Evaluation of the “Uroli App” for Urinary Stone Metaphylaxis

Sklorz, Katharina

UNIVERSITY OF SPLIT

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KATHARINA SKLORZ

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Diploma Thesis

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"Medicine is a science of uncertainty and the art of probability."

– William Osler

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Finally, I would like to dedicate this research to my wonderful parents.

LIST OF ABBREVIATIONS

2,8-DHA – Dihydroxyadenine

BMI – Body-Mass-Index

CT – Computed-Tomography

E. COLI – Escherichia coli

ESWL – Extracorporeal shock wave lithotripsy

ICD-10 – International Statistical Classification of Diseases and Related Health Problems Version 10

MDD – Medical Device Directive

MET – Medical expulsive therapy

NRS – Numeric rating scale

PCNL – Percutaneous nephrolithotomy

PEG – Percutaneous endoscopic gastrostomy

PKD – Polycystic kidney disease

RCT – Randomized controlled trial

SPP. – Species pluralis

URS – Ureterorenoscopy

WHO – World Health Organization

1. INTRODUCTION

1.1 General

Urolithiasis is a common condition where different types of a calculus can be formed in the kidney or at any level in the urinary collecting system of the human body (1). Urinary stones are one of the most common diseases worldwide and are considered the third most common urologic suffering, following urinary tract infections and pathologic conditions of the prostate (2).

Even Hippocrates brought up the connection between stones and putrefaction and advised that loin abscesses should only be treated by itinerant barber surgeons. In 1901, Brown supported Marcet´s hypothesis from 1817 in which he assumed that “alkalinization that attends putrefaction of urine unavoidably results in crystallization of dissolved urinary phosphates".
In 1925, with the assumption that urease was the biochemical basis for stone formation in infected urine, Hagar and McGrath paved the way for Sumner, who isolated urease only one year later. For the evidence that urease is a protein which catalyzes the hydrolysis of urea he not only won the Nobel Prize, but also laid the foundation for enzymology (3).

One might assume because the condition has been known for so long and people are more aware of diseases, treatments, and their own lifestyle, that the disease is declining, but the exact opposite is the case. Especially since the last century, the prevalence has been steadily increasing worldwide with rates as low as 1-5% in Asia, 5-9% in Europe, up to 7-13% in northern America (2,4). Changed living conditions and eating habits as the high-protein diet of affluent societies are certainly one reason for this. But also, the improved medical diagnostics with easy and non-invasive use of ultrasound devices or the fast intervention of computed tomographic (CT) cross-sectional imaging, cause more frequent detection of urolithiasis (5).

Urinary stones are also considered as a widespread disease in Germany. Rich meals and increased wine consumption were already suspected by Hildegard von Bingen (1098-1179) to promote stone formation, which is why she advised a more conscious lifestyle (6).
Based on a nationwide survey from 1979 to 2001 a tripling of the incidence and an increase prevalence (0.54% to 1.47% and 4.0% to 4.7%) was discovered (7). Apart from the assumption of being a predominantly male problem, there might also be trend of affecting more and more younger people. In 2000 only 5.9% of German women had a stone episode, while 9.7% of German men had one, ranging from ages 50 to 64 years; Meanwhile the incidence in the age group of 40 to 49 has been rising in the last two decades (6–8). Regional and demographic

differences can also be distinguished and even one's profession might have an influence on the risk factors of developing urolithiasis or not (6,8,9). While in eastern and southern German regions uric acid stones are the most common types of stones, infection stones were predominantly seen in east Germany (8). Younger patients were more prone to calcium phosphate stones, older patients were more likely to have uric acid and atypical stones (10).
Interestingly, among physicians, surgeons have the highest likelihood of suffering from a stone event. Reduced fluid intake seems to play an important role here (9).
For Germany it can be summarized that the peak incidence is between the ages of 30 and 60, men are affected more frequently than women and the lifetime prevalence is around 5% of the German population (11).

In general, however, it is the many factors such as dietary habits, personal habits, climate, environment, ethnicity, and heredity that make it so difficult to formulate a clear metaphylaxis (6).

The high recurrence rate of 50% with at least one stone recurrence and 10%-20% with at least three recurrences not only make it difficult to treat the disease but also cause high costs that the healthcare system must bear (5,6,12,13)
In the 1990s, spending on urolithiasis treatments in the US increased by 50% and was estimated at approximately $1.83 billion in 1995 (14,15). In a study from 2012, Strohmaier (13) examined the issue of costs and possible cost savings through coordinated metaphylaxis, based on a cooperation with a German health insurance company and a literature search between the years 1999-2011. At the time of the research, the annual costs of removing stones from inpatients and outpatients in Germany were around €590 million and €9 million, respectively. But despite the cost of the metabolic evaluation and the specific metaphylaxis of about €68.8 million, a total of about €171.2 million could be saved with rational use of the resources (13). However, one must remember that the metabolic evaluation is not an absolute diagnostic tool and is neither always necessary nor an absolute guarantee for avoiding recurrences. Because with idiopathic calcium stones, the most critical time for recurrence is about 4 years after the first stone event and the recurrence rate is only 30-40%. In addition, 50% of those recurrent stone formers are only likely to have one recurring stone in their lifetime, while only 10% have more than three recurrences. Therefore, the most important part of metaphylaxis is still increasing the drinking amount (16).

Especially regarding the climate change, this topic is more relevant than ever. It is assumed in some studies, that with the rise in global temperature, the prevalence of urolithiasis

will also increase by about 4% per °C temperature increase in the coming years. In 2050, annual healthcare spending could increase by another 25% (17). However, further studies on this topic are necessary because a clear connection between the temperature increase and the stone events is not yet clearly recognizable, since both hot and cold seasons have visible peaks (18).

Therefore, the question arises, how can the healthcare system be relieved and, above all, how can the high-risk patients be relieved? Can urolithiasis metaphylaxis be improved not only for patients but also for medical staff?

1.2 Types of Stones

Urinary stones can form at different locations in the urinary collecting system and can be made of different chemical substances. The chemical composition of the urinary stone is of great importance in connection with therapy and specific metaphylaxis. For this purpose, urinary stone analyses are carried out. More than half of the stones, about 60%, are mixed forms and therefore contain several substances (19).

1.2.1 Calcium Oxalate Stones

Calcium oxalate stones are yellow-brown urinary stones and are the most common type of stone in urolithiasis with a frequency of about 75 to >80% but they have one of the lowest recurrence rates among urinary stones (ca. 38-44%) (6,11,20).

They are divided into calcium oxalate monohydrate, so-called whewellite stones, and calcium oxalate dihydrate, so-called weddellite stones (1,19–21). Increased excretion of calcium, which is caused by an increased urinary calcium concentration favor the stone formation. When the solubility product is exceeded, calcium salts crystallize. This is often promoted by diets rich in calcium, sodium, and protein, therefore calcium oxalate stones are considered particularly amenable to dietary measures. But hyperparathyroidism and increased release of calcium from the bones may also cause calcium oxalate stones (21,22). Ample magnesium intake or citrate have an inhibitory effect and can therefore be recommended for prevention, but increased fluid intake of at least 2.5 L per day can also prevent recurrences. Foods high in oxalic acid should be avoided and calcium intake and salt intake should be reduced. Therefore, the consumption of e.g., spinach, cocoa, coffee, chard, beetroot, and rhubarb are not advisable (11,21).

1.2.3 Calcium Phosphate Stones

Depending on whether the urine is acidic or alkaline, calcium phosphate stones can be divided into two types. Calcium phosphate, so-called brushite stones, are formed in acidic urine and are mono mineral. Carbonate apatite stones, dahllite stones, occur in alkaline urine and are usually found in combination with magnesium-ammonium-phosphate, struvite (23). With a frequency of approximately around 5%, they belong to the rarer stones, but have a rather high recurrence rate (6,24).

Calcium phosphate crystals can be found in urine sediment of healthy humans. However, if there is a pathology, such as a urinary tract infection, it may present as a urinary concretion or a stone. These stones can pass spontaneously or, in complicated cases, can fill the entire renal pelvis. Etiologically, hyperparathyroidism or distal renal tubular acidosis are often present. Treating the cause is the priority (11,23).

1.2.4 Uric Acid Stones

With a percentage of 5-13%, uric acid stones are the second most common urinary stones and have a high recurrence rate of around 50% (6,11,20). As the name suggests, the main component of the stones is uric acid.

Due to our metabolism, uric acid is constantly produced when purine from animal proteins from our food is broken down. In healthy people, uric acid salts are normally dissolved. If the pH value of the urine is particularly low (pH value <6) and the excretion of uric acid increases, for instance due to a purine-rich diet, the salts can no longer be completely dissolved, and uric acid stones can form (25).

Low urine pH can be caused by insulin resistance, metabolic syndrome, or lactic acidosis. In each case, there is less ammonium excretion or increased acid production. A loss of bases due to severe diarrhea or a very high intake of animal proteins also bring the acid-base balance into imbalance. However, endogenous factors such as medication or catabolic metabolic states caused by fasting, but also diseases such as gout, tumor lysis syndrome or myeloproliferative disorders favor urinary stone formation (5). Men and patients suffering from gout disease are therefore more affected than females or people with healthy metabolisms (26). Therefore, a low-purine diet and an increase in fluid intake of at least 2.5-3 L per day are recommended to avoid recurrences (5).

1.2.5 Ammonium Urate Stones

Uric acid is also found in ammonium urate stones. Unlike pure uric acid stones, they do not require acidic urine. A neutral pH value of >6.5 is enough to cause stone formation.

Since ammonium urate stones are often associated with infection, both urine and blood uric acid should be measured, and a urine culture should be arranged to evaluate the cause.

A vegetarian diet with a high uric acid content, but also malnutrition or malabsorption syndromes are risk factors. Basic therapy and metaphylaxis approaches here are treatment of the infection with possible administration of antibiotics and uric acid reduction in urine and blood. The pH value of the urine should also be observed and acidified if necessary (5).

1.2.6 Struvite Stones

Struvite stones are usually caused by urinary tract infections triggered by urase-forming germs. The chemical components of the are magnesium ammonium phosphate hexahydrate, but when combined with carbonate apatite, they can form so-called infection stones (5). Their percentage of urinary stones is about 5% and the recurrence rate is about 42% (6,20).

Proteus species pluralis (spp.), Corynebacterium urealyticum, Ureaplasma urealyticum, Morganella morganii but also Klebsiella spp., Staphylococcus spp., Serratia marcescens belong to the urease-forming germs. Escherichia coli (E. coli) bacteria and Pseudomonas aeruginosa can also partially produce urease and must always be kept in mind (5).

Unlike the types of stones described so far, the metabolic analyzes should be considered less important, instead it is important to seek for the cause and appropriate antibacterial treatment. An antibiogram is one of the first steps, as well as a microbiological examination of the concretions. This helps to prescribe a specific antibiotic therapy, but also to track down the causative germs. A complete stone removal is of the utmost importance. Any residue of a calculus that remains in the body could still have bacteria attached and is therefore a risk for re-infection but also for new stone formation. A therapeutic acidification of the urine between pH values of 5.8 and 6.2 could also protect against recurrences in alkaline-loving germs. As a follow-up care, patients should be closely monitored (5).

1.2.7 Cystine Stones

With a frequency of less than 1% and a recurrence rate of 89%, cystine stones are rare, but must be taken very seriously (6,20).

Cystine stones are caused by a genetic disease. In cystinuria, which is inherited in an autosomal recessive manner, the solubility of cystine in the urine exceeds. As a result, homozygous patients form cystine stones (27). Since cystine stones are only formed in cystinuria, a stone analysis also makes this diagnosis (5). Patients should be closely monitored for their underlying disease and cysteine and methionine intake should be greatly reduced.

Vitamin C can inhibit the conversion of cysteine to cystine and can therefore moderate the concentration somewhat. At the same time, however, care should be taken to ensure adequate fluid intake and alkalinization of the urine, as this improves solubility (27). Since recurrences are frequent and stone formation already affects children, metaphylaxis and, above all, fluid intake is very difficult. Patients are recommended to drink more than 3.5 L per day. However, these should be evenly distributed over 24 hours. Especially in infancy, the failure of drinking prophylaxis can often lead to the installation of a percutaneous endoscopic gastrostomy (PEG) tube (5).

1.2.8 Rare Urinary Stones

2,8-dihydroxyadenine stones, xanthine stones, matrix stones and extremely rare drug-induced stones are very rare urinary stones and make up less than 1% (5,24).

Dihydroxyadenine (2,8-DHA) stones are caused by an autosomal recessive disorder in which the enzyme adenine phosphoribosyl transferase is defective, resulting in increased levels of 2,8-DHA in the urine. Due to the poor solubility in the urine, concretions form quickly. An increased drinking amount of 3.5-4 L per day is recommended. A low-purine diet can also be helpful in the context of metaphylaxis.

A genetic defect affecting the enzyme xanthine oxidase leads to poor solubility of xanthine in urine and therefore to xanthine stones. There is also an elevated level of uric acid in the blood. The defect is inherited in an autosomal recessive manner and no drug support in metaphylaxis is known to date. Instead, it is also recommended here to eat a low-purine diet and to drink more than 3 L.

Why matrix stones form has not yet been fully clarified. Matrix stones do not mineralize and consist of approximately 65% organic materials such as carbohydrates and proteins. Infections, demographic factors, or urine composition do not seem to be decisive so far since they have already been found in every patient constellation. For this reason, no metaphylaxis for matrix stones has yet been formulated.

Drug-induced urinary stones can occur in two different ways. Either the drug's active ingredient or one of its metabolites can crystallize and form into a stone. However, there are also medications that can disrupt the composition of the urine and promote stone formation. Allopurinol, for example, belongs to both representatives. Even if this drug can often help with high-risk stone builders, it should be noted that allopurinol itself can also lead to stones (5).

1.3 Pathophysiology of Urolithiasis

Although the terms urolithiasis or nephrolithiasis are used in clinical parlance, stone disease can be clearly defined depending on the localization of the calculus.

If a stone is found directly in the kidney, it is called nephrolithiasis. If it is a ureteral stone, it is defined as ureterolithiasis. Cystolithiasis means bladder stone and a stone in the urethra is urethral lithiasis (28). But most often urinary stones form within the kidney and migrate to the ureter, where they can cause symptoms (1).

As previously discussed, many different diseases can lead to urolithiasis. Nevertheless, urolithiasis can be seen as multifactorial since various processes lead to one goal: crystal formation (28). When certain solutes, which are normally dissolved in the urine, become too concentrated, they become supersaturated. Urinary supersaturation of certain solutes then results in nucleation, precipitation out of the solution and formation of small crystals. These crystals act as a nidus where more crystals can deposit. Over time they can build up a crystalline structure (29). All stones contain an organic matrix core which is composed of mucoproteins. This matrix weighs about 2.5% of the stone weight and is still discussed in connection with stone formation (1,28). In addition to so-called stone promotors, which are usually the substances the stones are made of, stone inhibitors such as magnesium, citrate, glycosaminoglycans, and pyrophosphate also play an important role in the pathophysiology of urolithiasis (30). If they lack, stone formation is favored (28).

Both promoters and inhibitors are diet dependent. Poor eating habits, such as too much animal protein, too little dietary fiber from vegetables and fruits, and above all not drinking enough fluids promote a mild metabolic acidosis. As a result, the body is likely to increase calcium resorption from the bones, inhibit resorption of calcium in the kidney's distal tubule, and increase glomerular calcium filtration. In healthy people, this initially has little effect, but the effect seems to be greater in people who form stones at risk. Increased calcium is also released with a sodium-rich diet. In contrast, stone forming inhibitors can be found in dietary fibers and may be protective by forming soluble complexes in the urine. It is suggested that vegetarians have a lower probability on developing urolithiasis because of the protective effect of fibers but also by avoiding animal proteins and too salty and preserved foods (31).

Bacteria per se can favor stone formation by serving as nidi, especially in patients with recurrent urinary tract infections who develop a persistently alkaline urine. Urease producing germs as Proteus spp. and staphylococci promote almost always struvite stones (1).

Like the calcium stones, uric acid stones are formed by a supersaturation of uric acids. This can be caused by gout or diseases with a rapid cell turnover, such as tumor lysis syndrome or leukemia. Interestingly, about 50% of the uric acid stone patients do not have increased values of urate in the urine. Even hyperuricemia might not be found. But those patients tend to have a low urinary pH (<5.5) which promotes uric acid aggregation (1).

Cystine stones are caused by an autosomal recessive inherited gene defect that is no longer able to carry out the renal tubular transport of certain amino acids. Ornithine, arginine, lysine and cystine can no longer be reabsorbed from the proximal tubule. The high concentration of cystine in the urine, but also the poor solubility cause stone formation (32).

In his 2012 study, Khan took up an aspect that has not been discussed much in textbooks yet and relates to inflammation throughout the human body. Inflammation in the body causes oxidative stress. This oxidative stress not only promotes urinary stones, but also hypertension, obesity, diabetes mellitus, metabolic syndrome, chronic kidney disease and even myocardial infarction. These conditions in turn again trigger oxidative stress. This creates an interplay between these different diseases and suggests that there is a connection between inflammation, urolithiasis, and other comorbidities. It can therefore be assumed that hypertension, diabetes mellitus and chronic kidney disease can lead to urolithiasis, but urinary stones can also lead to these same diseases as complications and can be additionally regarded as a metabolic condition. In the case of renal injury and inflammation, the environmental circumstances within the kidney play an additional role (33).

1.4 Risk Factors and High-Risk Patients

As there are numerous etiologies for urolithiasis, there are also numerous risk factors which can favor stone growth in the human body. Due to the high recurrence rate and the various complications that urolithiasis brings with it, it is important to recognize and care for the multitude of risk factors and high-risk patients.

Risk factors can be acquired by patients during lifetime or already exist genetically (5,34). Frequent risk factors, the avoidance of which is repeatedly taken up in metaphylaxis, are insufficient fluid intake and poor nutrition. Both are more likely to be acquired factors and both have an impact on urine concentration. Diets that are too salty or high in oxalates or purines are more likely to cause urinary stones than less salty and vegetarian diets (29,31). Nevertheless, caution is also required here, because oxalate is also present in otherwise healthy and vegetarian foods. These include beans, berries, some nuts, some teas, soda, spinach, potatoes. The popular

consumption of coffee or a piece of chocolate is also not advisable (29). In addition to other personal habits such as smoking, alcohol consumption, especially beer, but also opioid abuse, diabetes mellitus, high blood pressure, metabolic syndrome and above all a high Body-Mass-Index (BMI) are particularly risky (29,33,35,36).

In a 2012 study, Wrobel et al. examined the link between high BMI and calcium oxalate stones. They divided the patients with a diagnosis of calcium oxalate stones into three groups: patients with a BMI ≤25, patients with a BMI of 25.1-30 (=overweight) and patients with a BMI of >30 (=obesity). They found that more than two-thirds, namely 68% of the patients had a BMI >25 and were therefore considered at least overweight. 26% patients even had a BMI of >30, belonged to the third group and thus suffered from obesity. Furthermore, a difference in the urine pH and the urine citrate excretion could be determined. Patients with a BMI ≤25 had higher urine pH (median 6.20) than patients with a BMI 25.1-30 (median 6.06) or a BMI >30 (median 5.95). The median citrate excretion in the normal-weight group was 1.41 mmol/d, while it was 2.32 mmol/d and 1.92 mmol/d in the other two groups. This strongly suggests that obesity is associated with an increased risk of stone formation (35).

Diabetes mellitus, hyperlipidemia, and metabolic syndrome do not only entail general metabolic changes that affect urine composition, but precisely the insulin resistance that is present in diabetes promotes acidosis, uric acid excretion, and increased calcium in the urine. Malignancies and endocrine disorders also promote stone formation due to their influence on metabolism (29).

Other significant risk factors include a familial accumulation of stone events, but also early lifetime personal stone history has a higher probability of recurrences (37). Similar to that, a genetic predisposition of getting urolithiasis, genetic disorders directly causing urinary stones or simply just being male or Caucasian, have higher chances being affected (27,37,38).

Many risk factors can be eliminated with a healthy lifestyle that includes good daily hydration and a high-fiber diet. However, since urolithiasis is very complex in its development, avoiding the risk factors is not that easy. A little more expertise and interest is required from both doctors and patients.

1.5 Signs, Symptoms and Complications

Many people already have urolithiasis but are asymptomatic because, if the stones are still in the kidney, they usually do not cause pain. However, if the stone migrates and enters the ureter, the symptoms usually begin quickly and severely. Patients complain of severe, mostly

unilateral, colicky abdominal or flank pain, which is often clearly the main symptom (11,28,29,31).

General symptoms include a restless patient who often shifts around, groans and tries to find a comfort position. Pointed or sharp stones can damage the mucous membranes of the ureters and therefore cause gross hematuria. Dysuria or fever with chills may also be present.

Abdominal symptoms include colicky pain in the flank area and/or abdomen. This pain can also radiate to the back and lower abdomen. Appendicitis is therefore often to be considered as a differential diagnosis. If the stone is at or close to the ureterovesical junction, the pain can also radiate into the groin, labia, and testicles. A testicular torsion must be excluded urgently. In many patients, severe flank pain can be triggered by percussion. Pain-induced vomiting, nausea, and crying are also common symptoms. Additionally, a reflective paralytic sub ileus is also possible in urolithiasis and must always be kept in mind.

In more severe cases, the patients are hemodynamically unstable. The most common complication of urolithiasis is urinary tract infection. This can often lead to fever, pyelonephritis or even urosepsis. Urosepsis must be treated quickly because of its high mortality rate. In some cases, the stone can also trigger an obstruction with urinary retention. Again, caution is advised because the blocked urine can become infected in the kidney and cause an infected hydronephrosis. A urinary tract congestion can also result in a fornix rupture, in which the increased pressure tears the renal pelvis. This causes urine to leak out. Rapid diagnostics using CT would be recommended here (11,28,29).

Urinary stones and especially recurrent urolithiasis events disturb the kidneys in their normal function. This may lead to chronic kidney disease or end stage renal disease. The risk for developing chronic kidney disease is twice as high as in healthy people. Patients with a higher BMI or females are even more affected (39).

1.6 Diagnostics

As in any medical specialty, history and physical examination are essential when suspecting urolithiasis. In addition to the laboratory work, imaging is also required to rule out or confirm a stone. The size and location of the stone should also be determined, along with the nature of the urinary collecting system or any secondary pathologies. Since urolithiasis patients, and especially high-risk ones, have a higher radiation exposure from repetitive imaging methods such as X-rays or CT scans, the first choice for diagnostic imaging is always ultrasound. In addition to the cheap and quick availability, an ultrasound can also be used in

emergency situations as well as in general diagnostics and follow-up checks. Color Doppler examinations in particular can diagnose ureteral stones in acute phases and are not inferior to CT diagnosis without contrast medium. A sensitivity of 96% is also very high for ureteral stones >5 mm or kidney stones with calyx enlargement. This means that examinations can be carried out quickly and safely and the time in the emergency room before therapy can be significantly reduced.

X-ray properties of a stone, which serve to diagnose the type of stone and help with the therapy regime, can be determined with the help of an X-ray image.

Although a CT entails an increased radiation exposure, it is still suitable as a further diagnostic after a primary ultrasound examination. Here not only the high specificity and sensitivity prevail, but also the presentation of the anatomy and function of the urinary tract, the assessment of the heterogeneity and impaction, as well as the stone density in Hounsfield units. A quick CT scan should be considered, especially if an immediate diagnosis is required, for example if urosepsis, fever or kidney abnormalities are suspected.

Metabolic diagnostics are also of utmost importance. Any stone from a patients first stone event should be sent for urinary stone analysis. The urinary stone analysis provides information on the stone composition and points the way for a tailored metaphylaxis of the patient. But not every recurrence event needs to be analyzed again. If there is an early or particularly late recurrence, or if pharmacological prevention should be repeated, a new analysis should be carried out. High specificity and sensitivity in stone analysis is ensured by infrared spectroscopy and X-ray diffraction analysis, as well as polarization microscopy. They meet high quality standards and are completely sufficient for diagnostics. The situation is different with the wet-chemical analysis method. This no longer meets the standards and is therefore not used in analysis anymore.

After a stone analysis, further basic diagnostics include the classification into low- or high-risk patients. This can be determined based on the type of stone and the risk of recurrence. No further metabolic diagnostics or clarification is required for patients in the low-risk group. They can invoke a general urinary stone metaphylaxis.

This is different for patients who are divided into the high-risk group. General factors such as an early occurrence of stones as a child or adolescent, familial accumulations, stones containing brushite and uric acid, infectious stones or a solitary kidney are taken into account. Diseases associated with stone formation such as hyperparathyroidism, metabolic syndrome, nephrocalcinosis, polycystic kidney disease (PKD), chronic gastrointestinal diseases and genetically determined stone formation such as cystinuria, primary hyperoxaluria, renal tubular

acidosis (RTA) type I also play an important role in the classification. Anatomical abnormalities and environmental factors are also considered.

If patients are assigned to a high-risk group based on these factors, this results in extended metabolic diagnostics. The aim of this is to work out a targeted metaphylaxis based on the type of stone and the risk profile. An extended metabolic diagnosis includes a blood test, and two 24-hour urine analyzes. This involves searching for lithogenic but also inhibitory substances in the urine, which could provide further information on the disease or metaphylaxis. In the 24-hour urine collection examination, several things must be observed in order to avoid falsified results. First, two analyzes are recommended in order to rule out fluctuations caused by patient habits. The type of urine collection should be agreed in advance with the evaluating laboratory. In addition, the patient should be as stone-free as possible, and the last intervention should have taken place at least 3 weeks ago. A 24-hour urine test is also recommended as a follow-up examination. 3-6 months after drug metaphylaxis, the success of the therapy can be evaluated. Check-ups after successful therapy should be analyzed about 12 months later (5).

1.7 Therapy

The therapy of urinary stones is very versatile and can be divided into conservative, interventional and surgical treatment in addition to an acute pain therapy (5,11).

1.7.1 Pain Management

The treatment of patients with urolithiasis usually begins with analgetic treatment of the renal colic. The analgesic therapy is based on the World Health Organisation (WHO) analgesic ladder principle and initially includes a pain assessment by the patient, for example with the use of the numeric rating scale (NRS), in which the pain is rated on a scale of 0-10. "No pain" is given a 0 and "the worst pain imaginable" is given a 10 (5,40).

Then the analgesic therapy is gradually fine-tuned to the pain of the patient. First with non-opioid analgesics, then with low-potency opioid analgesics in combination with non-opioid analgesics, and finally with high-potency opioid analgesics in combination with non-opioid analgesics. The goal should be to adjust the patient to an NRS value ≤ 5 during acute colic and an NRS value ≤ 3 at rest (5,41,42).

However, opioids should only be used if non-opioids are not providing adequate pain relief. Due to undesirable side effects such as nausea, but also because they do not treat the cause of colic, but only the pain, opioids are inferior to non-opioids (5).

Non-opioids such as metamizole or diclofenac are therefore the first choice for severe or moderate pain. Paracetamol can be used as an alternative to the two medications mentioned above, especially in pregnant women. But it is metamizole that not only has a good analgesic effect, but also fights the cause of colic pain by reducing increased intraluminal pressure, as well as having a spasmolytic and antinociceptive effect on the ureter (5,11).

1.7.2 Conservative Therapy

Conservative therapy is often the right choice for newly diagnosed stones <7 mm. Spontaneous loss is very likely, especially with stones <5 mm. Within 40 days, 95% of ureteral stones <4 mm pass spontaneously and only about half of stones >5 mm requires interventional help. Therefore, a conservative approach with regular follow-up checks of the signs of infection, urinary transport, kidney function and sufficient pain medication is justified (5,43).

In addition to increased drinking and physical exercise, which are recommended but not yet evidence-based in studies, conservative therapy can be supported with so-called medical expulsive therapy (MET). Ureteral stones >5 mm in particular benefit from the effects of off-label use of various α-blockers such as tamsulosin, silodosin and the calcium antagonist nifedipine. These have a spasmolytic influence on the smooth muscles of the ureter by inhibiting the adrenergic influence and can therefore not only promote spontaneous discharge but also relieve pain. Therefore, they not only promote faster stone passage, but also reduce the need for pain medication. However, as already mentioned, MET is an off-label use in Germany and always requires patient information (5,11,44–47).

1.7.3 Interventional Therapy

Interventional therapy, which includes either urinary diversion or stone removal, is indicated when conservative therapy and pain medication are unsuccessful or spontaneous passage is no longer expected. Additionally, severe, and persistent obstructions with urinary stasis or even postrenal kidney failure initiate interventional measures (11).

Two methods can be used for urinary diversion. On the one hand, a ureterorenoscopy can be performed and the ureter splinted using a double-J catheter. The second option is a percutaneous nephrostomy, in which a renal pelvic calyx is punctured under sonographic and radiological control. Then a nephrostomy catheter is inserted using the Seldinger wire technique (5,11).

According to German guidelines, interventional stone removal is only considered if there is no urinary tract infection or antibiotic treatment has already begun. In addition, a urinary

diversion lasting several days in the case of obstruction or significant infection must have taken place beforehand (5,11).

Interventional techniques include ureterorenoscopy (URS) with stone removal, percutaneous nephrolithotomy (PCNL), and extracorporeal shock wave lithotripsy (ESWL).

In a URS, a retrograde either semi-rigid or flexible ureteral endoscopy is performed. The semi-rigid URS are more likely to be used for ureteral concretions and can also be used for easily accessible kidney stones, only, if necessary, while the flexible URS can extract or fragment almost all stones in the renal pelvis calyx system. Stones up to 2 cm in size are best suited for a URS, but larger stones can also be removed with it. Either small stones can be retrieved in one piece, or they can be fragmented with the help of laser lithotripsy. Since the procedure usually results in swelling of the mucous membrane of the ureter, which interferes with the outflow of urine, a temporary ureteral splint is inserted in most cases (5,11).

Up until the 1980s, open stone surgery was still widespread, but thanks to advances in technology, patients have long benefited from percutaneous nephrolithotomy, which can be used to retrieve even medium-sized stones without surgery. Hard-to-reach stones from 1.5 cm which are located in the lower calyx group, but especially stones >2 cm are the domain of the PCNL. A renal pelvic calyx is punctured under sonography and radiological control and splinted with the Seldinger wire technique. The stones are then fragmented and removed endoscopically using ultrasound lithotripsy probes and lasers. Percutaneous nephrostomies can also be used in more difficult cases (5,11,48–50).

The minimally invasive method of ESWL is suitable for most urinary stones, with proximal and small stones particularly benefiting from it. However, the size, composition and location of the stone must be considered in advance, as well as the anatomy of the patient. With ESWL, an energy source outside the body is directed at the stone using sonographic and X-ray control. Shock waves are then generated from there at a frequency of 1.0-1.5 Hz, which breaks the stones into small fragments (5,11,51,52). In general, ESWL is an elegant technique for removing stones from patients, but the presence of calculi that may be left behind has long been believed to result in higher stone recurrence rates. Nevertheless, the study situation has become somewhat opaquer due to more recent studies in this regard. No higher risk of recurrence is assumed here (53–56).

1.7.4 Open Surgical and Laparoscopic Interventions

The therapeutic value of laparoscopic or open surgical interventions has fallen sharply due to the improvement in endourology and the option of using an ESWL and is therefore only practiced in rare cases. Large kidney or ureter stones or a failed endourological treatment can also be handled laparoscopically or openly in exceptional cases. Another indication is the correction of anatomical anomalies, which, for example, can also result in obstructions to drainage (5).

1.8 Metaphylaxis

As already described in detail in "1.6 Diagnostics", according to the German guideline, every stone in a first stone event should undergo a urinary stone analysis, since the composition of the stone determines further steps or characterizes a specific metaphylaxis (5).

Based on the stone analysis and the basic diagnostics, stone patients are then divided into a low-risk group and a high-risk group. The basic diagnosis includes a general anamnesis with clarification of other personal or familial (chronic) diseases, a stone anamnesis, a drug anamnesis, and a nutritional anamnesis. In addition, a clinical examination, a blood laboratory with kidney parameters and electrolytes, and an ultrasound examination are carried out. Urine status tests are also important in basic diagnostics. If the patients are now divided into a high-risk group, further metabolic diagnostics are required. Subsequently, a specific urinary stone metaphylaxis, which corresponds to the type of stone, is recommended. The low-risk patients do not require any further diagnostics and already benefit from general metaphylaxis (5).

1.8.1 General Metaphylaxis

The most important recommendation of general metaphylaxis is to increase the amount of fluids intake to improve urine dilution and reduce the concentration of lithogenic substances in the urine (5,57). However, normal water is recommended here, as soft drinks can promote stone formation (58). The general metaphylaxis also includes recommendations for nutrition and lifestyle and basically applies to all types of stone and therefore to all urinary stone patients (5).

The following points can also be considered with regard to the recommendations for fluid intake: an increase in the amount of fluid to 2.5-3 L/day, the urine volume should be around 2.0-2.5 L/day, the amount of fluid should be evenly distributed over 24 hours, urine pH-neutral beverages should be consumed, plain tap water is best, and the urine density should be < 1.010 g/ml.

The diet should be balanced and high in fiber. The oxalate intake is supposed to be reduced, and the calcium intake should be between 1 and 1.2 g per day. Table salt must not exceed 6 g per day and protein intake is best between 0.8-1.0/kg bw/day.

Lifestyle changes involve more physical activity, normalizing weight and, most importantly, reducing stress (5).

1.8.2 Specific Metaphylaxis - Calcium Oxalate Stones

In addition to the basic diagnostics, if a calcium oxalate stone is present, parathyroid hormone, potassium, chloride and, if the calcium is increased, sodium value in the blood is determined. In addition, a daily urine pH profile must be drawn up, two 24-hour urine tests must be carried out. Urinary volume, urine density, calcium, oxalate, uric acid, citrate, and magnesium is also examined (5).

If the urinary oxalate value is >0.5 mmol/day, a diet high in oxalate should be reduced. This includes foods like Swiss chard, spinach, rhubarb, nuts, chocolate, and beetroot. Calcium or magnesium intake may decrease enteral absorption of dietary oxalate (59–62)

Based on the biochemical increases and risk factors, a pharmacological metaphylaxis is adjusted. This means that, depending on the condition, different drugs are used to bring the values back to normal in order to reduce the risk of a recurrence. For example, if hypercalciuria is present, alkaline citrates and/or thiazides are prescribed. If hyperoxaluria is found, oxalate restriction and alkaline citrate are used. Calcium or magnesium supplementation with meals may be considered in adults. Vitamin B6 is administered in primary hyperoxaluria. Hypocitraturia is usually treated with alkaline citrate or, alternatively, with sodium bicarbonate, and hyperuricosuria can be counteracted with alkaline citrate or, in the case of proven hyperuricemia, allopurinol (5).

1.8.3 Specific Metaphylaxis – Calcium Phosphate Stones

Similar to the calcium oxalate stones, in addition to the basic diagnostics, the blood is examined for the parathyroid hormone values, calcium in the case of a sodium increase, potassium and chloride. Further urine diagnostics also refer to a daily urine pH profile and two 24-hour urine tests. In addition, volume, urine density, calcium, phosphate, citrate, creatinine, and oxalate in the urine are determined (5).

Complete stone removal and antibiotic therapy are indispensable when there is a urinary tract infection causing a carbonate apatite stone. If the urinary tract infections keep reappearing, long-term antibiotic therapy can be considered (5).

In primary hyperparathyroidism, there is an increased concentration of calcium in the blood, which leads to hypercalciuria. This encourages calcium stone formation. After a laboratory, ultrasound or CT check of the neck region, primary hyperparathyroidism is usually treated surgically (5,63).

An autosomal dominant inherited renal tubular acidosis, as the name suggests, induces acidosis in the distal tubular cells. This leads to hypercalciuria, but also often to hypocitraturia and hyperoxaluria. The acidosis is balanced with alkali citrates or sodium bicarbonate. Thiazides can be added to normalize hypercalciuria (5).

If there is neither a urinary tract infection, nor primary hyperparathyroidism or renal tubular acidosis, the biochemical risk factors are decisive for a specific metaphylaxis after evaluation of the urine collection test. Hypercalciuria ranging between 5-8 mmol/d is treated with alkaline citrate. If the hypercalciuria is > 8 mmol/d, the therapy is extended to thiazides. Patients with a neutral to alkaline urine pH are given L-methionine to prevent recurrence. As already mentioned, urinary tract infections must be treated with antibiotics (5).

1.8.4 Specific Metaphylaxis – Uric Acid Stones

In the case of uric acid stones, the extended diagnosis is limited to a daily urine pH profile, two 24-hour urine tests, urine volume, urine density, and uric acid (5).

Nutritional recurrence prophylaxis includes increasing the fluid intake so that the urine volume is at least 2.5-3 L/day. Aside from that a low-purine diet should be aimed. The pH of the urine can be influenced medically with the help of alkali citrate or sodium carbonate. PH-values should range from 6.5 and 6.8. Allopurinol is used in both hyperuricosuria and hyperuricemia (5).

1.8.5 Specific Metaphylaxis - Ammonium Urate Stones

In the case of ammonium urate stones, a urine pH determination and a uric acid measurement in the blood and urine should be carried out. In addition, a urine culture is essential. Metaphylaxis includes therapy with L-methionine to bring the urine to a more acidic pH of 5.8-6.2. A urinary tract infection is always treated with antibiotics, and if hyperuricosuria is present, allopurinol or febuxostat is used (5).

1.8.6 Specific Metaphylaxis – Struvite Stones

Since struvite stones are caused by urinary tract infections, a urine pH daily profile and a urine culture are initiated as an extended diagnostic. An antibiogram is done to find the specific antibiotic therapy with which the urinary tract infection is treated. In addition, complete

stone removal is of the utmost importance so that the risk of recurrence can be significantly reduced. If recurrences do occur, the urine can be acidified with the help of L-methionine and pH values between 5.8 and 6.2 can be aimed for (5).

1.8.7 Specific Metaphylaxis – Cystine Stones

In the case of cystine stones, a daily urine pH profile and two 24-hour urine tests are also necessary. In addition, urine volume, urine density, cystine and creatinine are determined.

The nutritional therapy of metaphylaxis recommends a urine volume > 3.5 L/d for adults and a drinking volume for children >1.5 L/m2 body surface. It is important to ensure that the fluid intake is as even as possible throughout the day and night. A PEG tube should also be considered for children if the drinking amount cannot be reached.

The aim of pharmacological metaphylaxis is to increase the urine pH to values above 7.5. This is said to be achieved with alkaline citrates or sodium bicarbonate. If both the alkalinization and the increase in drinking volume fail, or if the cystine excretion is >3 mmol/d and there is a recurrence, tiopronin can be administered additionally (5).

1.8.8 Specific Metaphylaxis – Rare Stones

Allopurinol can reduce the excretion of 2,8-DHA and thus the likelihood of recurrence in dihydroxyadenine stones. An increased fluid intake of 3.5-4 L/day and a low-purine diet should also be implemented.

The same dietary recommendations also apply to xanthine stones. So far nothing can be done pharmacologically against the formation of xanthine stones. Drug-induced stones can be prevented by stopping and changing medication. There is currently no worked out metaphylaxis for matrix stones (5).

2 OBJECTIVES

The aim of our study was to analyze, how effective the “Uroli” application is to support the metaphylaxis of adult patients with urolithiasis after acute treatment of a kidney or ureter stone, compared to metaphylaxis without the “Uroli” application in terms of medical benefit and patient-relevant structural and procedural improvements.

We hypothesized that the urolithiasis patients using the "Uroli" application, have a higher compliance, a pH-value closer to references values, a lower specific weight and a higher fluid intake compared to patients sticking to conservative metaphylaxis. Additionally, we will examine the distribution of age, gender, and BMI of all test subjects, as well as an even distribution between the two groups if applicable.

Furthermore, we will examine the main reasons for rejection of participation, as well as the drop-out reasons.

3 SUBJECTS & METHODS

3.1 Ethical Approval

To conduct the multicenter study, an ethics application has been submitted to and was approved by the ethics committee of the medical faculty of the Carl von Ossietzky University of Oldenburg before the start of the study. The corresponding approval number is 2020-074.

No risks could be identified in advance for the implementation and participation in the study for “Uroli”. If health-damaging influences would have become known or if individuals experienced health restrictions because of “Uroli”, the study or participation in the study would have been terminated immediately. In this case, all study participants and the responsible ethics committee would have been informed.

3.2 Design and Description of the Study

The study took place at the urology department of the REGIOMED Hospital in Coburg. It was part of a bigger multicenter pilot study which was carried out at the University of Oldenburg and intended to examine methodological approaches of the prospective randomized controlled trial study (RCT) for their feasibility and to provide initial indications of positive health effects. The data of this thesis refer exclusively to the center of Coburg.

The overarching question of the study was: What is the effectiveness of the “Uroli” app to support metaphylaxis in adult patients with urolithiasis after acute treatment of a kidney or ureter stone compared to metaphylaxis without the “Uroli” app in terms of medical benefit and patient-relevant improvements in structure and experience?

The study was designed as a prospective randomized controlled trial study. There was no blinding of the study participants or of the directly interacting medical staff. In the study, patients were randomized by alternating 1:1 allocation to the groups.

As main outcomes, endpoints from the category of medical benefit (averages of drinking amount in ml, pH value, specific density in g/ml) are examined. The reference values for pH, specific gravity and drinking amount refers to the German S2K-guideline for urolithiasis metaphylaxis (5). Secondary outcome measures are from the category of patient-relevant structural and care improvements (therapy adherence), age, gender, weight (kg) and height (cm).

Subjects were adult patients hospitalized in the REGIOMED hospital Coburg because of urolithiasis according to the International Statistical Classification of Diseases and Related Health Problems Version 10 (ICD-10): N20. Patients had to fulfill all criteria for participating in the study.

The inclusion criteria upon admission were defined as patients with kidney/ureteral stones (ICD-10: N20) who require personalized stone remediation, regardless of stone type and regardless of whether it is new or recurring, persons over 18 years of age, regular use of a smartphone, including use of apps to ensure the usability of the “Uroli” app, and availability by email.

The exclusion criteria were defined as patients with acute symptoms of urolithiasis, patients who, according to a doctor's assessment, are restricted in fluid intake due to other illnesses or patients with clearly impaired renal function, defined by a serum creatinine value >2 mg/dl, individuals deemed unfit to participate in the study by an investigator, persons under 18 years of age, or persons not owning or regularly using a personal smartphone, as well as lack of an own e-mail address, individuals without consent to participate in the study, and language barrier to exclude potential user error.

3.3 Sample

The “Medipee” device and the “Uroli” app are suitable for all patients with urolithiasis, regardless of the type of stone or the number of stone recurrences.

The aim of the multicenter study is to find 30 subjects per study site. 15 of them are placed into the intervention group and the remaining 15 into the control group. Recruitment in Coburg started on 29.11.2022 and data collection per recruited patient lasted 3 months, starting the day after hospital discharge. The randomization of the patients was via a 1:1 alternating allocation and there was no blinding.

For this thesis all patients recruited until 30.04.2023 were taken into account, meaning these patients whose observation period ended by 30.07.2023. We were able to recruit 15 subjects instead of the 30 intended. Eight patients belong to the intervention group and seven patients to the control group. Of the total of 15 subjects, we had eight drop-outs, due to various reasons. Of the seven successfully terminated participants six belonged to the control group. Only one subject in the intervention group completed the study.

No deadline was set for the multicentric study until the target of 30 patients was reached.

3.4 Data Collection

The data which is used for this study is composed of urine pH, specific weight and amount of fluid intake which is recorded for three months by the patients themselves via “Uroli” device and app, or via urine test stripes. The urine was tested at least twice a day.

All study participants received information material as part of standard care, in which general and stone-specific measures of metaphylaxis, such as the recommended amount to drink, the desired pH value and the desired specific density of the urine are communicated. The treating physicians were responsible for determining the urine values to aim for and the recommended amount to drink.

Also, if possible, drop-outs were documented together with the reason for the termination, which is evaluated via a questionnaire.

From the medical charts we collected age, BMI, and gender.

3.4.1 Interventional Group – "Uroli" Application and Device

The "Uroli" digital health application consists of a smartphone- or tablet-based app ("Uroli" app) that is used with a hardware-based device ("Medipee" device). "Uroli" supports affected patients multimodally with a "Uroli" app certified as a class 1 medical product according to the Medical Device Directive (MDD) and a patented and CE-certified "Medipee" device. The aim of the digital health application "Uroli" is to improve the patient's metaphylaxis by recording key parameters of the fluid balance (amount consumed and specific gravity) and the pH value.

In consultation with the treating physicians, a desired drinking amount should be entered in the drinking diary of the "Uroli" app and used to monitor drinking behavior. Furthermore, limit values for the urine pH value and the specific density, which have been determined, should also be entered into the "Uroli" app. The urine values entered in the "Uroli" app can then be compared with the individual tolerance ranges previously defined. Exceeding as well as falling below those values are determined and reported back to the user. This should enable continuous, automated, and user-friendly observation and control of compliance with individual recommendations for metaphylaxis. Based on these values, the "Uroli" app provides users with information about their pH value and specific gravity as well as their fluid balance and instructions on how to improve their drinking habits. These include both tips to drink more and educational messages about the connection between drinking behavior and other health-related parameters such as the risk of recurrence. Furthermore, the "Uroli" app has the option of documenting the amount of urine excretion and deriving therapy-relevant behavior from this as part of a diary function.

The "Medipee" device is a compact toilet rim mounted system that is fully controlled and activated via the "Uroli" app. The device automatically recognizes the process of urination

via a thermal sensor system and triggers a process to determine the relevant parameters in the midstream urine. Test strips attached to a gripper arm are used to determine relevant urine parameters (specific density, pH value) in midstream urine.

The study participants were asked to use the device and application at least twice a day (e.g. morning and evening) to determine the urine pH value and specific density and also to document the daily drinking amount in the "Uroli" app. An upper limit for the number of urine value determinations was not specified. In addition, the study participants in the intervention group were asked to read and follow the information and recommendations provided in the "Uroli" app, e.g. on higher fluid intake.

3.4.2 Control Group – Web-based Documentation Table

Study participants in the control group received access to a web-based documentation interface provided by the German company "Leitz". On this cloud-platform each control group patient received its own Microsoft® Excel® for Microsoft 365, Version 2307 table, where they could enter their values. Additionally, they received 250 urine test strips for manual determination of urine values. The study participants were asked to determine their urine pH and specific gravity at least twice a day (e.g. morning and evening) using these urine test strips and additionally record the daily drinking amount via the web-based documentation interface. An upper limit for the number of urine value determinations was not specified.

3.5 Statistical Analysis

For processing our collected Data JASP Version 0.17.3 (JASP Team, University of Amsterdam, Amsterdam, The Netherlands) and Microsoft® Excel® for Microsoft 365, Version 2307 (Microsoft Corporation, Redmond, WA, USA) is used.

After our collected data is unconnected, we test its distribution using the Shapiro-Wilk test. If the *P*-value of the Shapiro-Wilk test is less than 0.05, the data is not normally distributed and therefore fluid intake, pH values, and specific gravity of the intervention group and the control group can be compared using the Mann-Whitney U test. This also applies if only one of the two groups to be compared has a normal distribution. Using the *P*-value of the Mann-Whitney U test, significant differences between the groups can be evaluated.

4. RESULTS

In our sample we had seven participants, who successfully terminated the study, six of those belonged to the control group and only one subject belonged to the intervention group. The differences in our measurements between the interventional group and the control group can be seen in Table 1.

Table 1. Descriptive Statistics

	Fluid Intake		**pH**		**Specific Weight**		**BMI**	
	IG*	**CG†**	**IG***	**CG†**	**IG***	**CG†**	**IG***	**CG†**
Valid	65	525	52	527	52	526	1	5
Missing	28	5	41	3	41	4		
Median	2550.000	2400.000	5.900	6.000	1.013	1.022	25.100	29.300
Mean	2474.692	2445.143	5.889	5.932	1.013	1.021	25.100	29.860
Std. Deviation	450.614	654.754	0.241	0.504	0.003	0.006		4.599
MAD	150.000	400.000	0.125	0.340	0.001	0.002	0.000	3.400
Shapiro-Wilk	0.841	0.949	0.978	0.949	0.888	0.946	NaN‡	0.989
P-value of Shapiro-Wilk	< .001	< .001	0.446	< .001	< .001	< .001	NaN‡	0.976
Minimum	200.000	300.000	5.200	5.000	1.009	1.002	25.100	24.100
Maximum	3600.000	5200.000	6.500	7.250	1.023	1.030	25.100	35.900
25th percentile	2300.000	2000.000	5.787	5.500	1.012	1.018	25.100	27.300
50th percentile	2550.000	2400.000	5.900	6.000	1.013	1.022	25.100	29.300
75th percentile	2700.000	2800.000	6.013	6.250	1.014	1.025	25.100	32.700

Legend:
* Intervention group
† Control group
‡ All values are identical

As shown in Table 1 the valid measuring days and the missing ones vary greatly between the intervention group and the control group, but also within the individual groups. While the control group had significantly more valid days, namely 525 for fluid intake, 527 for pH and 526 for specific weight, they only had 5, 3 and 3 days without entered data respectively. In comparison, the intervention group only had 65 valid days for the fluid intake, 52 for the pH and 52 for the specific weight and for each of them 28, 41 and 41 days without entry.

When testing deviation from normality with Shapiro-Wilk test, fluid intake has a $P<0.05$ in both groups, which shows no normal distribution. This also accounts for specific weight. Both Shapiro-Wilk tests result in $P<0.05$, and therefore do not indicate normal distribution. For pH we have a normal distribution in the intervention group, with a *P*-value of 0.446, but not in the control group.

If one looks at the median and the MAD of the fluid intake, it is noticeable that the median of the intervention group, at 2550 ml, is slightly higher than the median of the control group, at 2400 ml. The MAD of 150 ml in the intervention group and 400 ml in the control group, describe a smaller deviation from the median in the first one.

If one compares the median of the groups in the case of the pH value, the intervention group has a value of 5.9, while the control group has a value of 6.0. Both values are very close to each other and within the normal reference range of urine pH. But the MAD is higher in the control group at 0.340 than 0.125 in the intervention group.

The specific gravity has a median of 1.013 g/ml in the intervention group and 1.022 g/ml in the control group. The MAD are 0.001 and 0.002 respectively.

Comparing the BMI of both groups, we can use one BMI value from the intervention group and 5 values from the control group. One BMI of the control group could not be determined. The BMI of the patient in the intervention group is 25.1 and is therefore classified as overweight. The median of the control group patients is 29.3 and is higher in comparison to the patient in intervention group. The smallest BMI of the control group is in the normal range at 24.1, while the highest value of 35.9.

4.1 Differences in Fluid Intake

As can be seen from Table 2, this results in P=0.017 and thus shows a significant difference in fluid intake between the intervention group and the control group.

Table 2. Evaluation of Fluid Intake

				95% CI for Hodges-Lehmann Estimate	
	W	**df** **p**	**Hodges-Lehmann Estimate**	**Lower**	**Upper**
Fluid Intake	19799.000	0.017	150.000	50.000	∞

Note. For all tests, the alternative hypothesis specifies that group *1* is greater than group *2* .

4.2 Differences in pH

When we ran a Mann-Whitney U test to compare the pH values in intervention group and control group, no significant difference with P= 0.832 could be seen. (Table 3).

Table 3. Evaluation of pH-Values

				95% CI for Hodges-Lehmann Estimate	
	W	df	p	Hodges-Lehmann Estimate	Lower	Upper
pH	12607.000		0.832	-0.050	-0.100	∞

Note. For all tests, the alternative hypothesis specifies that group *1* is greater than group *2* .

4.3 Differences in Specific Weight

Analyzing the specific weight with the Mann-Whitney U test for both groups, intervention group and control group, as seen in Table 4, the result is *P*=1,000 and therefore there is no significant difference between the two groups here either.

Table 4. Evaluation of Specific Weight

				95% CI for Hodges-Lehmann Estimate	
	W	df	p	Hodges-Lehmann Estimate	Lower	Upper
Specific Weight	4566.000		1.000	-0.008	-0.009	∞

Note. For all tests, the alternative hypothesis specifies that group *1* is greater than group *2* .

4.4 Stone Type Distribution

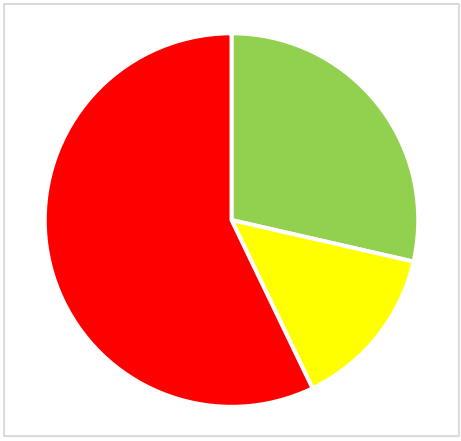
Table 5 shows the stone analyzes of the seven patients who successfully finished the study, divided into the intervention group and the control group. The only patient in the intervention group had a calcium oxalate stone. In the control group, a calcium oxalate stone and a uric acid stone were found after the stone analysis. Four stones could not be analyzed.

Table 5. Stone Types

Group/Stone	Calcium oxalate	Uric acid	No analysis
IG*	1	0	0
CG†	1	1	4

Legend:
***** Intervention group
† Control group

In Figure 1 the total distribution of the two calcium oxalate stones, one uric acid stones and four stones without analysis can be seen.



Legend:
- No analysis
- Calcium oxalate
- Uric acid

Figure 1. Stone Types

4.5 Intervention Group Errors

We were able to evaluate how many measurements in intervention group were taken with the “Medipee” device and what the error rate of the attempted automated measurements was. Out of a total of 166 measurements taken, 89 were successful and were able to display a result for pH and specific gravity. But the remaining 77 attempted measurements were incorrect due to failure of the device. This means that 53.61% of the measurements were able to provide an outcome and 46.39% did not yield a result.

4.6 Cancellation Reasons

Because of the high drop-out rate, we also documented the reasons for dropping out and were able to summarize them in Table 6.

Table 6. Drop-Out Reasons

Reason:	**IG***	**CG†**
Health related	1	0
Device malfunction	6	0
Web based table problem	0	1

Legend:
* Intervention group
† Control group

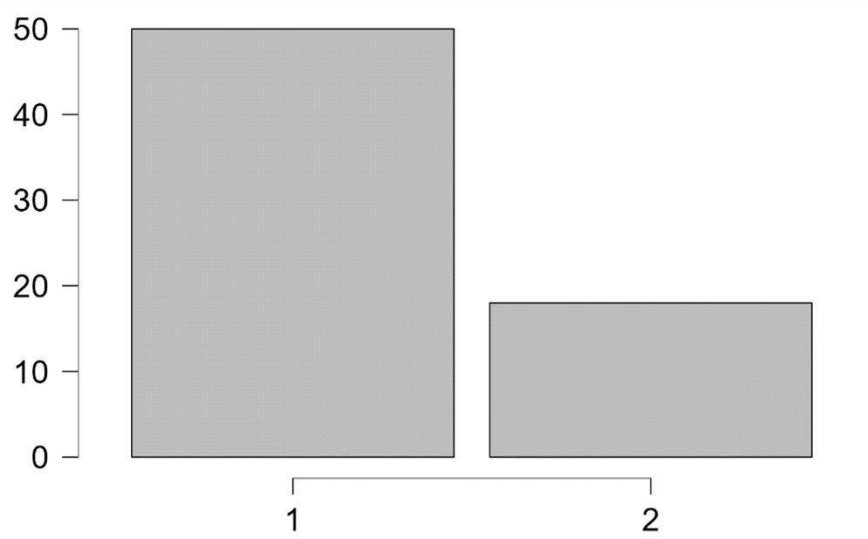
In the intervention group, the main reason for dropping out was difficulties with the "Medipee" device. These included connection problems with the app on the smartphone, incorrect measurements, as well as the incorrect retraction of the guide wire or the complicated

installation on the toilet edge. These problems led to six drop-outs in the intervention group. There was also one health-related termination to document. In the control group, there was only one early termination of the study, which was related to problems with the web-based table.

4.7 Requested Patients

In the period from 29.11.2022 to 30.04.2023, we were able to ask a total of 83 patients whether they were interested in taking part in the study. 15 of them were able and willing to participate, 68 patients could not participate due to various reasons. During this recruitment phase, we documented the reasons for rejection. Furthermore, we documented and analyzed the gender of the patients, as well as the age of most of these 68 people.

When comparing the gender distribution in Figure 2, it is very clear that there were more men among the patients asked, than women. With 50 men and only 18 women, the men's share is 73.47%, over 2.5 times more than the women's share.



Legend:
1= Male
2=Female

Figure 2. Gender Distribution among Requested Patients

Table 7. Age Distribution among Requested Patients

	Age
Valid	67
Missing	1
Median	56.000
Mean	53.000

Table 7. Age Distribution among Requested Patients

	Age
Std. Deviation	18.894
Shapiro-Wilk	0.963
P-value of Shapiro-Wilk	0.046
Minimum	19.000
Maximum	92.000

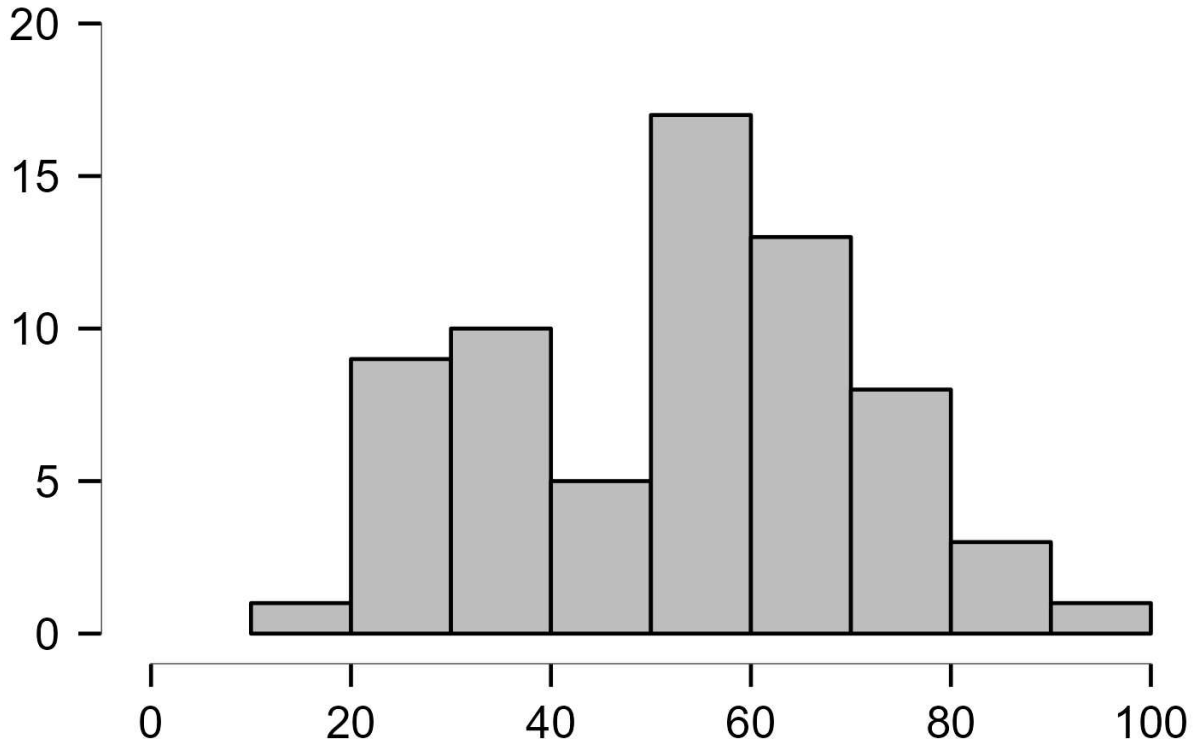


Figure 3. Age Distribution among Requested Patients

It was possible to document the age from 67 out of 68 patients. It is striking that there are 19 people between the age of 20 and 30, and therefore accounting for almost one third (28,36%) of the patients. Nevertheless, is the median age 56.00 years. The youngest patient was 19 and the oldest was 92 years old.

4.8 Rejections

In the case of rejection reasons, all values could be documented. The reasons were divided into categories: not interested, acute symptoms, no internet/no smartphone, language barrier, not suitable for the study.

Table 10. Rejections among Requested Patients

Reason	Frequency	Percent
Not interested	18	26.471
Acute Symptoms	21	30.882
No Internet/no Smartphone	3	4.412
Language Barrier	16	23.529
Not Suitable for the Study	10	14.706
Total	68	100.000

Analyzing the reasons, it is noticeable that the main exclusion factors was presence of acute symptoms (21 patients) or lack of interest in the study (18 patients). Closely followed with 16 patients, are those, who did not have a sufficient command of the German language. Ten patients were not eligible for the study, according to the study nurse. These included conditions, such as patients who are too old, suffer from dementia, multi-mobility, cognitive limitations, or disabilities. Only three patients reported no internet or smartphone (Table 10, Figure 4).

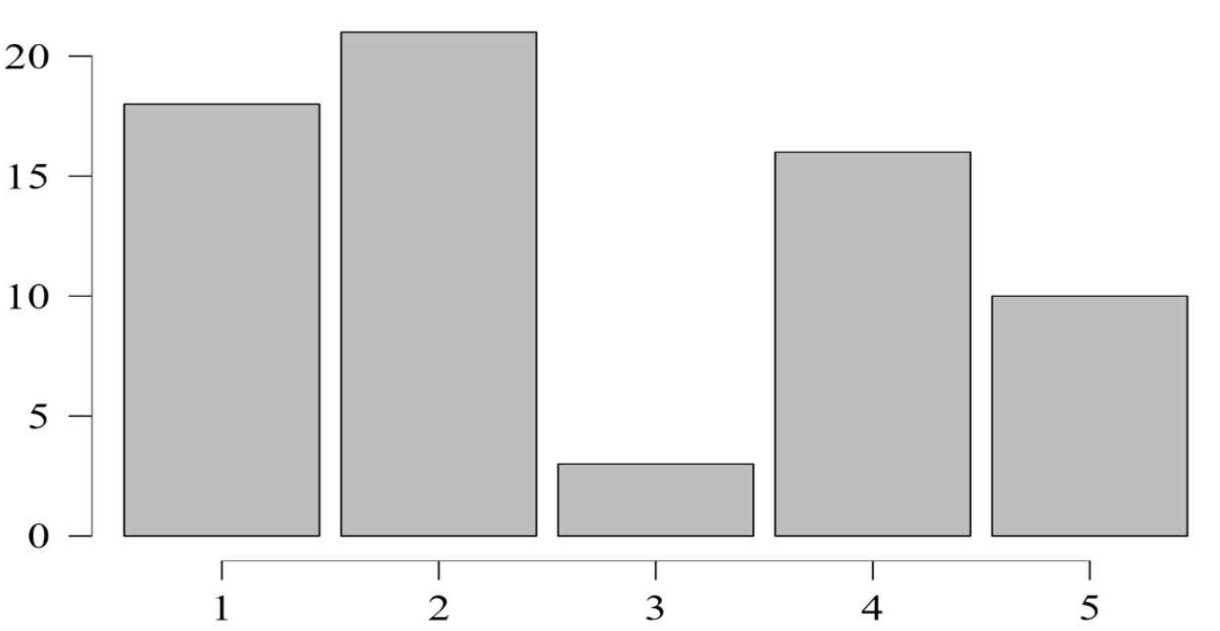


Figure 4. Rejections among Requested Patients

5. DISCUSSION

In our study, comparability of our two groups is difficult because of the increased drop-out rate in the intervention group. This left us with only one patient in the intervention group, whom we were able to compare with the six finishers from the control group.

Our initial assumption, that the metaphylaxis, supported by the "Uroli" app and the "Medipee" device, achieved better urine parameters than the control group, could not be confirmed. The pH value and the specific gravity differed only slightly rather than significantly in the respective groups The pH value in the intervention group was marginally more acidic at 5.9 than in the control group at 6.0. Nevertheless, both values are well within the normal range of 4.8-7.6 (64). The specific gravity in the control group was 1,022 g/ml, while the intervention group had a slightly lower specific gravity of 1,013 g/ml. This value is closer to the <1,010 g/ml target of the general metaphylaxis of the German guideline (5). This difference is not significant, but it still may be due to the significantly higher fluid intake, because the control group only drank 2400 ml on average, whereas the intervention group drank 2550 ml. Due to the fast and uncomplicated recording of drinks in the "Uroli" application, it could be seen that the respective daily drinking values were entered evenly distributed over the day. This cannot be reproduced in the control group. Although the participants had the opportunity to use as many rows of the table as they wanted, most patients only used about 3 rows and indicated high drinking quantities there, such as 1000 ml. This could be attributed to the fact that the app reminds the participants regularly to drink, but also that most people always have their smartphone with them, and that recording into the app is user-friendly. The web-based spreadsheet cannot provide this. For technical reasons, it had to be opened on a laptop or personal computer, which prompted the participants to enter the amount they had drunk at the end of the day. However, this also makes the entries susceptible to errors or rough estimates, which in turn could falsify the data.

Like Wrobel *et al*, Carbone *et al*, and Asplin, we found that obesity may well be associated with urolithiasis, raising the question of whether targeted weight loss as part of metaphylaxis would be beneficial (35,65,66). Both groups examined had a median BMI of over 25 and can therefore be classified as overweight. However, obesity is a general problem of our time and society and should not only be addressed in connection with urolithiasis, but also as a fundamental problem (67).

Analyzing the intervention group errors, we must also take a closer look at the cancellation reasons. The "Medipee" device had an error rate of 46.39% in the measurements

and a rate of successful measurements of 53.61% in the patients in the intervention group, so only about half of the measurements worked properly. This requires not only time but also patience from the patient. In addition, many patients often still have problems urinating after their stone events and have had to hold their urine until the device triggered correctly. This made the whole application difficult, although the intention of the device and the app should be a clear facilitation of metaphylaxis in everyday life.

This is also the reason why so many participants in the intervention group dropped out. One patient could not continue for health reasons, the remaining six dropped out due to problems with the device. The reported faults among all intervention group participants were almost identical: the device had connection problems, the installation on the toilet was not fully developed, the wire got stuck or could no longer be retracted, test strips could not be extended, or the device could no longer be charged. The patient from the intervention group who completed the study also reported the same problems but was motivated to complete the study anyway. Over the course of his documentation time, he needed four devices to continue his recordings. In contrast, no periods of use could be documented from the drop-outs in order to perhaps get more information about how long the patients tried to continue the study.

Since the hospital of Coburg was one site of a multi-center study, it would have been interesting whether the other site, University hospital of Oldenburg, achieved similar results or whether the patients in Coburg were more likely to drop out. However, we were not able to gain any insight into the drop-out rate of Oldenburg.

Limitations that could affect the results of our study are the small number of study participants and, as already mentioned, the high dropout rate, which does not allow for a sufficient evaluation. Due to the technical problems with the device, there were also fewer days and values to evaluate in the intervention group compared to the control group. Furthermore, the use of the Medipee device is limited to one location due to the installation on the toilet and is not as regularly usable for the working population as the urine test strips that you could take with you to work. But the web-based platform could also affect the data because it was only accessible on a laptop or personal computer. The patients did not document every single drink they drank but entered their daily values collectively. This not only leads to errors in the documentation in general but also to estimates that may not be true. In addition, there was no fixed number of urine measurement values per day, so that there can be high variance in the daily average if only 1-2, possibly extreme, values were collected.

The “Uroli” app on its own worked flawlessly, was easy to use, and had a positive impact on drinking levels thanks to the continuous drinking reminders. Streeper *et al* investigated something similar this year in their study on “sipIT”, a system that is also supposed to improve drinking behavior via an app and an associated water bottle. Like us, they too concluded that fluid intake can be improved with digital support (68). Such apps, as well as wearable self-tracking devices, can create an effect of sense of accomplishment and give self-improvement, or in this case metaphylaxis, a more tangible sense (68,69). Nevertheless, their benefit has been limited so far, mainly because the development of such apps and devices is still in its infancy. There is still a lot of research to be done, but also a lot to be improved so that devices like the “Medipee” device have a chance to establish themselves as a beneficial health-care device (70). The intentions to link our digital availability with health self-optimization appears to be the right way to support and relieve the patients as well as the health system.

6. CONCLUSION

1. Due to the high rate of drop-outs in the intervention group, there is no sufficient comparability between the intervention group and the control group.
2. The “Uroli” application together with the “Medipee” device did not show a significant different impact on urinary pH or on urinary specific weight compared to conservative metaphylaxis.
3. The “Uroli” application supported the daily drinking habits positively and therefore showed a significantly higher fluid intake with a median of 2550 ml.
4. Both groups showed an increased BMI over 25 and were therefore classified as overweight.

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8. SUMMARY

Objectives: The aim of our study was to analyze, how effective the “Uroli” application is to support the metaphylaxis of adult patients with urolithiasis after acute treatment of a kidney or ureter stone, compared to metaphylaxis without the “Uroli” application in terms of medical benefit and patient-relevant structural and procedural improvements. Fluid intake, urine pH values and specific gravity were examined in the respective groups.

Materials and Methods: This prospective RCT study took place at the urology department of the REGIOMED Hospital in Coburg and was part of a bigger multicenter pilot study. As main outcomes, endpoints from the category of medical benefit (averages of drinking amount in ml, pH value, specific density in g/ml) are examined. The reference values for pH, specific gravity and drinking amount refers to the German S2K guideline for urolithiasis metaphylaxis. Secondary outcome measures are from the category of patient-relevant structural and care improvements (therapy adherence), age, gender, and BMI. For this thesis, all patients matching inclusion criteria and recruited until April 30, 2023, were considered, meaning these patients whose observation period ended by July 30, 2023. We recruited 15 patients and categorized eight of them in the intervention group, who received the “Uroli” app and the associated “Medipee” device for documentation, and seven patients in the control group, who used ordinary urine test strips and a web-based table for documentation.

Results: In our sample we had seven participants who successfully terminated the study, six of those belonged to the control group and only one subject belonged to the intervention group. We could find a significant difference in fluid intake (P=0.017) with a median of 2550 ml in the intervention group and a median of 2400 ml in the control group. No significant difference with P=0.832 could be seen in the pH values. Comparing the median of the groups, the intervention group has a pH value of 5.9, while the control group has a pH value of 6.0. Both values are very close to each other and within the normal reference range of urine pH. Analyzing the differences in specific weight, the result is P=1.000 and therefore there is no significant difference between the two groups here either. The specific gravity has a median of 1.013 g/ml in the intervention group and 1.022 g/ml in the control group. The BMI of the patient in the intervention group is 25.1 and the median of the control group patients is 29.3. Both are classified as overweight.

Conclusion: High drop-out rates in the intervention group, made it difficult to compare both groups. The “Uroli” application together with the “Medipee” device did not show a significant

different impact on urinary pH or on urinary specific weight but a significant increase in fluid intake compared to conservative metaphylaxis.

9. CROATIAN SUMMARY

Naslov: Procjena „aplikacije Uroli“ za metafilaksu mokraćnih kamena

Ciljevi: Cilj našeg istraživanja bio je analizirati koliko je učinkovita aplikacija „Uroli“ u potpori metafilakse odraslih bolesnika s urolitijazom nakon akutnog liječenja kamenca u bubregu ili ureteru, u usporedbi s metafilaksom bez aplikacije „Uroli“ u smislu medicinske koristi i strukturnog i proceduralnog poboljšanja relevantnog za pacijenta. U pojedinim skupinama ispitivani su unos tekućine, pH vrijednosti urina i specifičnu težinu.
Materijali i metode: Ova prospektivna RCT studija provedena je na urološkom odjelu bolnice REGIOMED u Coburgu i bila je dio veće multicentrične pilot studije. Kao glavni ishodi ispituju se krajnje točke iz kategorije medicinske koristi (prosjeci popijenih količina u ml, pH vrijednost, specifična gustoća u g/ml). Referentne vrijednosti za pH, specifičnu težinu i količinu za piće odnose se na njemačke S2K smjernice za metafilaksu urolitijaze. Sekundarni rezultati ishoda studje pripadaju pacijent-relevantnim podacima i izražavaju strukturu pacijenata s obzirom na dob, spol, BMI i usklađenost sa terapijom. Za ovu tezu uzeti su u obzir svi pacijenti koji odgovaraju kriterijima uključivanja i regrutirani do 30. travnja 2023., što znači ti pacijenti čije je razdoblje promatranja završeno do 30. srpnja 2023. Regrutirali smo 15 pacijenata i kategorizirali od njih osam u intervencijsku skupinu, koji su primili aplikacija „Uroli“ i pripadajući uređaj „Medipee“ za dokumentiranje, te sedam pacijenata u kontrolnu skupinu, koji su za dokumentiranje koristili obične urin test trake i web tablicu.
Rezultati: U našem uzorku imali smo sedam sudionika koji su uspješno prekinuli studiju, šest ih je pripadalo kontrolnoj skupini, a samo jedan ispitanik pripadao je intervencijskoj skupini. Mogli smo pronaći značajnu razliku u unosu tekućine (P=0,017) s medijanom od 2550 ml u intervencijskoj skupini i medijanom od 2400 ml u kontrolnoj skupini. Nije bilo značajne razlike s P=0,832 u pH vrijednostima. Uspoređujući medijan skupina, intervencijska skupina ima pH vrijednost 5,9, dok kontrolna skupina ima pH vrijednost 6,0. Obje vrijednosti su vrlo blizu jedna drugoj i unutar normalnog referentnog raspona pH urina. Analizirajući razlike u specifičnoj težini, rezultat je P=1.000 te stoga ni ovdje nema značajne razlike između dvije skupine. Specifična težina ima medijan od 1,013 g/ml u intervencijskoj skupini i 1,022 g/ml u kontrolnoj skupini. BMI bolesnika u intervencijskoj skupini iznosi 25,1, a medijan pacijenata kontrolne skupine iznosi 29,3. Obje su klasificirane kao pretile.
Zaključak: Visoke stope odustajanja u intervencijskoj skupini otežale su usporedbu objih skupina. Aplikacija „Uroli“ zajedno s uređajem „Medipee“ nije pokazala značajno drugačiji utjecaj na pH urina ili na specifičnu težinu urina, ali značajno povećanje unosa tekućine u odnosu na konzervativnu metafilaksu.