EXPERT OPINION

Breaking the Rule of Stone: Expanding Urolithiasis Analysis to the Microbiome and Metabolome

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INTRODUCTION

Urolithiasis is the most prevalent urological disorders and continues to rise in parallel with obesity, diabetes, westernized diets, sedentary lifestyles, and climate-related dehydration.[1,5,7] Technological progress has transformed intervention; flexible ureteroscopy, laser lithotripsy, and ambulatory pathways have made stone treatment safer and more effective than ever before.[6,12] Yet, recurrence remains common, with many patients returning with new stone events despite successful surgical clearance.[4,8] Despite advances in minimally invasive surgery, recurrence remains a major challenge, emphasizing the need to move beyond procedural success toward personalized preventive strategies.[3,4] A urinary stone is frequently the final manifestation of an ongoing metabolic or environmental process rather than an isolated disease entity.[10]

Recent global epidemiological analyses demonstrate a paradoxical trend in urolithiasis burden: while the absolute number of cases continues to rise substantially, the age-standardized incidence rate has modestly declined. In 2021, an estimated 106 million new cases of urolithiasis were reported worldwide, representing a marked increase from 1990 and reflecting the effects of population growth and demographic aging. However, the global age-standardized incidence rate showed a gradual reduction over the same period, with an annual average percentage change (AAPC) of 0.81% between 1990 and 2021.[5] These findings suggest that the increasing healthcare burden of stone disease is driven primarily by demographic changes rather than an intrinsic rise in individual disease risk. Consequently, healthcare systems are likely to face escalating demands for stone-related care despite improvements in prevention and risk reduction strategies. This trend highlights the importance of implementing effective preventive measures, optimizing resource allocation, and developing precision medicine approaches to mitigate the growing socioeconomic impact of urolithiasis in aging populations.[5]

Thus, clinical experience dictates a strategic shift in our approach. For too long, the field has been restricted to a mechanical and surgical mindset, prioritizing stone removal while ignoring the biological drivers that guarantee the recurrence. We must recognize urolithiasis for what it is: a complex metabolic disorder rooted in the "gut-kidney axis." Understanding the microbiome's role in systemic oxalate regulation is no longer an optional academic pursuit; it is a strategic imperative. The gut-kidney axis serves as the primary physiological interface where intestinal health dictates renal burden.

Current State of Urolithiasis Management

According to the European Association of Urology (EAU) Guidelines, all patients presenting with urolithiasis should undergo standardized clinical evaluation including imaging confirmation, serum biochemistry, urinalysis, and stone analysis whenever material is available.[3] Patients should subsequently be stratified into low- and high-risk groups for recurrence.[3] High-risk stone formers require comprehensive metabolic evaluation, including 24-hour urine analysis and targeted laboratory investigations to facilitate individualized preventive strategies.[3,4] Subsequently intervention required to remove the stone and the stone fragment will sent for analysis.

The analysis of urinary stone composition has evolved substantially over the past century, progressing from simple macroscopic examination to advanced analytical techniques such as X-ray diffraction (XRD) and Fourier-

transform infrared spectroscopy (FTIR).[2] FTIR is currently regarded as the reference standard for stone analysis because of its high accuracy and ability to identify both crystalline and amorphous components[2]. More recently, advanced technologies including scanning electron microscopy, Raman spectroscopy, laser-induced breakdown spectroscopy, metabolomics, and proteomics have expanded our understanding of stone mineralogy and pathogenesis.[2,10]

Identification of stone composition enables tailored preventive interventions. For example, uric acid stones can be managed through urine alkalinization and metabolic syndrome control, whereas infection stones require eradication of urease-producing organisms and complete stone clearance.[3,8,11] Detail specific preventive therapy base on specific stone type shown in Table 1.

Table 1: Targeted preventive therapy for specific type of stone

Stone Type	Primary Metabolic Drivers / Associations	Targeted Preventive Interventions
Calcium Oxalate	Hypercalciuria, hyperoxaluria, hypocitraturia, high sodium/ protein intake	High fluid intake, sodium restriction, normal dietary calcium, citrate supplementation
Uric Acid	Acidic urine, obesity, insulin resistance, metabolic syndrome	Urine alkalinization, weight reduction, glycemic control, purine moderation
Struvite	Urease-producing infections.	Complete stone clearance, infection eradication, surveillance for regrowth
Cystine	Genetic (High-risk, recurrent, often in younger patients).	Aggressive hydration, urine alkalinization, sodium restriction, thiol-binding drugs
Brushite / Rare	Matrix stones, drug-induced compositions, or treatment-resistant systemic factors.	Specialized metabolic review, medication adjustment, and intensive surveillance.

Microbiome Depletion as a Pathophysiology of Oxalate Stone Formation

Recent evidence suggests that metabolic risk factors for urolithiasis may vary substantially across geographic regions, challenging the applicability of traditional Western metabolic profiles to non-Western populations. In industrialized Western countries, hypercalciuria has historically been regarded as the predominant urinary abnormality associated with calcium stone formation. However, studies from Peninsular Malaysia demonstrate a markedly different pattern, with hyperoxaluria (61.4%) emerging as the most prevalent metabolic abnormality, followed by hypomagnesuria (59.3%) and hypocitraturia (57.2%).[1] These findings indicate that regional dietary habits, environmental exposures, genetic factors, and lifestyle characteristics may significantly influence urinary biochemical profiles and stone pathogenesis. Consequently, precision management of urolithiasis requires the development of population-specific metabolic reference data rather than reliance on foreign models, as the adoption of non-representative metabolic profiles may result in suboptimal risk stratification, inappropriate preventive strategies, and less effective therapeutic interventions.[1]

Similarly, the recent study found regulation of *Oxalobacter formigenes*, a specialized anaerobic bacterium that regulates oxalate homeostasis by degrading dietary oxalate in the gut, thereby limiting its systemic absorption and subsequent renal excretion. When this gatekeeper is lost, the resulting "oxalate leak" into the bloodstream places an unsustainable burden on the kidneys, leading to crystallization[10] Such observations highlight the importance of localized epidemiological and metabolic studies to support precision stone medicine and optimize recurrence prevention in diverse populations. Thus, in population with high oxaluria possible predictive model for stone formation can be elaborated as shows in Figure 1.

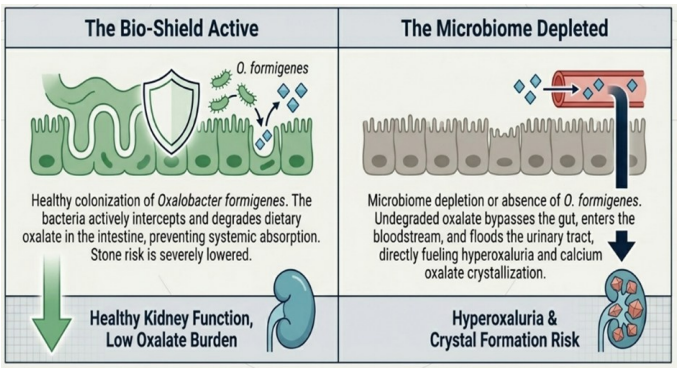

Figure 1: Microbiome dysbiosis causing hyperoxaluria

Development of new model to predict stone type

Traditionally, stone analysis has relied on postoperative physical and chemical laboratory examinations of retrieved calculi. In contrast, precision stone medicine integrates multi-omics technologies, artificial intelligence (AI), advanced imaging modalities such as spectral and dual-energy computed tomography, and comprehensive patient profiling to decipher the underlying biological mechanisms of stone formation.[1,2,13] Crucially, this approach shifts the focus from a single specimen to a

holistic biological ecosystem. By leveraging the combinatory power of the gut microbiome and host metabolome, we can now map how systemic microbial communities interact with biochemical metabolites to drive biomineralization. Rather than viewing these data streams in isolation, AI serves as the core predictive engine, synthesizing these complex multi-omic datasets alongside clinical variables to forecast stone characteristics.

Consequently, emerging predictive models combine these clinical, biochemical, metabolomic, and microbial profiles within advanced scoring systems capable of estimating stone composition and recurrence risk even before stone retrieval. Such integrative frameworks have the potential to bypass traditional, stone-dependent analyses, enabling earlier diagnosis, personalized preventive strategies, targeted therapeutic interventions, and more effective long-term recurrence prevention. As these technologies mature, precision stone medicine is expected to transform urolithiasis management from episodic treatment to proactive risk prediction and individualized disease prevention. To this end, we propose that the conceptual framework outlined above (Figure 2) be further developed and trained on AI architectures to optimize pre-operative stone type prediction.

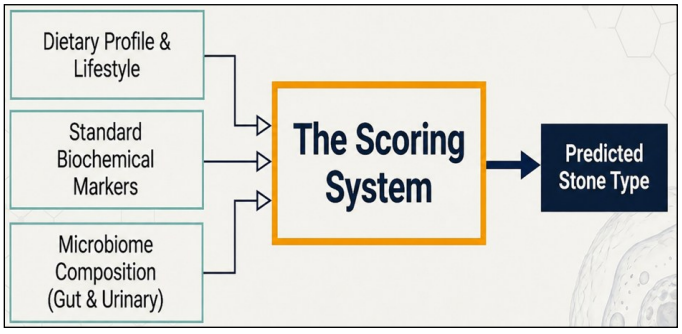

Figure 2: The pre-operative prediction stone type model

CONCLUSION

Stone analysis remains a simple, practical, and clinically meaningful tool for recurrence prevention. The high prevalence of calcium oxalate stones in Asian populations and the predominance of hyperoxaluria in Malaysian cohorts underscore the limitations of adopting non-local metabolic models and highlight the importance of precision medicine approaches tailored to regional characteristics. Future advances integrating artificial intelligence, metabolomics, microbiome science, and individualized risk assessment are expected to transform urolithiasis management from reactive treatment to proactive prevention.

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