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Tailored metabolic workup for urolithiasis – the debate continues

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DEBATE

Tailored Metabolic Workup for Urolithiasis – The Debate Continues

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Abstract

Urolithiasis is one of the commonest afflictions of the urinary tract. Stones are of various chemical compositions, some share some common etiology; but most are specific to the structure and composition of stone. In view of highly recurrent nature of this condition, it is logical to have strategies for prevention. However, due to multiple factors most patients receive no or fragmented information on prevention. The current controversy is to the extent of metabolic workup in adult first time stone former. This requires longitudinal studies to show benefit in prevention strategies. Patients at high risk can have recurrence in weeks to years, depending upon the composition and attending risk factor. They should be targeted with concentric and tailored prevention protocols. The major urological guidelines (EAU and AUA) recommend basic stone workup for all patients. However, indication for detailed workup are less well documented, so one potential solution is to tailor metaphylaxis strategies for individual patient.

Key Words: *Urolithiasis. Metabolic workup. Hyperoxaluria. Hyperuricemia. Hypocitraturia.*

INTRODUCTION

Urolithiasis is a complex condition with many etiologies.[1] Vast majority of stones are either calcium containing (oxalate and phosphate) or uric acid.[2] There are various clinical, biochemical, metabolic, and genetic characteristics of the inherited diseases which lead to nephrolithiasis/nephrocalcinosis, such as: Idiopathic hypercalciuria, renal hypophosphatemia, renal tubular acidosis, idiopathic infantile hypercalcemia, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, hypocitraturia, cystinuria, primary hyperoxaluria and renal hypouricemia.[3] The term urolithiasis in itself, groups multitude of stones each with some common and other discrete etiologies. Diet, presence of metabolic syndrome, and some genetic abnormalities are major causes of recurrent urolithiasis. Several factors may be related to susceptibility to urinary lithiasis such as race, gender, dietary intake, genetics, climatic aspects, and metabolic changes.[4]

Urolithiasis is a highly recurrent condition. The lifetime risk of developing stone is 1 in10,[5] compared to a risk of 9 in 10 for recurrence at 10 years.[6] It is characterized by a recurrence rate around 50%,[7] reaching 70% within 10 years. Careful history and metabolic evaluation are the key to prevention strategies. However, prevention strategies and metabolic evaluation is one of the most controversial areas in stone management.[8] A recent survey by McGuire and colleagues[8] in North American urologists noted that practices in the metabolic investigation of stone-forming patients demonstrate wide ranging variations. This is partly because metabolic evaluation and then interpretation is cumbersome, it is expensive and then often there are no clear answers, particularly in mixed stones, long-term medical therapy; and life-style modifications have poor compliance and partly because there is insufficient strong evidence that for most stones, medical therapy significantly impact stone recurrence. Although there is a dearth of strong scientific evidence for the benefit of selective versus non-selective prevention of recurrence in patients with calcium stone disease, there is currently both convincing and logical information in support of tailored/selective treatment regimens aiming at correction of abnormal target variables.[9] The poor results of metaphylaxis are partly due to low and diminishing long-term compliance to the intervention, although strict adherence has been shown to prevent chronic kidney disease.[10] It is, therefore, imperative to have a tailored approach to target patients at most risk of recurrence.

Urolithiasis management has become less invasive with the introduction of lithotripsy and endourology. Minimally, invasive options on one hand have made management of urolithiasis less morbid intervention. However, it has downside. The keenness to do metabolic and long-term medical interventions are partly dampened by advances in endourology. Sininsky *et al*. noted that low education, high poverty, and younger age are associated with suboptimal evaluation follow-up.[11] Of note, the lowest adherence was in younger patients, a population that requires the most urgent workup.

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The training of urologists in metabolic evaluation and interpretation is also lacking. It is, therefore, not surprising that urologist managing stones, have issues in interpretation and ordering appropriate dietary and medical advice. As a consequence, often the metabolic workup is either not ordered or not followed-up. It is important to develop tailored approach to order and follow metabolic evaluation of patients, treated recently for urolithiasis. Urological association guidelines have consistently underscored the importance of urologists to be involved in the metabolic evaluation and follow-up of stone patients. The EAU guidelines recommend use of general measures for patients with low risk for recurrence, and specific metabolic interventions for patient at high risk for recurrence.[12] An AUA guideline recommends that clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries and urinalysis on a patient newly diagnosed with kidney or ureteral stones.[13] Twenty-hour urinary estimation of super saturation of various salts is implicated in stone formation. Dietary and life-style modifications are recommended for most stone formers; however, additional use of medical management is directed for specific metabolic abnormalities.

In view of the highly recurrent nature of this condition, it is logical to have strategies for prevention. The major debate in urology is to do or not to do metabolic workup. There is a controversy as to how much information is given to patients on prevention. Due to multiple factors, most patients receive no or fragmented information on prevention, often the metabolic abnormalities differ significantly in repeat analysis.[14] The factors for lack of metabolic evaluation and implementation of recommendations are attributable to both the physicians (urologists) and patients. Most urologists are reluctant to recommend metabolic workup and refer patient for metaphylaxis. This is partly due to the poor understanding of the biochemistry of urolithiasis; as most are not convinced that prevention strategies work, and think that with modern endourological means it is easier to treat stone. In long-term, the results obtained with preventive interventions is disappointing. Patients are motivated following a recent painful episode of urolithiasis, however, long-term compliance is poor.

The current writeup is aimed to define a tailored approach to ordering and implementing metabolic workup and suggests life-style modifications to decrease the rate of recurrence for urolithiasis.

DISCUSSION

Why to do metabolic workups for stone patient?: Metabolic workup for stone patients is performed to identify potential anomalies, to identify if stone is secondary to specific disorder, and to identify risk factors contributing to urolithiasis. Urolithiasis is a complex medical condition. It is not only related to various metabolic and biochemical errors, but to some generic medical conditions like metabolic syndrome. The workup is clinical, radiological and biochemical evaluation. With this comprehensive evaluation, it is possible to establish a preventive intervention strategy.

There is often an argument in favour and against metabolic workup. The proponents of metabolic workup propose screening as urolithiasis is a highly recurrent condition. Screening also helps to define and correct a metabolic error. However, since urolithiasis is a common condition, it is likely to put an enormous financial and manpower burden on the healthcare system. In France, the annual budget impact for stone disease based on 65 million inhabitants is €590 million for the payer.[15] The budget impact analyses show that prevention of nephrolithiasis can have a significant cost savings for a payer in a healthcare system and reduce the stone burden significantly. However, opponents of metabolic workup contend that the metabolic workup and evaluation is expensive, strenuous and difficult to interpret. In addition, there are few trials showing that there is benefits of a pharmacological approach in stone prevention.

Stone former classification and risk stratification: Most adults' first time stone formers (first episode of documented stone disease) are likely not to form another stone in their lifetime; particularly, if they are not at high risk for an stone event. Recurrent stone formers (previous documented history of urolithiasis) are, however, at a much higher risk for recurrence. In comparison pediatric patients are considered high risk even following first event of urolithiasis. Certain stone formers are at high risk from a stone event and therefore, even with first event they should undergo defined preventive strategy. These are patients with bilateral stones disease, solitary kidney, anatomical anomalies, obstructive pyelonephritis, or stone during pregnancy, renal insufficiency or inflammatory bowel disease.

From stone analysis to preventive strategy: The EAU guidelines on urolithiasis describe the development of preventive strategy, based on stone analysis and risk factors. Reliable stone analysis and basic metabolic evaluation are highly recommended in all patients after stone passage (grade A recommendation).[12] Every patient should be assigned to a low- or high-risk group for stone formation. Patients with whewellite stones are frequently seen with hyperoxaluria and medullary sponge kidney, whereas wedillite are associated with hypercalciuria. In patients with uric acid stones, the causal factors could be low urinary pH, hypercalciuria, and high uric acid output. The carbapatite is more often associated with high urinary pH, hypercalciuria, and primary hyperoxaluria. The brushite stones are seen in

patients with primary hyperoxaluria, hypercalciuria and sponge kidney. The second most important factor is identification of the risk factors following stone composition. Specific metabolic workups and preventive strategies can be instituted, which are likely to be cost effective.

Common stone types and metabolic abnormalities: Calcium stones are the commonest stone type. About 80% of stones are calcium-containing stones. Urinary super saturation is often observed in these patients for calcium oxalate and calcium phosphate. The associated metabolic abnormalities include hyper-oxaluria, hypocitraturia, persistently elevated urine pH, and increased urinary uric acid excretion. However, the most common abnormality is idiopathic hypercalciuria (IH). Spivacow *et al*.[16] noted 57% to be having IH in a cohort of 3,040 patients with urolithiasis. Treatment of IH is often with thiazide diuretics. Several RCTs have shown that the stone recurrence is decreased with the use of thiazide for IH.[17]

The protective effects of citrate in urine on urolithiasis are well known. It not only chelates calcium ions but also prevent nucleation and growth at the crystal surface. Barcelo and colleagues[18] compared the efficacy of potassium citrate with placebo in patients with hypo-citraturic CaOx stones.[18] In 3 years of follow-up in patients taking potassium citrate, they noted a significant reduction in stone formation rate from 1.2 to 0.1 per patient-year ($p<0.001$). Patients with normal urinary citrate level may also benefit from citrate supple-mentation due to lowered calcium oxalate super saturation and subsequent crystallisation.[19]

Hyperoxaluria is another common metabolic derangement; of the various types of hyperoxaluria, idiopathic variety is commonest. It is often due to excessive oxalate intake in the diet, decreased dietary calcium, or increased endogenous production. Dietary advises of cutting oxalate-rich diet and taking recommended calcium, to help binding oxalate in the gut, are reasonable advises.

Calcium phosphate stones are frequently found as mixed stones with CaOx. They typically constitute <50% of the stones. Pure calcium phosphate stones are associated with renal acid excretion defect, most commonly due to distal RTA. The treatment strategies are similar to CaOx, i.e. reduced dietary sodium and protein, high fluid intake, and may be thiazides and citrate.

Uric acid stones are formed in patients with low urine pH, low urine volume and hyperuricosuria, of which the former is the most common cause. Urinary alkalization with potassium citrate and curtailing animal protein intake to less than 20 g/kg/day and in refractory cases of hyperuricemia allopurinol or febuoxstat can be added.

Struvite stones and infection stones or magnesium ammonium phosphate stones are seen in patients with infection from urea-splitting bacteria such as *Proteus, Providencia*; and sometimes *Klebsiella, Pseudomonas*, and *Enterococci*. Staghorn stones are treated by interventional treatment including endourology and lithotripsy, following culture specific antibiotics. Only small residual stones can be eradicated by minimising urease concentration.[20] Long-term, low dose culture-specific antimicrobials are important to prevent new stone growth and progression, after surgery.

In most series, 10% stones are infection stones. They are characterised by high recurrence rate and are more commonly seen in women, boys and elderly patients. They have a very rapid growth rate and can recur in 4-6 weeks.[21] The chemical composition of infection stone is carbonate-apatite. Following interventional treatment of stone, these patients would require long-term antibiotics (~3 months) either culture-sensitive or flouroquinolones. Use of urease inhibitor acetylhydroxamic acid is also recommended along with acidification of urine.

Cysteine stones results from cystinuria, which is an autosomal recessive disorder of renal tubular and intestinal transport of dibasic amino acids, with consequent increased urinary excretion of cysteine, ornithine, lysine and arginine. Treatment of cystinuria is by increasing fluids, using alkalinising agents (to maintain urine pH at around 7), chelation therapy and decreasing salt and protein in the diet.

Risk stratification of patients with urolithiasis: The EAU guidelines recommend stone analysis and basic metabolic workup for all patients; however, classify patients into high versus low risk for stone recurrence for intervention to decrease recurrence.[16] Those at high risk for recurrence are recommended to have detailed workup and specifically treated for decreasing stone recurrence, whereas low risk patients should at least follow the general measures.[22]

Stone at young age and those with family history are considered at risk. Certain stone compositions like brushite, uric acid and urate containing and infectious stone are also highly recurrent types. Genetic disorders like cystinuria, pH, distal RTA, xanthinuria, and Lesch-Nyhan syndrome are also associated with frequent stone recurrence. Patients with hyperparathyroidism, nephrocalcinosis, following by intestinal pass and bariatric surgery are predisposed to recurrent urolithiasis. Structural abnormalities of urinary tract like ureteropelvic junction obstruction horseshoe kidney, medullary sponge kidney, and ureterocoele again results in stasis and consequent recurrent urolithiasis.

Workup for stone former: Following a basic clinical workup with detailed history (focusing particularly on dietary habits and family history) and physical examination, urinalysis, creatinine serum calcium (corrected values), and uric acid should be done for all patients. Stone analysis using FTIR or X-ray diffraction

is highly recommended. Stone composition varies in episodes; therefore, it should be done each time for person passes stone. Patients at high risk of recurrence should undergo further detailed metabolic workup.

Fourier transform infrared spectroscopy (FTIR) is a method of stone analysis, which gets to the core of the stone. With the help of FTIR, a semi-quantitative methodology or analysis is done from all identifiable layers of the stone. Unlike previous laboratory practices, composition of stone core (nidus) is reported in stones that can be sliced, separately from the composition of the body of the stone. The composition of the core may be entirely different from that of the peripheral layers and suggests the formative cause of the stone. This gives the treating physician a greater insight and broader vision in determining the cause of stone formation; and helps in decision-takings for treatment, and future prevention. FTIR compares the results with a basic library of multiple spectra of pre-analysed synthetic kidney stone samples. This data of synthetic samples are prepared by mixing various combinations of pure standard materials. The results include a reliability factor for the analysis, which can be stored with the sample spectrum. The software provides features that allow the laboratory to easily display and compare the spectrum of the unknown sample along with the library reference spectrum.

CONCLUSION

Risk stratification and determination of stone composition can help in defining a structured approach to the detailed metabolic workup. This tailored approach will help in identifying patients with more detailed workup in those who are more likely to benefit from metabolic evaluation. Children, however, are different as they are likely to recur; and all children with stones need assessment to develop a preventive strategy. As a rule, the earlier a child forms a stone, more likely it is that another stone will ensue in the lifetime of the child.

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