a]	58.840	2.173	6.889
U-pH	381	0	5.885	5.900	5.9	0.2543	-0.132	4.636
U-Vol (L)	381	0	2.417	2.200	2.0	1.1829	0.982	1.191
U-Crea (mg/dL)	381	0	14.0414	13.3000	17.00	5.81381	0.642	0.554
U-Ca (mmol/24h)	381	0	3.085	2.400	1.2	2.4312	1.986	6.928
U-UA (mmol/24h)	381	0	3.5338	3.3000	2.90	1.62647	1.036	1.816
U-Citrate (g/24h)	381	0	1.4660	1.1000	0.10	1.30377	1.564	3.150
U-Urea (mmol/24h)	381	0	363.64	350.00	306[a]	160.602	0.788	1.189
U-Ammon. (mmol/24h)	381	0	37.977	33.000	27.0[a]	22.0147	1.328	2.395

BMI: Body Mass Index, RRd: Diastolic blood pressure, RRs: Systolic blood pressure, S-Ca: Serum calcium, S-Crea: Serum creatinine, S-Gluc: Serum glucose, S-K: Serum potassium, S-Na: Serum sodium, S-UA: Serum uric acid, U-Ammon.: Urine ammonia, U-Ca: Urine calcium, U-Citrate: Urine citrate, U-Crea: Urine creatinine, U-pH: Urine pH, U-UA: Urine uric acid, U-Urea: Urine urea, U-Vol: Urine volume

a. Multiple modes exist. The smallest value is shown

4.2. Inductive statistics

The relationship between stone episodes and various demographic and clinical variables was explored using Spearman´s rank correlation coefficient. The statistically significant results of the correlation analysis are shown in Table 3.

Table 3. Spearman´s correlations

			Gender	Age	S-K (mmol/L)	U-Ca (mmol/24h)	U-Crea (mg/dL)
Spearman's rho	Stone_episodes	r	-0.111*	-0.120*	0.132**	0.101*	0.106*
		p	0.030	0.019	0.010	0.049	0.038
		n	381	381	381	381	381

S-K: Serum potassium, U-Ca: Urine calcium, U-Crea: Urine creatinine
*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Age showed a weak negative correlation with stone episodes (r = -0.120, *P* = 0.019), indicating that as age increased, there was a slight tendency for a lower number of stone episodes. A similar correlation was identified between gender and stone episodes (r = -0.111, *P* = 0.030), which suggests a mild tendency towards a higher prevalence of stone episodes in males. For the correlation between serum potassium and stone episodes, Spearman´s coefficient was calculated to be 0.132 with a *P*-value of 0.010. Urine creatinine exhibited a slightly positive correlation with stone episodes (r = 0.106) with a *P*-value of 0.038. Furthermore, a weak positive correlation between urine calcium and stone episodes was discovered (r = 0.101, *P* = 0.049)
Serum calcium showed a weak positive correlation with stone episodes, although statistical significance was not met (*P* = 0.101).

In summary, Spearman´s correlation analysis revealed weak but statistically significant associations between age, gender, urine creatinine, urine calcium and the number of stone episodes. For all other variables, the significance criteria were not met.

For further investigation, the population was categorized into three groups according to the frequency of stone episodes. The distribution of patients across these groups is presented in Table 4.

Table 4. Patient distribution across groups of stone episodes

Groups	Frequency	Per cent	Valid Percent	Cumulative Percent
1.00	170	44.6	44.6	44.6
2.00	132	34.6	34.6	79.3
3.00	79	20.7	20.7	100.0
Total	381	100.0	100.0	

Group 1 consisted of 170 patients without stone recurrence (just one stone episode) representing 44.6% of the total sample. Group 2 included patients with two and three episodes, which was observed in 132 patients or 34.6% of all patients. Group 3 comprised frequent stone formers with four or more stone episodes including 79 patients, making up 20.7% of the study population.

The three groups served as the dependent variable in the following ordinal logistic regression analysis.

To create the ordinal logistic regression model, initial variables were chosen according to the results of Spearman´s correlation analysis. Variables with statistically significant correlations (gender, age, serum potassium, urine creatinine and urine calcium) were included in the first regression model and the results are shown in Table 5.

Table 5. Initial ordinal logistic regression model

		Estimate	Std. Error	Wald	Sig.
Threshold	[Group = 1.00]	1.677	1.204	1.940	0.164
	[Group = 2.00]	3.290	1.213	7.356	0.007
Location	Age	-0.017	0.009	3.299	0.069
	S-K (mmol/L)	0.589	0.241	5.979	0.014
	U-Crea (mg/dL)	0.006	0.022	0.081	0.776
	U-Ca (mmol/24h)	0.033	0.045	0.552	0.457
	[Gender=Male]	0.350	0.259	1.825	0.177
	[Gender=Female]	.	.	.	.

S-K: Serum potassium, U-Ca: Urine calcium, U-Crea: Urine creatinine

Performing backward selection, the primary results were assessed for statistical significance, and variables without statistical significance were removed. This included stepwise removal of the variables urine creatinine and urine calcium. In the first regression model, serum potassium was the only independent variable with statistical significance (P = 0.014). Urine creatinine had a significance value of 0.776 and was therefore removed from the initial model. In the second regression model (Table 6), which investigated the dependent variable and the independent variables age, gender, serum potassium and urine calcium, age reached the level of statistical significance with P = 0.035 in addition to serum potassium with P = 0.015.

Table 6. Second ordinal logistic regression model

		Estimate	Std. Error	Wald	Sig.
Threshold	[Group = 1.00]	1.553	1.131	1.884	0.170
	[Group = 2.00]	3.165	1.140	7.707	0.006
Location	Age	-0.018	0.008	4.453	0.035
	S-K (mmol/L)	0.588	0.241	5.965	0.015
	U-Ca (mmol/24h)	0.037	0.042	0.778	0.378
	[Gender=Male]	0.380	0.239	2.531	0.112
	[Gender=Female]	.	.	.	.

S-K: Serum potassium, U-Ca: Urine calcium

In this second regression model, urine calcium was identified to be the least significant (significance value 0.378) and was therefore removed from the model.
The final model, shown in Table 7, included the dependent variable in addition to the independent variables age, gender and serum potassium.

Table 7. Final ordinal logistic regression model

		Estimate	Std. Error	Wald	Sig.
Threshold	[Group = 1.00]	1.288	1.095	1.382	0.240
	[Group = 2.00]	2.897	1.104	6.892	0.009
Location	Age	-0.020	0.008	6.562	0.010
	S-K (mmol/L)	0.587	0.241	5.940	0.015
	[Gender=Male]	0.399	0.238	2.815	0.093
	[Gender=Female]	.	.	.	.

Serum potassium levels showed a coefficient estimate of 0.587 with a significance value of 0.015 indicating that higher levels of serum potassium were associated with increased log odds of experiencing greater numbers of stone episodes. Age exhibited a coefficient of -0.020 ($P = 0.010$), indicating a significant negative effect of age on stone episodes. Gender, specifically in males, demonstrated a coefficient of 0.399 with a *P*-value of 0.093, representing non-significant results. The coefficient for females was set to zero due to redundancy.

Further assessment of the regression model included evaluating model fit, using the -2 Log Likelihood and Chi-Square tests, as well as conducting Pearson and Deviance goodness-of-fit Chi-Square tests. Results are shown in Table 8.

Table 8. Model Fitting and Goodness-of-Fit statistics

Model Fitting Information

Model	-2 Log Likelihood	Chi-Square	Sig.
Intercept Only	745.604		
Final	728.867	16.738	<0.001

Goodness-of-Fit

	Chi-Square	df	Sig.
Pearson	638.918	627	0.362
Deviance	676.840	627	0.082

Link function: Logit.

Comparing the intercept-only model to the final regression model, there is a notable reduction in the -2 Log Likelihood value from 745.604 to 728.867. This reduction corresponds to a Chi-Square statistic of 16.738, with a *P*-value of less than 0.001. These results suggest that the predictor variables integrated into the final model significantly contribute to explaining the variation in the recurrence of uric acid urolithiasis.

Two Chi-Square tests, specifically the Pearson Chi-Square and the Deviance Chi-Square tests were conducted in the goodness-of-fit analysis. For the Pearson test, the Chi-Square statistic was 638.918 with $P = 0.362$. The Deviance test yielded a Chi-Square statistic of 676.840 with a *P*-value of 0.082, also not reaching statistical significance. These non-significant *P*–values collectively support model fit.

We then performed the test of Parallel lines for our regression model.

The null hypothesis of the test of Parallel Lines asserted that the location parameters (slope coefficients) of the predictors are equal across all response categories, indicating that the relationships between the predictors and the outcome variable are parallel. The alternative hypothesis considered non-parallel relationships.

The results of the test of Parallel Lines (Table 9) indicated that the -2 Log Likelihood value decreased from 728.867 under the null hypothesis to 727.929 under the general hypothesis, resulting in a Chi-Square statistic of 0.938. The corresponding significance level for this Chi-Square statistic was 0.816. This suggests that the assumption of parallel lines is met, and the effects of the predictor variables on the cumulative log odds are consistent across all categories of the ordinal outcome variable.

Table 9. Test of parallel lines

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Null Hypothesis	728.867			
General	727.929	0.938	3	0.816

The null hypothesis states that the location parameters (slope coefficients) are the same across response categories.
Link function: Logit.

We further conducted Kruskal-Wallis analysis and pairwise comparisons of the significant variables age and serum potassium to explore differences in the medians among the groups of stone episodes. The Kruskal-Wallis statistic was calculated as 5.977 with a *P*-value of 0.050, indicating non-significant results. The pairwise comparison of age is shown in Table 10. Only the median age of group 3 compared to the median age of group 1 showed a statistically significant difference with a *P*-value of 0.048, after applying the Bonferroni correction for multiple tests, as visualized in Figure 2.

Table 10: Pairwise comparisons of age across grouped stone episodes

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
3.00-2.00	19.569	15.660	1.250	0.211	0.634
3.00-1.00	36.083	14.990	2.407	0.016	0.048
2.00-1.00	16.514	12.771	1.293	0.196	0.588

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.
a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

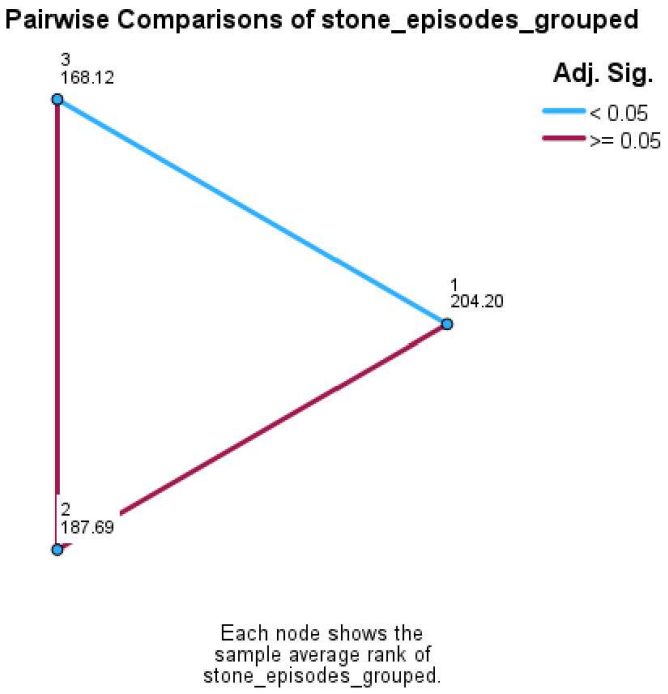

Figure 2. Age across grouped stone episodes

The Kruskal-Wallis test for serum potassium resulted in a test statistic of 7.927 with a *P*-value of 0.019, indicating a significant difference in serum potassium levels across the groups of stone episodes. Similar to age, the pairwise comparison (Table 11) only revealed significant differences in the serum potassium medians between group 3 and group 1, as seen in Figure 3

Table 11. Pairwise comparisons of serum potassium across grouped stone episodes

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
1.00-2.00	-22.654	12.738	-1.778	0.075	0.226
1.00-3.00	-40.220	14.951	-2.690	0.007	0.021
2.00-3.00	-17.566	15.619	-1.125	0.261	0.782

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

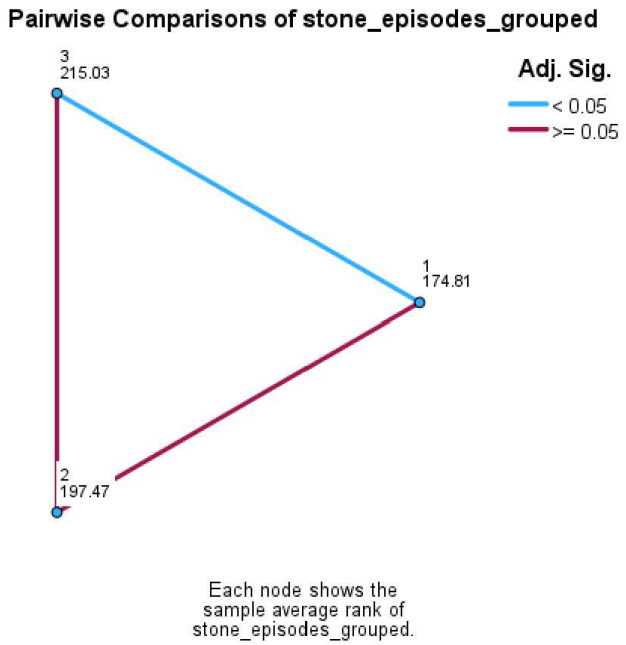

Figure 3. Serum Potassium across grouped Stone Episodes

5. DISCUSSION

5.1. Key results

Our analysis of 381 urolithiasis patients revealed a considerable male predominance among stone formers, concurring with the current literature. Among the defined variables for calcium, only urine calcium (U-Ca) exhibited a significant (positive) correlation with the number of stone episodes, although the correlation was weak. When included in the ordinal logistic regression model, however, urine calcium did not achieve statistical significance. There were also weak negative associations between stone episodes and gender, as well as urine creatinine. However, both variables did not reach statistical significance in the regression model. Age showed a weak, but significant negative correlation with stone episodes. In the regression model, age maintained its significance and demonstrated a negative estimate. Serum potassium positively correlated with the number of stone episodes and remained significant in the ordinal logistic regression model. Further assessment of the medians of the variables age and serum potassium among the groups of stone episodes revealed significant differences between groups 3 and 1 for both variables, but not between group 1 and group 2, or group 2 and group 3.

To summarize, five variables of the dataset, including gender, age, serum potassium, urine calcium and urine creatinine correlated significantly with the number of stone episodes. Among these variables, only urine calcium was defined as playing a role in calcium metabolism. In the ordinal logistic regression model, significant associations of the variables age and serum potassium with the groups of stone episodes could be identified. However, none of the variables for calcium metabolism met the significance threshold to be included in the final regression model.

5.2. Limitations

Several limitations to the study were identified. The study was conducted as a single-center observational study within the Regiomed Klinikum Coburg, which served as the primary source of patient data. This geographic restriction could potentially limit the generalizability of the findings to broader and more diverse populations with different healthcare systems, socioeconomic conditions, and environmental influences. Furthermore, the retrospective design of the study makes it rely on pre-existing data from medical records. This introduces the potential for selection bias and limited control over the quality and completeness of recorded information. Specific patient characteristics, lifestyle factors, and dietary habits were either missing or insufficiently detailed in the medical records. This limitation restricted our ability to comprehensively account for potential confounding variables that could impact the observed associations. Consequently, the inability to include these specific variables of interest hindered the extent of our statistical analysis, constraining it to the data collected in the past. Additionally, due to the retrospective nature of the study, the incorporation of new variables into the analysis was not feasible, limiting the exploration of potential factors that could contribute to stone recurrence. A significant limitation pertains to the variability in data collection techniques, particularly with respect to blood sampling and laboratory procedures. While the general methods and techniques for diagnostic procedures were provided, the study relied on existing medical records, which often lacked detailed documentation of specific techniques employed for blood sampling and subsequent analysis. In particular, serum potassium levels are susceptible to inaccuracies due to factors such as complicated or inadequate blood sampling, duration of the diagnostic procedure, improper storage, and suboptimal handling of samples. The inability to create specific guidelines for these methods in the retrospective data posed challenges in accounting for potential errors or inconsistencies introduced during the process.

5.3. Interpretation

Uric acid urolithiasis, a relatively common form of urinary stone disease, presents notable challenges to the healthcare system and requires a deeper understanding of its recurrence patterns, especially in regions of high prevalence. This study aimed to explore the association and interplay of calcium-related factors contributing to disease development and recurrence, as proposed by researchers and to shed light into further factors affecting the disease. The results provide valuable insights, while further emphasizing the intricacy of this multifactorial disease.

The demographic aspects of the study population, specifically the gender distribution exhibited a significant male predominance, with males constituting 76.9% of the participants. Although very pronounced, this male predominance aligns with established trends in urolithiasis cases. This gender-based variance may result from dietary habits, anatomical variations, and hormonal differences. In our regression model, however, gender did not meet the significance level. A possible explanation for this discrepancy could be, that while there might be a correlation between gender and stone episodes, the strength of this relationship might not be substantial enough to predict stone episodes in the presence of other variables in the regression model. Conducting a gender-specific factor analysis that explores these possible influences would be beneficial in order to uncover the underlying processes behind this gender disparity.

The distribution of stone episodes demonstrated positive skewness, suggesting that a majority of patients experienced fewer episodes. This skewness was evident from the substantial proportion (44.6%) of patients who reported only a single stone episode. Due to the missing information on disease management, caution should be exercised, when interpreting these results. It remains unclear whether this trend is observed due to successful treatment and metaphylaxis or rather represents an intrinsic disease characteristic.

Higher levels of urine creatinine also correlated mildly with stone episodes. Interestingly this correlation could not be explained within our ordinal logistic regression model. This divergence implies that while there may be a correlation between urine creatinine and stone recurrence, other variables within the regression model might have overshadowed its predictive significance.

Although the exact mechanism isn't fully understood, a study investigating the association of urine creatinine with kidney stone prevalence in the US, suggests that individuals with kidney stones (independent of stone composition) exhibit higher urine creatinine levels, due to some level of renal injury or dysfunction. However, the authors did not definitively establish whether kidney stones directly cause kidney damage that leads to elevated creatinine levels or whether other factors might be at play. It's important to note that while their study confirms a relationship between urine creatinine and kidney stone formation, and elevated urine creatinine was established as a risk factor for urolithiasis, further research is needed to fully elucidate the mechanisms underlying this association and the potential causal relationships involved (106).

Regarding our hypothesis of calcium metabolism contributing to the recurrence of uric acid urolithiasis, we defined the variables serum calcium, urine calcium, urine citrate and urine pH as relevant. Among those, only urine calcium showed a significant correlation with the number of uric acid stone episodes. Interestingly, it did not reach significance in the regression model. To our knowledge no current studies exist, that would potentially explain this significant correlation in pure uric acid stone formation. However, in cases of mixed uric acid and calcium oxalate stones, hypercalciuria seems to play a role in stone development via heterogeneous nucleation (107). To comprehensively understand the relationship between calcium metabolism and uric acid urolithiasis, further studies involving more calcium-specific parameters (e.g. PTH, calcitonin, vitamin D) and a more diverse study population would be necessary.

Significant associations were found for serum potassium, with higher values increasing the likelihood of frequent uric acid stone episodes. Further regression analysis was significant and was concurring with the findings. This observation may suggest a potential relationship between potassium homeostasis and stone formation mechanisms. Detailed exploration of this relationship could illuminate the potential interplay between systemic electrolyte levels and uric acid stone recurrence. However, interpretation should be performed cautiously. As indicated earlier, our study presented several limitations, including the lack of information about patient treatment and details about diagnostic methods and procedures. While our results suggest that high serum potassium levels increase the likelihood of experiencing stone episodes, there could be different reasons for these associations. Blood samples are prone to errors, especially regarding potassium measurements. Errors in potassium measurement can lead to pseudohyperkalemia, falsely elevating serum potassium levels. Factors such as hemolysis, mechanical trauma during blood collection and processing, temperature fluctuations, and certain patient conditions can contribute to this phenomenon (108).

The inverse correlation observed between age and the recurrence of uric acid urolithiasis suggests a potential protective effect of advancing age against frequent stone episodes. In contrast to our findings, old age is considered a risk factor for uric acid urolithiasis in the current literature (109). Due to our study design, we did not compare uric acid stone formers with healthy individuals. However, one possible explanation for the reduction of stone episodes with older age could be, that disease awareness and adherence to therapy and behavioural modifications after diagnosis increase with age, as suggested by Fernandez-Lazaro et al. (110). Our correlation analysis could not support diabetes, obesity (BMI), hypertension, hyperuricosuria, low urine volume and low urinary pH as being risk factors for urolithiasis, as commonly described in the literature (73, 89). We suspect successful treatment and lifestyle changes being accountable for this observation, although the exact reasons could not be determined.
Our study could not confirm the findings, Strohmaier, Hörmann and Schubert reported in their investigations of uric acid urolithiasis. Especially the correlation between serum calcium and stone episodes, described by the researchers, that led us to further investigate the influence of calcium metabolism on uric acid stone disease, could not be supported. Since our study included 381 patients, while Strohmaier, Hörmann and Schubert analysed data from 30 patients, study size is a likely cause of the discrepancy in our findings.

6. CONCLUSION

Our study yielded several noteworthy findings through the correlation analysis and the implementation of a regression model. Notably, our investigation revealed a correlation between urine calcium levels and the recurrence of uric acid urolithiasis. This observation aligns with our initial hypothesis, suggesting that calcium plays a potential role in uric acid stone formation. Furthermore, our investigations suggested a potential protective effect of old age and considered high serum potassium levels as a predictor for uric acid stone recurrence. While we could not confirm our hypothesis with absolute certainty, the significant correlation between urine calcium levels and stone recurrence confirms its potential as a contributing factor. However, it is essential to emphasize the limitations inherent in our study, primarily stemming from its single-center observational design and the retrospective nature of data collection. The geographic restriction of our study site may limit the generalizability of our findings to more diverse populations, and the reliance on pre-existing medical records introduces potential selection bias and limited control over data quality and completeness. Despite these constraints, our results provide valuable insights into the influence of specific variables, such as age, gender, serum potassium, urine creatinine and urine calcium, on the recurrence of uric acid urolithiasis.

Future research should consider these findings and address the limitations, to further expand our understanding and to ultimately lead to improved strategies for preventing and managing uric acid urolithiasis.

7. REFERENCES

1. Herold G. Innere Medizin: eine vorlesungsorientierte Darstellung. Köln: Gerd Herold; 2020. 656 p.
2. Kumar P, Nargund V. Samuel Pepys. A patient perspective of lithotomy in 17th century England. J Urol. 2006;175:1221-4.
3. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol. 2010;25:49–59.
4. Tefekli A, Cezayirli F. The history of urinary stones: in parallel with civilization. ScientificWorldJournal. 2013:423964.
5. Markel H. "I swear by Apollo"--on taking the Hippocratic oath. N Engl J Med. 2004;350:2026-9.
6. European Association of Urology. European Museum of Urology [Internet]. Leicester (GB): Goddard J; 2023 [cited 2023 Jun 13]. Available from: https://history.uroweb.org/history-of-urology/early-urological-interventions/cutting-for-the-stone/the-celsian-method-the-apparatus-minor/
7. Bichler KH, Strohmaier WL, Eipper E, Lahme S. Das Harnsteinleiden. Berlin: Lehmanns Media LOB.de; 2007. (GEK, Gmünder Ersatzkasse, editor. GEK-Edition : Schriftenreihe zur Gesundheitsanalyse; vol. 52).
8. Zhang L, Zhang X, Pu Y, Zhang Y, Fan J. Global, regional, and national burden of urolithiasis from 1990 to 2019: a systematic analysis for the global burden of disease study 2019. Clin Epidemiol. 2022;14:971–83.
9. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y. Epidemiology of stone disease across the world. World J Urol. 2017;35:1301–20.
10. Abou-Elela A. Epidemiology, pathophysiology, and management of uric acid urolithiasis: A narrative review. J Adv Res. 2017;8:513–27.
11. Qian X, Wan J, Xu J, Liu C, Zhong M, Zhang J et al. Epidemiological trends of urolithiasis at the global, regional, and national levels: a population-based study. Int J Clin Pract. 2022;2022:6807203
12. Zhu C, Wang DQ, Zi H, Huang Q, Gu JM, Li LY et al. Epidemiological trends of urinary tract infections, urolithiasis and benign prostatic hyperplasia in 203 countries and territories from 1990 to 2019. Military Med Res. 2021;8:64.
13. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investig Clin Urol. 2017;58:299–306.

14. Rule AD, Lieske JC, Li X, Melton LJ, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol. 2014;25:2878-86.
15. Siener R, Laube N, Strohmaier WL. Rezidivprävention der Urolithiasis unter Berücksichtigung ökonomischer Aspekte. Urologe. 2011;50:1276–82.
16. Li S, Huang X, Liu J, Yue S, Hou X, Hu L et al. Trends in the incidence and DALYs of urolithiasis from 1990 to 2019: results from the global burden of disease study 2019. Front Public Health. 2022;10:825541.
17. Wang K, Ge J, Han W, Wang D, Zhao Y, Shen Y et al. Risk factors for kidney stone disease recurrence: a comprehensive meta-analysis. BMC Urol. 2022;22:62.
18. Calculate by QxMD [Internet]. [cited 2023 Jun 19]. ROKS – Recurrence of kidney stone (2018) | QxMD. Available from: https://qxmd.com/calculate/calculator_438/roks-recurrence-of-kidney-stone-2018
19. Eisner BH, Goldfarb DS. A nomogram for the prediction of kidney stone recurrence. J Am Soc Nephrol. 2014;25:2685-7.
20. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. J Nephrol. 2000;13 Suppl 3:S45-50.
21. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. J Urol. 2011;185:1304-1.
22. Strohmaier WL, Seilnacht J. 362 Is undue acidity in uric acid stone formers caused by a decreased excretion of ammonia or by excessive protein intake? European Urology Supplements. 2007;6:113.
23. Siener R, Herwig H, Rüdy J, Schaefer RM, Lossin P, Hesse A. Urinary stone composition in Germany: results from 45,783 stone analyses. World J Urol. 2022;40:1813–20.
24. Freeg MAHA, Sreedharan J, Muttappallymyalil J, Venkatramana M, Shaafie IA, Mathew E et al. A retrospective study of the seasonal pattern of urolithiasis. Saudi J Kidney Dis Transpl. 2012;23:1232–7.
25. Fakheri RJ, Goldfarb DS. Ambient temperature as a contributor to kidney stone formation: implications of global warming. Kidney Int. 2011;79:1178–85.
26. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. Proceedings of the National Academy of Sciences. 2008;105:9841–6.

27. Fukuhara H, Ichiyanagi O, Kakizaki H, Naito S, Tsuchiya N. Clinical relevance of seasonal changes in the prevalence of ureterolithiasis in the diagnosis of renal colic. Urolithiasis. 2016;44:529–37.
28. Tasian GE, Pulido JE, Gasparrini A, Saigal CS, Horton BP, Landis JR et al. Daily mean temperature and clinical kidney stone presentation in five U.S. metropolitan areas: a time-series analysis. Environ Health Perspect. 2014;122:1081-7.
29. Li Z, Li Y, Wang X, Liu G, Hao Y. Extreme temperature exposure and urolithiasis: A time series analysis in Ganzhou, China. Front Public Health. 2022;10:1075428.
30. Cervellin G, Comelli I, Comelli D, Meschi T, Lippi G, Borghi L. Mean temperature and humidity variations, along with patient age, predict the number of visits for renal colic in a large urban Emergency Department: results of a 9-year survey. J Epidemiol Glob Health. 2012;2:31–8.
31. Lo SS, Johnston R, Al Sameraaii A, Metcalf PA, Rice ML, Masters JG. Seasonal variation in the acute presentation of urinary calculi over 8 years in Auckland, New Zealand. BJU Int. 2010;106:96–101.
32. Alkhayal A, Alfraidi O, Almudlaj T, Nazer A, Albogami N, Alrabeeah K, Alathel A. Seasonal variation in the incidence of acute renal colic. Saudi J Kidney Dis Transpl. 2021;32:371-376.
33. Chen YK, Lin HC, Chen CS, Yeh SD. Seasonal variations in urinary calculi attacks and their association with climate: a population based study. J Urol. 2008;179:564-9.
34. Park HK, Bae SR, Kim SE, Choi WS, Paick SH, Ho K et al. The effect of climate variability on urinary stone attacks: increased incidence associated with temperature over 18 °C: a population-based study. Urolithiasis. 2015;43:89–94.
35. Zhang Y, Long G, Ding B, Sun G, Ouyang W, Liu M et al. The impact of ambient temperature on the incidence of urolithiasis: a systematic review and meta-analysis. Scand J Work Environ Health. 2020 1;46:117–26.
36. Lin KJ, Lin PH, Chu SH, Chen HW, Wang TM, Chiang YJ et al. The impact of climate factors on the prevalence of urolithiasis in Northern Taiwan. Biomed J. 2014;37:24–30.
37. Kaufman J, Vicedo-Cabrera AM, Tam V, Song L, Coffel E, Tasian G. The impact of heat on kidney stone presentations in South Carolina under two climate change scenarios. Sci Rep. 2022;12:369.
38. Lin CY, Juan YS, Huang TY, Lee HY. The influence of climatic factors in the seasonal fluctuation of urolithiasis and the trend of stone disease management in the southern Taiwan. Urolithiasis. 2023;51:55.

39. Stamatelou K, Goldfarb DS. Epidemiology of kidney stones. Healthcare. 2023;11:424.
40. Chen YK, Lin HC, Chen CS, Yeh SD. Seasonal variations in urinary calculi attacks and their association with climate: a population based study. J Urol. 2008;179:564–9.
41. Soucie JM, Coates RJ, McClellan W, Austin H, Thun M. Relation between geographic variability in kidney stones prevalence and risk factors for stones. Am J Epidemiol. 1996;143:487-95.
42. Strohmaier WL, Bonkovic-Őszi J. Are there seasonal variations in renal colic in uric acid stone formers in Germany? World J Urol. 2022;40:2099–103.
43. Strohmaier, W.L., Bonkovic-Oszi, J., Bruckner B. Are there seasonal variations of renal colic in calcium oxalate stone formers in Germany? Urologiya. 2021;25:165–171.
44. Meinshausen M, Smith SJ, Calvin K, Daniel JS, Kainuma MLT, Lamarque JF et al. The RCP greenhouse gas concentrations and their extensions from 1765 to 2300. Climatic Change. 2011;109:213.
45. Özsoy M, Somani B, Seitz C, Veser J, Kallidonis P. Sex differences in the therapy of kidney and ureteral stones. Curr Opin Urol. 2019;29:261–6.
46. Chien TM, Lu YM, Li CC, Wu WJ, Chang HW, Chou YH. A retrospective study on sex difference in patients with urolithiasis: who is more vulnerable to chronic kidney disease? Biol Sex Differ. 2021;12:40.
47. Xu JZ, Li C, Xia QD, Lu JL, Wan ZC, Hu L, Lv YM, Lei XM, Guan W, Xun Y, Wang SG. Sex disparities and the risk of urolithiasis: a large cross-sectional study. Ann Med. 2022;54:1627-35.
48. Wagner CA. Etiopathogenic factors of urolithiasis. Arch Esp Urol. 2021;74:16–23.
49. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H. Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. 2021;48:149.
50. Peerapen P, Thongboonkerd V. Protective cellular mechanism of estrogen against kidney stone formation: a proteomics approach and functional validation. Proteomics. 2019;19:1900095.
51. Gillams K, Juliebø-Jones P, Juliebø SØ, Somani BK. Gender differences in kidney stone disease (KSD): findings from a systematic review. Curr Urol Rep. 2021;22:50.
52. Siener R, Strohmaier WL, Neisius A. Urolithiasis-therapy and recurrence prevention taking into account gender-specific aspects. Urologie. 2022;61:1076–82.
53. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160–5.

54. Rodgers AL. Race, ethnicity and urolithiasis: a critical review. Urolithiasis. 2013;41:99–103.
55. Feng X, Wu W, Zhao F, Xu F, Han D, Guo X, Lyu J. Association between physical activity and kidney stones based on dose-response analyses using restricted cubic splines. Eur J Public Health. 2020;30:1206-11.
56. Zisman AL, Coe FL, Cohen AJ, Riedinger CB, Worcester EM. Racial differences in risk factors for kidney stone formation. Clin J Am Soc Nephrol. 2020;15:1166–73.
57. Siener R. Nutrition and Kidney Stone Disease. Nutrients. 2021;13:1917.
58. Cheungpasitporn W, Rossetti S, Friend K, Erickson SB, Lieske JC. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. J Nephrol. 2016;29:211–9.
59. Lin BB, Lin ME, Huang RH, Hong YK, Lin BL, He XJ. Dietary and lifestyle factors for primary prevention of nephrolithiasis: a systematic review and meta-analysis. BMC Nephrology. 2020;21:267.
60. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192:316-24.
61. Knoll T, Bach T, Humke U, Neisius A, Stein R, Schönthaler M et al. S2k-Leitlinie zur Diagnostik, Therapie und Metaphylaxe der Urolithiasis (AWMF 043/025): Kurzfassung. Urologe. 2016;55:904–22.
62. Barghouthy Y, Corrales M, Somani B. The relationship between modern fad diets and kidney stone disease: a systematic review of literature. Nutrients. 2021;13:4270.
63. Leone A, Fernández-Montero A, Fuente-Arrillaga C de la, Martínez-González MÁ, Bertoli S, Battezzati A et al. Adherence to the mediterranean dietary pattern and incidence of nephrolithiasis in the Seguimiento Universidad de Navarra follow-up (SUN) cohort. American Journal of Kidney Diseases. 2017;70:778–86.
64. Grases F, Isern B, Sanchis P, Perello J, Torres JJ, Costa-Bauza A. Phytate acts as an inhibitor in formation of renal calculi. FBL. 2007;12:2580–7.
65. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367:333–44.
66. Alelign T, Petros B. Kidney Stone Disease: An update on current concepts. Adv Urol. 2018;2018:3068365.
67. Pak CYC, Poindexter JR, Adams-Huet B, Pearle MS. Predictive value of kidney stone composition in the detection of metabolic abnormalities. Am J Med. 2003;115:26–32.

68. Singh I. Renal geology (quantitative renal stone analysis) by 'Fourier transform infrared spectroscopy'. Int Urol Nephrol. 2008;40:595–602.
69. Spivacow FR, Del Valle EE, Lores E, Rey PG. Kidney stones: Composition, frequency and relation to metabolic diagnosis. Medicina (B Aires). 2016;76:343-348.
70. Kijvikai K, De La Rosette JJM. Assessment of stone composition in the management of urinary stones. Nat Rev Urol. 2011;8:81–5.
71. Viljoen A, Chaudhry R, Bycroft J. Renal stones. Ann Clin Biochem. 2019;56:15–27.
72. Tanagho EA, McAninch JW. Smith's General Urology. 17th Edition. New York: McGraw-Hill Medical; 2007. 246–277 p.
73. Song L, Maalouf NM. Nephrolithiasis. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2023 Jul 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279069/
74. Pak CY, Arnold LH. Heterogeneous nucleation of calcium oxalate by seeds of monosodium urate. Proc Soc Exp Biol Med. 1975;149:930–2.
75. Zerwekh JE, Holt K, Pak CY. Natural urinary macromolecular inhibitors: attenuation of inhibitory activity by urate salts. Kidney Int. 1983;23:838–41.
76. Grover PK, Marshall VR, Ryall RL. Dissolved urate salts out calcium oxalate in undiluted human urine in vitro: implications for calcium oxalate stone genesis. Chem Biol. 2003;10:271–8.
77. Geraghty R, Wood K, Sayer JA. Calcium oxalate crystal deposition in the kidney: identification, causes and consequences. Urolithiasis. 2020;48:377–84.
78. Thakore P, Liang TH. Urolithiasis [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559101/
79. Geerlings SE. Clinical presentations and epidemiology of urinary tract infections. Microbiol Spectr. 2016;4.
80. Martell HJ, Wong KA, Martin JF, Kassam Z, Thomas K, Wass MN. Associating mutations causing cystinuria with disease severity with the aim of providing precision medicine. BMC Genomics. 2017;18:550.
81. Strohmaier WL. Recent advances in understanding and managing urolithiasis. F1000Res. 2016;5:2651.
82. Strohmaier WL, Seilnacht J, Schubert G. Clinical significance of uric acid dihydrate in urinary stones. Urol Res. 2011;39:357–60.

83. Barr WG. Uric Acid.. Clinical Methods: The history, physical, and laboratory examinations [Internet]. 3rd ed. Boston: Butterworths; 1990 [cited 2023 Jul 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK273/
84. Adomako E, Moe OW. Uric acid and urate in urolithiasis: The innocent bystander, instigator, and perpetrator. Semin Nephrol. 2020;40:564–73.
85. Low RK, Stoller ML. Uric acid–related nephrolithiasis. Urologic Clinics of North America. 1997;24:135–48.
86. Cameron MA, Sakhaee K. Uric acid nephrolithiasis. Urol Clin North Am. 2007;34:335–46.
87. Ratkalkar VN, Kleinman JG. Mechanisms of stone formation. Clin Rev Bone Miner Metab. 2011;9:187–97.
88. Paliouras C, Tsampikaki E, Alivanis P, Aperis G. Pathophysiology of nephrolithiasis. Nephrology Research & Reviews. 2012;4:58–65.
89. Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S et al. Kidney stones. Nat Rev Dis Primers. 2016;2:16008.
90. Khan SR. Histological aspects of the 'fixed-particle' model of stone-formation: animal studies. Urolithiasis. 2017;45:75–87.
91. Kok DJ, Boellaard W, Ridwan Y, Levchenko VA. Timelines of the "free-particle" and "fixed-particle" models of stone-formation: theoretical and experimental investigations. Urolithiasis. 2017;45:33–41.
92. Khan SR, Canales BK. A Unified Theory on the pathogenesis of randall's plaques and plugs. Urolithiasis. 2015;43:109–23.
93. Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: Molecular mechanism of renal stone formation and the critical role played by modulators. Biomed Res Int. 2013;2013:292953.
94. Khan SR. Inflammation and injury: what role do they play in the development of Randall's plaques and formation of calcium oxalate kidney stones? Comptes Rendus Chimie. 2022;25:355–72.
95. Rodgers AL. Physicochemical mechanisms of stone formation. Urolithiasis. 2017;45:27–32.
96. Basavaraj DR, Biyani CS, Browning AJ, Cartledge JJ. The Role of Urinary Kidney Stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. EAU-EBU Update Series. 2007;5:126–36.

97. Gupta S, Kanwar SS. Kidney stones: Mechanism of formation, pathogenesis and possible treatments. J Biomol Biochem. 2018;2:1-5
98. AWMF Leitlinienregister. S2k-Leitlinie zur Diagnostik, Therapie und Metaphylaxe der Urolithiasis [Internet].Düsseldorf GER: Arbeitskreis Harnsteine der Akademie der Deutschen Urologen, Deutsche Gesellschaft für Urologie e. V.; 2019[cited 2023 Jul 8]. Available from: https://register.awmf.org/de/leitlinien/detail/043-025
99. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu -Ciocca Cynthia J., Matlaga BR et al. Medical management of kidney stones: AUA Guideline. Journal of Urology. 2014;192:316–24.
100. Viljoen A, Chaudhry R, Bycroft J. Renal stones. Ann Clin Biochem. 2019;56:15–27.
101. Al-Shawi MM, Aljama NA, Aljedani R, Alsaleh MH, Atyia N, Alsedrah A et al. The role of radiological imaging in the diagnosis and treatment of urolithiasis: a narrative review. Cureus. 2022;14:e33041.
102. Fontenelle LF, Sarti TD. kidney stones: treatment and prevention. Am Fam Physician. 2019;99:490-496.
103. Skolarikos A, Jung H, Neisius A, Petřík A, Somani B, Tailly T et al. EAU Guidelines on Urolithiasis [Internet]. Arnhem NED: EAU Guidelines Office;2023 [cited 2023 Jul 9]. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urolithiasis-2023.pdf
104. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. European Urology. 2016;69:468–74.
105. Strohmaier W, Hörmann M, Schubert G. Papillary calcifications in uric acid stone formers (UASF) - first results. Urologe 2015;54:92.
106. Shen X, Chen Y, Zhang Y, Xia K, Chen Y, Hao Z. The association of urine creatinine with kidney stone prevalence in US adults: data from NHANES 2009–2018. Front Med. 2022;9:819738.
107. Siener R, Löhr P, Hesse A. Urinary risk profile, impact of diet, and risk of calcium oxalate urolithiasis in idiopathic uric acid stone disease. Nutrients. 2023;15:572.
108. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. N Am J Med Sci. 2013;5:255–9.
109. Manish KC, Leslie SW. Uric Acid Nephrolithiasis [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Aug 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560726/

110. Fernandez-Lazaro CI, García-González JM, Adams DP, Fernandez-Lazaro D, Mielgo-Ayuso J, Caballero-Garcia A et al. Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study. BMC Family Practice. 2019;20:132.

8. ENGLISH SUMMARY

Introduction: Uric acid urolithiasis, a prevalent type of urinary stone disease, poses significant healthcare challenges. Effective treatment requires an understanding of factors contributing to stone formation and recurrence. We conducted a single-center observational study to explore these factors.

Objectives: Our study aimed to investigate the relationship between specific demographic and clinical variables and the recurrence of uric acid urolithiasis. We hypothesized that factors related to calcium metabolism would play a significant role in the pathophysiologic processes of uric acid stone recurrence.

Patients and methods: We analysed various variables from a database of uric acid stone formers, including age, gender, serum potassium, calcium-related variables and more. 381 urolithiasis patients were analyzed for a correlation with stone episodes, and an ordinal logistic regression model was employed to identify predictors of stone recurrence.

Results: The study revealed a male predominance among uric acid stone formers (76.9%). Age and gender correlated negatively with stone episodes ($P = 0.019$ and $P = 0.030$, respectively), while serum potassium correlated positively ($P = 0.010$), as well as urine calcium ($P = 0.049$), and urine creatinine ($P = 0.038$). Our regression analysis revealed a potential protective effect of older age on stone episodes ($P = 0.010$) and suggested that elevated serum potassium levels could be a predictor of recurrence ($P = 0.015$)

Conclusion: Our results proposed a potential role of urine calcium in uric acid stone recurrence, although it did not maintain significance in the regression model. Age and serum potassium were identified as significant predictors of recurrence.

9. CROATIAN SUMMARY

Uvod: Kamenci podrijetlom iz mokraćne kiseline vrlo su učestali predstavljaju značajan izazov za zdravstveni sustav. Učinkovito liječenje zahtijeva razumijevanje faktora koji doprinose stvaranju i ponovnom javljanju kamenaca. Proveli smo monocentričnu opservacijsku studiju kako bismo istražili ove faktore.

Ciljevi: Naša studija imala je za cilj istražiti odnos između određenih demografskih i kliničkih varijabli te ponovnog javljanja uratnih kamenaca. Pretpostavili smo da će faktori povezani s metabolizmom kalcija odigravati značajnu ulogu u patofiziološkim procesima ponovnog javljanja uratnih kamenaca.

Bolesnici i metode: Analizirali smo različite varijable iz baze podataka bolesnika s uratnim kamencima, uključujući dob, spol, razinu serumskog kalija, varijable povezane s kalcijem i druge. Analizirano je ukupno 381 bolesnik s urolitijazom kako bi se utvrdila povezanost s brojem epizoda kamenaca, te je korištena ordinalna logistička regresijska analiza kako bi se identificirali prediktori ponovnog javljanja kamenaca.

Rezultati: Studija je otkrila premoć muškaraca među bolesnicima s uratnim kamenjem (76.9%). Dob i spol su negativno korelirali s brojem epizoda kamenaca (P = 0.019, odnosno P = 0.030), dok je serumski kalij pokazao pozitivnu korelaciju (P = 0.010), kao i razina urinarnog kalcija (P = 0.049), i kreatinina (P = 0.038). Regresijska analiza otkrila je potencijalno zaštitno djelovanje starije dobi u odnosu na broj epizoda kamenaca (P = 0.010), te je sugerirala da povišene razine serumskog kalija mogu biti prediktor ponovnog javljanja (P = 0.015).

Zaključak: Naši rezultati sugeriraju potencijalnu ulogu urinarnog kalcija u ponovnom javljanju uratnih kamenaca, iako taj faktor nije održao značajnost u regresijskom modelu. Dob i serumski kalij identificirani su kao značajni prediktori ponovnog javljanja.