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REVIEW

Optimal Delivery of Follow-Up Care for the Prevention of Stone Recurrence in Urolithiasis Patients: Improving Outcomes

Lazaros Tzelves, Marinos Berdempes, Panagiotis Mourmouris, Iraklis Mitsogiannis, Andreas Skolarikos

Second Department of Urology, National and Kapodistrian University of Athens, Sismanogleio General Hospital, Athens, Greece

Correspondence: Andreas Skolarikos, Tel +30 2132058253, Email andskol@yahoo.com

Abstract: Urolithiasis is a common clinical condition with frequent recurrences. Advances in knowledge of pathophysiological mechanisms permit the categorization of patients to low and high risk for recurrence, with specific metabolic abnormalities diagnosed in the second category. Follow-up is essential for patients with urolithiasis and consists of both imaging and metabolic follow-up with urine studies. No formal guidelines or solid evidence currently exists regarding frequency and type of follow-up studies to be performed in each category. This review aims to summarize existing evidence regarding follow-up, in order to guide clinicians on how and when to follow-up urolithiasis patients according to existing clinical scenario.

Keywords: urolithiasis, imaging follow-up, metabolic follow-up, recurrence

Introduction

Urolithiasis prevalence shows increasing trends, with an estimated proportion of 10.6% in males and 7.1% in females.[1] Although this is a non-malignant condition, its association with metabolic syndrome and cardiovascular disease,[2] chronic kidney disease[3] and its large economic burden to healthcare systems[4] make urolithiasis a multifaceted urological condition.

Dehydration, arid climate, obesity and metabolic syndrome, genetic predisposition, as well as certain urinary metabolic abnormalities are linked to increased kidney stone formation.[5] Although the etiology is multifactorial and not yet clarified, the sequence of pathophysiological events until urolithiasis occurrence is unraveled to a satisfying degree. Initially, Randall's plaque is formed in the renal papillae from calcium phosphate.[6] In patients with urine supersaturation of calcium/oxalate/phosphate ions, crystals accumulate along with organic material (proteins, glycosaminoglycan, mucus) on Randall's plaques, and stone crystals are formed.[6] The crystal fusion finally leads to stone formation in considerable sizes. Advances in knowledge of stone disease pathophysiology led to subcategorization of these patients into low and high-risk stone formers, according to underlying existing metabolic abnormalities, patient comorbidities, stone composition and number of recurrences.[5]

Older studies, which are cited as the gold standard for urolithiasis recurrence, report a 50% relapse rate after 5 years and 75% after 20 years from initial stone episode.[7,8] The importance of proper follow-up is highlighted when considering these very high relapse rates in order to establish an appropriate and practical protocol. The European Association of Urology Guidelines Urolithiasis Panel has recently underlined the necessity for the existence of such an algorithm,[9] since no solid evidence yet exists to support guidance, neither from EAU Guidelines,[5] nor from American Urological Association (AUA) Guidelines.[10]

There are several issues to be considered before establishing a successful follow-up algorithm. First, every patient differs according to stone composition, location and burden, associated comorbidities, social status and personal

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preferences. Importantly, access to a stone specialist (urologist, nephrologist) is not always possible in order to ensure proper follow-up. In case of imaging, the modality to be used depends on desired sensitivity, while always weighing the associated risks, such as radiation exposure and costs. In patients with urinary metabolic abnormalities, who are under medical treatment, adherence to both regimen and follow-up is questionable. Hsi et al reported some interesting findings regarding differences in adults who receive empiric versus those receiving selective medical treatment for kidney stones.[11] Around 75% of patients received empiric treatment, especially older, non-white males with hypertension.[11] Citrate was given more often in patients who received selective treatment, while thiazides were give more often in patients under empiric treatment.[11] No differences were detected in terms of recurrence, hospitalizations and emergency department visits during a follow-up of two years.[11] Although there is certain benefit from preventive drug therapy in high-risk patients, there are also several dietary interventions which help decrease recurrences. A recent systematic review and meta-analysis showed that low protein intake with or without high fiber diet does not lower recurrence rate compared to controls, while increased fluid intake and a low sodium, normal calcium diet importantly decrease recurrences in patients with calcium stones.[12] A possible explanation is the different role of animal and plant protein in stone recurrence prevention, but the difficulty of conducting long-term trials to compare these two sources of protein renders conclusions unsafe.[12] In patients with residual fragments after surgical treatment, there is a debate regarding the safe cut-off size to characterize fragments as clinically insignificant and propose follow-up or re-intervention. Finally, due to all these discrepancies existing in the urolithiasis literature, it is very impractical to conduct trials with homogeneous populations.

Imaging Follow-Up

The catastrophic consequences after the atomic bomb explosion in Hiroshima and Nagasaki made obvious the serious health risks associated with ionizing radiation exposure. Its effects are either deterministic, which occur when a threshold is passed (skin erythema, cataracts, hypogonadism, hypothyroidism, acute radiation syndrome),[13] or stochastic, which occur with cumulative doses of radiation (carcinogenesis).[14] Therefore, the International Atomic Energy Association (IAEA) has set annual limits of 50 millisieverts (mSv) for total body radiation and 500 mSv for target organ radiation.[15] Exposure to radiation is not negligible intraoperatively, both for patients[16] and for operating urologists.[17] Unfortunately, the level of knowledge and understanding of mechanisms, harms and safe limits for radiation exposure are not satisfactory among endourologists according to a recent survey.[18]

The gold standard for diagnosis of urolithiasis is low-dose computed tomography (CT scan), with an estimated sensitivity of 93.1% and specificity of 96.6%.[19] Newer, dual-energy CT protocols can even differentiate between urate and calcium stones.[20] X-ray and ultrasound (U/S) of kidneys, ureters and bladder (KUB) offer significantly less sensitivity/specificity equal to 44–77% and 45–94%, respectively.[21,22] Sensitivity of U/S for stones <3 mm is less, since these fragments may not produce an acoustic shadow and the physician has to differentiate between echogenic renal sinus fat and stone particles, while, for X-ray, sensitivity drops significantly for stones <5 mm.[23] Significantly, U/S seems to overestimate stone size in nearly 50% of cases compared to CT scan, especially for smaller stones,[23] while X-ray underestimates size compared to CT scan.[24]

The radiation dose received from a standard dose CT is 10 mSv, from low-dose CT ~3 mSv, from X-ray 0.7 mSv, while U/S is a safe, radiation-free method.[25] Low-dose CT protocols contain 30 milliamperes (mA), instead of 100 mA in standard protocols,[26] resulting in reduced radiation without loss in sensitivity or specificity, which remain at 99% and 94%, respectively, according to a recent meta-analysis.[27] The main drawback of low-dose CT protocols is lower discriminative ability in patients with body mass index >30 kg/m^2.[5]

The fact that radiation exposure equal to 100 mSv can lead to a malignancy-related death in 1/100,000 patients[28] led to the establishment of annual threshold equal to 50 mSv for a year or 20 mSv for a period of 5 years.[29] Fahmy et al performed a study to evaluate the cumulative radiation exposure during a 2-year follow-up period in patients with symptomatic stone episodes.[30] The effective dose received in each patient was calculated using the dose length product, with a mean of 23.16 mSv for CT scans and 2.21 mSv for X-rays.[30] The mean effective radiation exposure (MERE) per patient during the first year was 29.29 mSv, with 17.3% of patients exceeding the annual limit of 50 mSv, while during the second year a MERE equal to 8.04 mSv was found with none of patients exceeding the annual threshold.[30]

Importantly, stone location and patient demographic characteristics did not affect MERE, which was significantly higher in patients who were followed-up using more CT scans and fewer ultrasounds.[30] Another important finding of this study was that urologists and emergency department physicians asked for CT scans more frequently compared to nephrologists.[30] In a similar study assessing the effective radiation dose during the first year of follow-up after an acute stone episode, Ferrandino et al reported that 20% of patients exceeded the 50 mSv limit.[31] The median MERE per patient was 29.7 mSv, while patients received a mean of 1.2 X-rays, 1.7 CT scans and 1 intravenous pyelography.[31] Similarly to findings of Fahmy et al,[30] no association was detected between stone burden, anatomic location and composition, as well as with patient baseline characteristics with the possibility to exceed annual permitted radiation dose.[31] Considering the harms and increased cost of CT scan compared to X-ray and U/S, a reasonable plan of follow-up would be to perform a combination of X-ray and U/S, rather than CT scan, which could be obtained in cases of symptom recurrence and pre-operative planning. The combination of X-ray and U/S can achieve excellent rates of accuracy (95%), sensitivity (96%) and specificity (91%).[32]

The EAU Guidelines Urolithiasis Panel recently evaluated literature regarding stone disease follow-up in order to provide a flow chart based on Panel member consensus and on a benefit/harm principle.[33] After critical appraisal of existing literature with inclusion of 76 studies, an algorithm was proposed according to patient stone status.[33] In patients who are stone-free after surgical treatment and belong to general population, imaging follow-up is suggested at 6 and 12 months, while after 36 months patients could be either discharged or counseled for further imaging assuming no recurrence occurred in the meantime.[33] In stone-free patients with diagnosed urinary metabolic abnormalities, closer imaging is suggested at 6 and 12 months and annually thereafter.[33] In patients with residual fragments ≤4 mm, commonly considered as clinically insignificant, Panel consensus proposed imaging at 6 and 12 months and then every 12 months, while for cases with residuals >4 mm, re-intervention should be planned.[33] Importantly, imaging follow-up consists of X-ray and U/S KUB based on clinicians' preference, imaging availability and stone characteristics, while CT scan should be offered for symptomatic recurrence or before intervention.[33]

Metabolic Follow-Up

The understanding of the pathophysiological mechanisms regarding lithogenesis has led to the subcategorization of patients to low- and high-risk stone formers, according to the widely adopted definition provided by EAU Guidelines.[5] After categorizing a patient as high risk for urolithiasis recurrence, the patient is strongly recommended to undergo serum chemistries, measurement of parathormone and a 24-hour urine test, which aids to identify specific metabolic abnormalities (measurement of excreted calcium, phosphate, potassium, sodium, urate, citrates, oxalate, magnesium, urine pH and volume) and dictates appropriate preventive measures.[5] Both EAU[5] and AUA[10] Guidelines suggest this type of testing, as well as several urological associations.[34] Urine testing is suggested to be performed after achieving stone-free status for at least 3 weeks, under normal dietary habits.[35] Optimal collection methods using bottles prepared with a solution of 5% thymol in isopropanol, storage at <8°C or boric acid are proposed,[5,36] while two consecutive samples seem to be more reliable instead of a single urine collection.[37] Regarding follow-up of patients who initiate targeted preventive therapy, monitoring of urine parameters seems imperative to evaluate response to treatment. Although there is a paucity of high-quality evidence, the EAU suggests a first 24-hour urine collection 2–3 months after initiation of treatment and annually thereafter.[5] In cases of inability to collect 24-hour urine, an alternative is to analyze spot urine samples and correlate findings to estimate 24-hour measurements, although this is only a rough estimation due to high variability of results according to patient characteristics, diet and time of collection.[5]

A 24-hour urine collection seems to lead to reduced stone recurrence and growth rate in high-risk stone formers by proposing appropriate preventive drug regimens.[38–40] Despite its clinical usefulness and non-invasive nature, it is an underutilized test. Milose et al studied claim databases regarding 28,836 urolithiasis patients and reported that metabolic urine testing was performed in 7.4% overall and in 16.8% in those patients with recurrent disease.[41] Patients who are older, healthy, receive a monthly salary and live in urban locations seem to adhere better to urine testing.[41] Follow-up performed by a urologist or nephrologist was also associated with higher odds of getting tested.[41] Dauw et al found that only 16% of patients return for another follow-up test after 6 months from treatment initiation.[42] In a recent study, assessing prescription patterns for urolithiasis drugs in veterans, Song et al report that 13% of 130,489 patients underwent

24-hour urine test.[43] Prescription of diuretics, alkalinization therapy and allopurinol were more frequent in this minority of patients who completed urine testing, therefore implying that treating physicians rely on 24-hour urine test findings to guide decision making.[43] A significant observation was that patients who had metabolic testing and were assessed by a stone disease expert (urologist or nephrologist) were more likely to initiate targeted preventive therapy, while approximately 20% were not followed-up by a specialist and were not offered such interventions.[43]

Preventive drug treatments for high-risk stone formers are commonly associated with a wide variety of side effects. Thiazide diuretics act mainly by increasing calcium reabsorption in distal nephrons, therefore decreasing calcinuria, and they are proved to be effective in urolithiasis patients.[44] Thiazides are related with low levels of citrate, hypokalemia and acidosis, which can be corrected with potassium citrate supplementation.[45] Other side effects which can lead to drug discontinuation in up to one of six patients are postural hypotension, fatigue, gastrointestinal disturbance, weakness, rashes and disarrangement of blood glucose and uric acid levels.[46,47] Therefore, patients on thiazides should also be monitored for calcium, potassium, serum levels of uric acid and glucose. Urinary alkalization therapy with potassium citrate or sodium bicarbonate is an essential component of treatment for a variety of stone compositions (calcium oxalate, urate, cystine), with a dual mechanism of action: increase of urinary pH to increase solubility of ions; and increase of urinary citrate, which is a stone inhibitor, to decrease crystallization rate.[10] Target urinary pH is ~6.5, while over-alkalization above 7.0 has the risk of calcium phosphate stone formation, thus patients should frequently monitor urinary pH using dipsticks.[5] Gastrointestinal upset is a common side effect, which can be ameliorated when drugs are taken with water and after meals.[47] Although potassium citrate is the most commonly used drug over sodium bicarbonate to avoid fluid retention and increased sodium load, it can lead to life-threatening hyperkalemia in cases of renal failure, necessitating monitoring of serum electrolytes.[47,48] Allopurinol, a xanthine oxidase inhibitor, is commonly used to reduce serum and urine urate levels in patients with uric acid urolithiasis. It is a generally safe drug, with gastrointestinal disturbances being the most common side effect, with very rarely observed bone marrow suppression, hepatitis and toxic epidermal necrolysis.[47] In cases of concomitant prescription with thiazides, renal and liver function monitoring is suggested.[47,49] In patients with cystinuria and high levels of urinary cystine, thiol-binding drugs are commonly prescribed to convert insoluble cystine molecules to a more soluble product, which is excreted more easily.[47] Several side effects, such as proteinuria, nephrotic syndrome, hematologic abnormalities, pulmonary manifestations, gastrointestinal upset and skin rashes necessitate follow-up of patients under these drugs, with renal, liver and hematological testing.[47]

The Agency for Healthcare Research and Quality (AHRQ) assessed existing randomized clinical trials (RCTs) on pharmacological interventions for stone patients and reported that baseline levels of urinary calcium, citrate and oxalate are not predictive of disease recurrence, while no data existed to support that follow-up biochemistry studies can predict treatment effectiveness.[40] Despite the lack of strong evidence to support follow-up metabolic testing, it is clinically reasonable and suggested to follow-up patients with specific metabolic abnormalities under targeted treatment with urine testing. Initially a 3–6 month period from drug initiation could aid to adjust the appropriate dose, and annual testing thereafter is suggested. Importantly, monitoring of side effects according to the safety profile of the prescribed drug is strongly advised. According to existing data, a stone disease expert seems to be the most appropriate physician to evaluate and monitor patients under drug treatment.[41,43]

Observation of Asymptomatic Renal Stones

The use of advanced imaging like CT scan has led to an increase in diagnosis of asymptomatic stone disease.[50] Observation of stones <20 mm is an option, but the natural history of asymptomatic stones cannot be safely predicted and depends on several factors, such as patient metabolic states, stone size, composition and location, as well as anatomic variations. Recently, Lovegrove et al performed a systematic review and meta-analysis to appraise the literature regarding data on small, asymptomatic renal stones.[51] Although several studies suggest that stone size is a predictor of symptom occurrence (pain, fever, infection, hematuria), with stones >5 mm showing greater chance of causing symptoms,[52] pooled analysis did not detect significant difference for symptom occurrence in stones <5 mm compared to >5 mm, or stones <10 mm compared to >10 mm.[51] Lower calyx location and right-sided stones may have a protective role.[52] However, heterogeneity among studies does not permit safe conclusions to be drawn. Intervention rates were found to be

significantly lower for stones <5 mm compared to >5 mm and those <10 mm compared to >10 mm,[51] while upper pole stones, patients <50 years old and those with prior stone-related procedures were more likely to require intervention in the future.[53,54] Therefore, simple follow-up can be proposed to patients with asymptomatic renal stones, especially those with <5–10 mm size, non-upper pole location and in patients without a history of surgery related to urolithiasis.

Clinically Insignificant Residual Fragments (CIRFs) After Stone Surgery

The ideal surgical intervention would render a patient completely stone-free. Since this is rarely the outcome, the term of CIRFs is commonly described, with the most widely used cut-off size being ≤4 mm.[55] However, this perspective is debated, since even a particle of dust equal to 1 mm can act as a nidus for stone regrowth and lead to symptomatic recurrence.[56] In a recent meta-analysis, Brain et al evaluated literature regarding natural history of post-treatment renal stone fragments and concluded that patients with residuals >4 mm carry a significantly increased risk of intervention compared to fragments ≤4 mm.[57] Disease progression did not differ significantly between the two groups.[57] The EAU Guideline Urolithiasis Panel performed a systematic appraisal of the literature, concluding that for residuals ≤4 mm intervention was in the range 17–29%, disease progression 9–34% and spontaneous expulsion 21–34% during 4 years of follow-up, while for fragments >4 mm, intervention was in the range 24–100%.[58] Raman et al evaluated patients with residuals after percutaneous nephrolithotomy (PNL) and found that patients with fragments 2–4 mm experienced more symptomatic episodes and re-interventions compared to those with fragments <2 mm.[59] Data derived from the literature imply that patients with residuals up to 4 mm, especially those with <2 mm, can be followed-up without immediate intervention, but patients should be counseled that progression rates are not negligible and re-intervention cannot be excluded. Residuals >4 mm should be treated with appropriate auxiliary procedure due to high rates of progression and symptomatic disease.

Post-Ureteroscopy Follow-Up

Ureteroscopy (URS) has revolutionized management of ureteric calculi. Although URS achieves high stone-free rates, follow-up is needed to visualize fragment clearance, hydronephrosis recession and ensure no asymptomatic hydronephrosis develops due to ureteral stricture.[25] Fulgham et al provided clinical protocols regarding imaging in the management of ureteral stones.[25] The authors suggest to guide imaging according to whether a stone was removed intact or intracorporeal lithotripsy was used to produce fragments.[25] In intact stone removal without symptoms, U/S is enough to confirm resolution of hydronephrosis, while in patients with persistent hydronephrosis or symptoms a CT scan with contrast is warranted.[25] In cases with fragmented stones but no symptomatic disease, U/S and X-ray (for radiopaque stones) are suggested to assess hydronephrosis.[25] Again, if hydronephrosis persists, further imaging is performed with CT scan, while radiopaque fragments can be followed-up with X-ray.[25] In cases of symptomatic fragments, X-ray and U/S can be used for radiopaque stones and CT scan for radiolucent fragments.[25] Considering the low incidence rate of ureteral strictures after URS (1–4%)[60,61] and the number of patients needed to assess with imaging (number needed to treat=25) to detect a patient with silent hydronephrosis,[62] further imaging after hydronephrosis and symptom resolution is recommended in cases of laborious surgery, ureteral trauma, impacted stones and in patients at high risk for chronic kidney disease or those with anatomic abnormalities.

Proper Timepoint to Discharge a Patient

Following the principle for oncologic patients, an ideal scenario would be to define the proper timepoint to discharge a patient with urolithiasis from further follow-up. No algorithm or guidelines exists to suggest the proper duration of follow-up. Recently, the EAU Guidelines Urolithiasis Panel performed an extensive literature review regarding urolithiasis follow-up.[58] After performing a pooled analysis of more than 5,000 patients who are stone-free after surgery, the Panel suggest imaging for at least 2 years for radiopaque stones (X-ray) and at least 3 years for radiolucent stones (X-ray and U/S) to achieve an 80% stone-free "safety margin", while a minimum of 5 years of imaging follow-up is suggested to achieve a 90% "safety margin".[58] Data regarding high-risk stone formers are scarce, but due to high rates of recurrence and associated drug side effects long-term follow-up is recommended.

Special Populations

Special populations, such as children and elderly people with specific comorbidities, should be considered since variable follow-up strategies may be more appropriate. Chao et al studied the risk of urolithiasis in patients with diabetes mellitus, who are defined as physically frail.[63] They found that increasing frailty in diabetic patients is linked with higher risk of urolithiasis occurrence within a span of 4.2 years of follow-up.[63] This observation may apply not only to incidence but also to recurrence risk.[63] Several mechanisms are proposed for this phenomenon: low physical activity that can lead to immobilization, subsequent bone resorption and hypercalciuria, increased protein intake to balance muscle loss and fluid loss/dehydration.[63] Coexisting comorbidities, such as gout, hypertension, metabolic syndrome and obesity, further increase the risk for persistent urinary abnormalities and recurrent urolithiasis in this group of patients, thus making intensive follow-up necessary to avoid complications.[63] Pediatric population with stone disease is commonly associated high rates of coexisting metabolic abnormalities. Vieira et al recently studied the association between dietary patterns and metabolic disorders in children and adolescents with stone disease.[64] They reported that the majority of patients (95%) suffered from coexisting abnormalities, most commonly hypocitraturia, one in four had higher than normal BMI, 65% consumed low fiber and 55% reported higher than normal sodium intake.[64] Therefore, in the pediatric population metabolic assessment and close follow-up is essential, since the lifetime risk of recurrences and subsequent kidney damage is very high.[64]

Conclusions

Ionizing radiation exposure can be dangerous during imaging follow-up of urolithiasis patients. A combination of ultrasound and X-ray should be preferred for follow-up, except in cases of symptomatic recurrence or preoperative planning. Metabolic assessment and follow-up using urine testing is strongly advised in high-risk patients under targeted treatment, while patients who receive drug therapy should be monitored regarding side effects. Observation of asymptomatic renal stones may be more appropriate in small stones <5–10 mm, non-upper pole location and in patients without a history of interventions, but the existing literature is weak. In patients after surgical treatment, observation may be more appropriate in patients with residuals 2–4 mm, but for larger fragments re-intervention is more suitable. When factors such as laborious surgery, impacted stones, ureteral trauma and anatomic alterations are present, imaging follow-up for resolution of hydronephrosis is indicated in ureteroscopy cases. Nevertheless, a structured follow-up plan is needed in patients with urolithiasis, since recurrence rates are high.

Disclosure

Lazaros Tzelves is a Research Associate of the European Association of Urology Guidelines Panel for Urolithiasis and Bladder Stones. Andreas Skolarikos is the Chair of the European Association of Urology Guidelines Urolithiasis Panel. The authors report no other conflicts of interest in this work.

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