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Association between Urinary Flora and Urinary Stones

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Keywords
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Abstract
Background: Urinary system stones are a common clinical disease, with significant differences in incidence and recurrence rates between different countries and regions. The etiology and pathogenesis of urinary system stones have not been fully elucidated, but many studies have found that some bacteria and fungi that are difficult to detect in urine constitute a unique urinary microbiome. This special urinary microbiome is closely related to the occurrence and development of urinary system stones. By analyzing the urinary microbiome and its metabolic products, early diagnosis and treatment of urinary system stones can be carried out. ***Summary:*** This article reviews the relationship between the urinary microbiome and urinary system stones, discusses the impact of the microbiome on the formation of urinary system stones and its potential therapeutic value, with the aim of providing a reference for the early diagnosis, prevention, and treatment of urinary system stones. ***Key Messages:*** (i) Urinary stones are a common and recurrent disease, and there is no good way to prevent them. (ii) With advances in testing technology, studies have found that healthy human urine also contains various types of bacteria. (iii) Is there a potential connection between the urinary microbiota and urinary stones, and if so, can understanding these connections offer fresh perspectives and strategies for the diagnosis, treatment, and prevention of urinary stones?

Introduction

Urinary system stones are among the most common diseases in urology, with the earliest records dating back thousands of years. In China, the earliest related record can be found in the "Shennong Bencao Jing" from the Han dynasty; in the West, the earliest records trace back to the 4th century BC [1]. Throughout this long history, the exploration of the mechanisms of urolithiasis and the update of treatment methods have never ceased. With the advancement of examination techniques and the application and popularization of various new minimally invasive treatment technologies, the diagnosis and treatment of urinary tract stones have made significant progress. However, the prevention and treatment of urinary tract stones still have a long way to go. As a multifactorial disease, its pathogenesis is not yet clear, and preventive measures are relatively scarce. Furthermore, its incidence is on the rise globally [2–4], which not only affects the quality of life of patients with stones but also brings a significant economic burden to the treatment of stone patients [5].

The microbiome refers to the collective term for all microbial organisms in a specific environment at a specific time. For the human body, this includes microorganisms that inhabit different parts of the body, consisting possibly of viruses, bacteria, and fungi [6–8]. The functions of the microbiome vary significantly based on its composition and distribution. Among these, the well-known gut microbiome is closely related to human

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health [9]; for instance, lactobacilli in the female vagina play a crucial role in maintaining the balance of the vaginal ecosystem and defending against other pathogens [10, 11].

In the past, urine from healthy individuals was often considered to be sterile. However, with the development and innovation of detection technologies, especially the advancement of 16S rRNA gene sequencing technology, researchers have found a significant presence of bacteria in urine from healthy individuals [12–14]. These bacteria cannot be detected by conventional clinical microbiological laboratory culturing methods. Urinary tract stones, as the most common disease in urology, are widely considered to be primarily caused by the supersaturation of minerals in urine, leading to crystal formation, growth, aggregation, and retention within the urinary system [15, 16]. This discovery has led to further contemplation: could the microbiome in urine affect the host's health similar to the gut microbiome? Is there a connection between stone formation and the urinary microbiome? This article aims to systematically review the potential link between the urinary microbiome and urinary tract stones.

Background

Urinary tract stones are commonly formed by the abnormal accumulation of substances such as calcium, oxalate, uric acid, and cysteine in the kidneys and other areas, making them one of the common diseases in urology [2]. Despite the complex etiology of stones, there is still no comprehensive consensus on their formation mechanism.

It is widely believed that, regardless of the type of stone, its formation is a multi-step complex process primarily involving urine supersaturation, crystal nucleation, crystal growth, and aggregation as the four key stages [17, 18]. Additionally, an imbalance of inhibitory factors in the urine, urinary tract anatomical abnormalities, genetic factors, dietary habits, and certain metabolic disorders within the body may also significantly impact stone formation.

Based on the main components of stones, they are commonly classified into four major types: calcium stones, uric acid stones, struvite stones (infection stones), and cystine stones. Among these, calcium stones are the most common type, with approximately 80% of kidney stones in clinical practice belonging to this category. These stones typically appear in the form of CaOx and CaP, either alone or in combination. CaOx often exists as a monohydrate or dihydrate, with the monohydrate usually crystallizing into a "dumbbell shape" and the dihydrate forming the more characteristic "octahedral shape." CaP stones frequently manifest as apatite (calcium phosphate) or brushite (hydroxyapatite), often appearing as radially arranged thin plate crystals [2]. Unlike calcium stones, uric acid stones account for about 8%–10% of urinary stones, and their formation is often attributed to excessive acidification of urine (pH < 5.6) [19]. Due to their dense structure, most uric acid stones resemble pebbles in appearance [20, 21]. Struvite stones, also known as "infection stones," are typically caused by the increased production of ammonia resulting from bacterial infections in the urinary tract that can produce urease, forming in an alkaline urine environment. Due to their rapid growth and ease of being molded by the renal collecting system, they often form "stag-horn" shapes [22]. Lastly, cystine stones are caused by congenital cystinuria, an autosomal recessive genetic disorder caused by a defect in the reabsorption mechanism of the proximal renal tubules [23]. This often results in the formation of characteristic hexagonal cystine crystals, which are dense, slightly opaque, and amber-colored.

As one of the most common diseases in urology, the incidence and recurrence rates of urinary tract stones are both on the rise. A review of epidemiological data from multiple countries reveals that the prevalence of urinary tract stones ranges from 1.7% to 14.8% and is increasing in almost all countries [3]. According to statistics, from 1976 to 2010, the prevalence of kidney stones in the USA nearly tripled [24]; during the same period, the prevalence of urinary tract stones in the UK also increased by 63% [25]. Over the past 50 years, the global prevalence of urinary tract stones has continued to rise, with a recurrence rate of up to 50% within 5 years. Furthermore, this trend is expected to increase further in the future [26].

The occurrence and development of urinary tract stones are closely related to lifestyle, dietary habits, and global warming. Additionally, diabetes [27], obesity, hypertension, and metabolic syndrome [28, 29] are considered significant risk factors for stone formation. Correspondingly, the risk of hypertension [30], end-stage renal disease [31], and chronic kidney disease [32] also increases in patients with stones. Moreover, studies have shown that women with a history of stones have an increased risk of cardiovascular diseases [33]; and patients with a history of stones have a higher risk of myocardial infarction than the general population [34].

The microbiome refers to the collective term for all microbial organisms at a specific time in a specific

environment [8]. The human microbiome refers to microbial communities living inside and outside the human body, which show significant differences in composition and function due to their different locations. In the past, urine from healthy individuals was often considered sterile, so the kidneys, which filter urine, and the bladder, which stores urine, were not included in the study of the human microbiome. However, with the advancement of detection technologies, especially through 16S rRNA gene sequencing, scientists have discovered that even urine from healthy individuals contains a large number of bacteria [35]. This finding challenges the traditional notion that urine is sterile and raises a new theory: if the gut microbiome of healthy individuals provides important health benefits to the host, might the urinary microbiome also play a crucial role in the host's health?

According to related studies, the urinary microbiome in healthy women's bladders significantly overlaps with the vaginal microbiome in function and classification, showing high similarity in four genera of bacteria, including *Actinomyces*, *Lactobacillus iners*, *Lactobacillus gasseri*, and *Lactobacillus crispatus* [14]. Furthermore, research by Nelson et al. [36] suggests that the composition of the male urinary microbiome may be related to asymptomatic sexually transmitted diseases. An increasing number of studies have revealed a close association between the urinary microbiome and urinary urgency, urinary tract infections, response to anticholinergic drugs, and urinary tract stones.

Methods for the Study of the Urinary Microbiota

Currently, there are various methods for studying the urinary microbiome, among which the most representative and commonly used are Enhanced Quantitative Urine Culture (EQUC) developed by Hilt et al. [12] and 16S rRNA sequencing technology. Compared to traditional clinical testing techniques, EQUC has the advantage of increasing the initial sample detection volume and enriching the diversity of culture media and testing environments. This method can isolate and identify many microorganisms that traditional clinical tests miss. Compared to traditional clinical testing techniques, EQUC has revealed that the false-negative rate of traditional methods can be as high as 90%. However, EQUC has limitations because some bacteria are unculturable, meaning that even with EQUC, these microorganisms cannot be detected. At this point, the advantage of 16S rRNA sequencing technology becomes particularly important as it can effectively and accurately detect urinary-related microbial populations without the need for special culturing of microorganisms [37]. However, the information provided by 16S rRNA sequencing technology is limited to a single gene locus. In current applications, the gene loci measured by amplicon sequencing are often restricted to a region of 100–500 nucleotides, reducing researchers' ability to differentiate related strains and identify organisms with thicker cell walls (such as Gram-positive bacteria) [38]. To further investigate the potential relationship between the urinary microbiome and urinary tract stones, combining the advantages and limitations of EQUC and 16S rRNA sequencing technology can help researchers better explore the relationship between the two.

Intestinal Flora and Urinary Stones

With the introduction of the brain-gut axis and gut-kidney axis concepts, increasing evidence suggests a bidirectional connection between the gut and the kidneys [39], revealing that the gut microbiome plays a crucial role in the gut-kidney axis [40]. Disruption and imbalance of the gut microbiome not only directly affect the occurrence and development of urinary system diseases but can also exert an indirect impact, involving diseases including but not limited to chronic kidney disease, hypertension [41], and urinary tract stones [42].

Early in the last century, research by Allison et al. [43] first discovered a new genus of oxalate-degrading bacteria in the intestines of humans and animals, namely, *Oxalobacter formigenes*. With advancements in detection technology, the absence of *O. formigenes* and its association with stone formation were also confirmed [44]. Further research by Siener et al. [45] showed that colonization by *O. formigenes* is related to a reduced risk of hyperoxaluria and the formation of calcium oxalate stones. Additionally, a pilot study by Stern et al. [46] comparing the gut microbiomes of stone patients with non-stone patients found that the abundance of *Bacteroides* in the stone group was 3.4 times that of the control group, while *Prevotella* was 2.8 times more abundant in the control group than in the stone group. In 11 patients who completed 24 h urine analysis, *Eubacterium* was negatively correlated with oxalate levels, and *Escherichia* was negatively correlated with citrate levels. Deng et al. [47] used 16S rRNA gene sequencing technology to describe the characteristics of the gut microbiome before and after surgery in patients with their first occurrence of kidney stones. Their study showed differences in the gut microbiome composition before

surgery (RS1 group) and 1 month post-surgery (RS2 group), with a higher prevalence of Pseudomonadaceae, Pseudomonadales, and *Pseudomonas* in the RS1 group and a higher prevalence of Enterobacteriaceae, Enterobacteriales, Gammaproteobacteria, and *Escherichia* in the RS2 group. Correlation analysis showed that the prevalence of Enterobacteriaceae, Gammaproteobacteria, and *Escherichia* was related to reduced levels of urea, while decreased levels of creatinine were associated with increased prevalence of *Escherichia*. This further proves the significant role of the gut microbiome in kidney stone formation and offers a new perspective for the prevention, diagnosis, and treatment of kidney stones. Furthermore, research by Yuan et al. [48] revealed that individual dietary habits can affect the prevention and treatment of calcium oxalate stones by regulating the homeostasis of the gut microbiome.

With the rapid development of big data model analysis, constructing machine learning models to analyze clinical diseases has become a current research hotspot. In a study by Xiang et al. [49], a machine learning model was developed that predicts the likelihood of calcium oxalate stone occurrence based on a combination of clinical and gut microbiome characteristics. The experiment included data from 180 participants, with the data from 120 participants allocated to the training set for constructing the big data model and the data from the remaining 60 participants used for model validation. The model predicts by identifying three types of bacteria associated with stones: *Flavobacterium*, *Rhodobacter*, and *Gordonia*. Clinical data include five features: oxalate concentration, acetate concentration, citrate concentration, phosphate concentration, and urine pH value. The study results indicate that the gut microbiome plays a significant role in the formation of calcium oxalate stones. However, future research still needs to collect more related data to further analyze and validate these findings through machine learning.

Evidence for an Association between the Urinary Microbiota and Urinary Tract Stones

Early studies on the urinary microbiome from the last century discovered that bacteria producing urease are related to the formation of stones [50]. Urease is an enzyme that catalyzes the hydrolysis of urea to produce ammonia and carbon dioxide, considered to be one of the culprits behind diseases such as pyelonephritis [51, 52], urine alkalinization, and infectious stones [53]. Bacteria known to produce urease include *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, among others. These bacteria often cause renal tubular damage and urine alkalinization, leading to the formation of phosphate and subsequently stones [54]. Recent studies indicate that Enterobacteriaceae in the urinary microbiome, including *Escherichia coli*, also have a potential relationship with the occurrence of urolithiasis. In one study investigating whether the presence of pathogenic *E. coli* in the urinary tract affects calcium deposition in mice, it was found that calcium deposition increased by 2.7 times in mice inoculated with *E. coli* [55]. Hirano's research suggests that the adhesive properties of certain bacteria may be an important cause of crystal and organic matter aggregation in the urine of stone patients [56].

Venkatesan and colleagues also found that *E. coli* and *P. mirabilis* exacerbated the formation of calcium oxalate calcification shells on the surface of polyurethane membranes used in ureteral stents, further proposing that biofilms produced by these bacteria may facilitate the formation of calcium oxalate shells [57]. Ultimately, bacteria bind with calcium oxalate crystals, causing pyelonephritis, which leads to changes in the renal units and the formation of Randall's plaques. *E. coli* reduces citrate levels by secreting citrate lyase, leading to the supersaturation of calcium oxalate [55]. Bacteria adhere to the urinary epithelium and repeat this process, ultimately forming stones.

Prevention and Treatment of Urinary Stones

Furthermore, some bacteria have the function of inhibiting stone formation, such as *O. formigenes*, which can promote the secretion of endogenous oxalate in the intestinal mucosa while reducing the excretion of oxalate in the urine [44]. To explore new treatments for hyperoxaluria and urolithiasis, Hoppe and others conducted a clinical study involving 16 patients with urolithiasis. Patients were divided into two groups and orally administered with a frozen paste (IxOC-2) and enteric-coated capsules (IxOC-3) made from *O. formigenes*, continuing for 4 weeks. By analyzing blood and urine samples, it was found that ingestion of *O. formigenes* significantly reduced the urinary oxalate levels in patients with urolithiasis (IxOC-2: 22–48%, IxOC-3: 38.5–92%) [58]. However, due to its low sensitivity to antibiotics and requirement for a low pH environment, *O. formigenes* is not an ideal probiotic candidate.

Therefore, the combined use of various probiotics has become an effective solution to the problem of antibiotic

sensitivity. This approach helps mitigate the intestinal colonization issues caused by antibiotic use, as a complete gut microbiome can participate in the degradation of oxalates and reduce their excretion in urine [59]. Therefore, supplementing with a variety of probiotics can effectively restore microbial balance and provide effective help in the prevention of urolithiasis. Subsequent research focuses on some well-known probiotics, including *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *E. coli* [59]. Turroni and others assessed the oxalate-degrading activity of *Lactobacillus* in commonly available probiotic dairy products and pharmaceutical preparations, finding that *Lactobacillus acidophilus* and *L. gasseri* had the highest activity against oxalates, confirming the potential significance of *Lactobacillus* in the degradation of oxalates and prevention of stones [60]. Campieri and colleagues found that after taking a mixture of freeze-dried *Lactobacillus* for 4 weeks, 6 patients with idiopathic calcium oxalate urolithiasis and mild hyperoxaluria showed a significant reduction in urinary oxalate excretion (about a 40% reduction) [61]. Therefore, combining different probiotics to participate in the decomposition of oxalates and reduce their excretion in urine is an effective strategy for controlling stone formation [61, 62]. However, current research primarily consists of in vitro studies and animal experiments, with relatively few human trials, which often have limitations such as small sample sizes and difficulties in controlling participants' diets. Moreover, existing studies on microbial communities are often singular, lacking research that analyzes the microbial community as a whole. Therefore, directly translating current research findings into clinical practice is contentious. Thus, conducting more strictly controlled studies involving a broad population, as well as enriching research designs and methodologies, is crucial.

Currently, research on the urinary microbiome mainly focuses on two methods: Enhanced Quantitative Urine Culture (EQUC) and 16S rRNA. To further investigate the connection between the urinary microbiome and urinary tract stones, research integrating multi-omics approaches will become a future direction. For instance, Moustafa et al. [63] studied the microbiome of urinary tract infections using metagenomic sequencing, a method that can more comprehensively describe the urinary microbiome. Gao et al. [64] discovered distinct features between the urinary microbiome and metabolic profiles of kidney stone patients and healthy controls through untargeted metabolomics research, identifying new biomarkers for the early diagnosis and prevention of kidney stones. Therefore, by employing a richer array of research methods to further explore the link between kidney stones and the urinary microbiome, more targeted intervention measures can be taken in the future to modulate the urinary microbiome, thus preventing the formation of stones.

Future Research Direction

To further elucidate the relationship between urinary microbiota and urinary stones, future research should focus on the following areas: (1) The relationship between microbiota and the recurrence of urinary stones: investigate whether the presence or absence of specific microbiota is associated with the recurrence rate of certain types of urinary stones. Conduct longitudinal studies to observe changes in the microbiota of stone patients after the removal of urinary stones and analyze the correlation with recurrence rates. Stern et al. [46] study indicates that the gut microbiota of urinary stone patients differs significantly from that of non-stone patients, suggesting that the microbiota may play an important role in stone recurrence. Additionally, a prospective study by Kim et al. [65] on the incidence and prevalence of kidney stones and their relationship with gut microbiota also confirmed that changes in gut microbiota composition are associated with the incidence and prevalence of kidney stones compared to normal controls. They also discovered new functional pathways, in addition to the known oxalate degradation pathways, that require further validation. (2) Metabolic pathways of microbiota and stone formation: use metabolomics techniques to analyze metabolites in urine and combine these data with microbiome data to explore the relationship between microbial metabolic activities and stone formation. A study by Gao et al. [64] used 16S rRNA gene sequencing and liquid chromatography-mass spectrometry to separately analyze the gut microbiome and metabolome and ultimately identified two significantly enriched metabolic pathways in kidney stone patients: the synthesis of unsaturated fatty acids and the metabolism of tryptophan. Additionally, in exploring the relationship between the composition and function of the gut microbiome and calcium oxalate kidney stones, Denburg et al. [66] found that in children with calcium oxalate kidney stones, the absence of gut bacteria that produce butyrate and degrade oxalate is closely related to metabolic dysregulation. They further hypothesized that the metabolome might be an upstream determinant of early calcium oxalate kidney stone disease. (3) Microbiota interventions as a method to prevent stones: study the effects of probiotic or

antibiotic treatment on the gut microbiota and urinary microbiota of stone patients. Stepanova et al. [67] conducted an animal experiment to evaluate whether ceftriaxone treatment affects the number of oxalate-degrading bacteria in the rat gut and the impact of commercially available probiotics on oxalate-degrading activity in rat feces. This study provides new insights for developing predictive diagnostic methods, targeted prevention, and personalized treatment of kidney stone disease. (4) Urinary microbiota and immune response in stone patients: study the relationship between changes in the urinary microbiota and urinary tract infections in stone patients and analyze the impact of the microbiota on local immune responses (such as inflammatory response and immune cell infiltration). A retrospective study found that the occurrence of urolithiasis was observed in 61.5% of cases with urinary tract infections, whereas only 12.5% of cases in the control group without urinary tract infections observed urolithiasis [68]. This study clearly demonstrates a close relationship between urinary tract infections and the development of urinary stones. Urinary tract infections inevitably lead to changes in the urinary microbiota and significantly affect the host's immune response. Therefore, future research should focus on the dynamic changes of the urinary microbiota and deeply analyze how the microbiota regulates local immune responses. This will help to understand the role of microbiota in urinary tract infections and stone formation. These research directions will help to deepen the understanding of the role of urinary microbiota in the formation and recurrence of urinary stones, thereby providing a theoretical foundation for the development of new prevention and treatment strategies.

Conclusions and Outlook

Existing research indicates that the urinary microbiome can lead to the formation of stones by affecting the excretion of certain metabolites. However, related research is scarce, and there is a lack of standardized research designs regarding urinary tract stones and the urinary microbiome, making it challenging to generalize some of the current research findings for clinical application. Therefore, this article focuses on elucidating the latest research from three aspects: research methods of the urinary microbiome, evidence of the association between the urinary microbiome and urinary tract stones, and the potential therapeutic significance. By conducting a comprehensive analysis of the urinary microbiome, we can better understand the formation process of urinary tract stones and provide new ideas and directions for the treatment and prevention of urinary tract stones.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Concept, design, and data collection and processing: S.Q. and J.Y.; supervision: L.Y.; literature search and writing: S.Q.; and critical review: S.Q., J.Y., and L.Y.

References

1 Tefekli A, Cezayirli F. The history of urinary stones: in parallel with civilization. Sci World J. 2013;2013(1):423964. https://doi.org/10.1155/2013/423964
2 Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S, et al. Kidney stones. Nat Rev Dis Primers. 2016;2(1):16008. https://doi.org/10.1038/nrdp.2016.8
3 Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2–3):e86–96.
4 Wigner P, Grębowski R, Bijak M, Szemraj J, Saluk-Bijak J. The molecular aspect of nephrolithiasis development. Cells. 2021;10(8):1926. https://doi.org/10.3390/cells10081926
5 Yang S-Y, Jung HD, Lee E-K, Kwon S-H, Lee JY, Lee S-H. Does early retrograde intrarenal surgery improve the cost-effectiveness of renal stone management? Yonsei Med J. 2020;61(6):515–23. https://doi.org/10.3349/ymj.2020.61.6.515
6 Marchesi JR, Ravel J. The vocabulary of microbiome research: a proposal. Microbiome. 2015;3(1):31. https://doi.org/10.1186/s40168-015-0094-5
7 Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121–41. https://doi.org/10.1016/j.cell.2014.03.011
8 Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207–14. https://doi.org/10.1038/nature11234
9 Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol. 2019;16(1):35–56. https://doi.org/10.1038/s41575-018-0061-2
10 Chee WJY, Chew SY, Than LTL. Vaginal microbiota and the potential of Lactobacillus derivatives in maintaining vaginal health. Microb Cell Fact. 2020;19(1):203. https://doi.org/10.1186/s12934-020-01464-4
11 France M, Alizadeh M, Brown S, Ma B, Ravel J. Towards a deeper understanding of the vaginal microbiota. Nat Microbiol. 2022;7(3):367–78. https://doi.org/10.1038/s41564-022-01083-2

12 Hilt EE, McKinley K, Pearce MM, Rosenfeld AB, Zilliox MJ, Mueller ER, et al. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. J Clin Microbiol. 2014; 52(3):871–6. https://doi.org/10.1128/JCM.02876-13
13 Lewis DA, Brown R, Williams J, White P, Jacobson SK, Marchesi JR, et al. The human urinary microbiome; bacterial DNA in voided urine of asymptomatic adults. Front Cell Infect Microbiol. 2013;3:41. https://doi.org/10.3389/fcimb.2013.00041
14 Thomas-White K, Forster SC, Kumar N, Van Kuiken M, Putonti C, Stares MD, et al. Culturing of female bladder bacteria reveals an interconnected urogenital microbiota. Nat Commun. 2018;9(1):1557. https://doi.org/10.1038/s41467-018-03968-5
15 Wang Z, Zhang Y, Zhang J, Deng Q, Liang H. Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. 2021;48(2):149–10. https://doi.org/10.3892/ijmm.2021.4982
16 Kok DJ. Clinical implications of physicochemistry of stone formation. Endocrinol Metab Clin North Am. 2002;31(4):855–67. https://doi.org/10.1016/s0889-8529(02)00037-3
17 Hamamoto S, Taguchi K, Fujii Y. Molecular mechanism of renal stone formation. Clin Calcium. 2011;21(10):1481–7.
18 Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. BioMed Res Int. 2013; 2013:292953. https://doi.org/10.1155/2013/292953
19 Sakhaee K, Adams-Huet B, Moe OW, Pak CYC. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int. 2002;62(3):971–9. https://doi.org/10.1046/j.1523-1755.2002.00508.x
20 Grases F, Villacampa AI, Costa-Bauzá A, Söhnel O. Uric acid calculi: types, etiology and mechanisms of formation. Clin Chim Acta. 2000;302(1–2):89–104. https://doi.org/10.1016/s0009-8981(00)00359-4
21 Khan SR, Hackett RL, Finlayson B. Morphology of urinary stone particles resulting from ESWL treatment. J Urol. 1986;136(6): 1367–72. https://doi.org/10.1016/s0022-5347(17)45340-7
22 Griffith DP, Osborne CA. Infection (urease) stones. Miner Electrolyte Metab. 1987;13(4): 278–85.
23 Biyani CS, Cartledge JJ. Cystinuria–diagnosis and management. EAU-EBU Update Ser. 2006;4(5):175–83. https://doi.org/10.1016/j.eeus.2006.06.001
24 Scales CD, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–5. https://doi.org/10.1016/j.eururo.2012.03.052
25 Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. BJUI. 2012;109(7):1082–7. https://doi.org/10.1111/j.1464-410X.2011.10495.x
26 Fink HA, Wilt , Eidman KE, Garimella PS, MacDonald R, Rutks IR, Brasure M, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013; 158(7):535–43. https://doi.org/10.7326/0003-4819-158-7-201304020-00005
27 Pak CYC, Sakhaee K, Moe OW, Preminger GM, Poindexter JR, Peterson RD, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology. 2003; 61(3):523–7. https://doi.org/10.1016/s0090-4295(02)02421-4
28 Devarajan A. Cross-talk between renal lithogenesis and atherosclerosis: an unveiled link between kidney stone formation and cardiovascular diseases. Clin Sci. 2018;132(6): 615–26. https://doi.org/10.1042/CS20171574
29 Wong Y, Cook P, Roderick P, Somani BK. Metabolic syndrome and kidney stone disease: a systematic review of literature. J Endourol. 2016;30(3):246–53. https://doi.org/10.1089/end.2015.0567
30 Kittanamongkolchai W, Mara KC, Mehta RA, Vaughan LE, Denic A, Knoedler JJ, et al. Risk of hypertension among first-time symptomatic kidney stone formers. Clin J Am Soc Nephrol. 2017;12(3):476–82. https://doi.org/10.2215/CJN.06600616
31 Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. Curr Opin Nephrol Hypertens. 2013;22(4):390–6. https://doi.org/10.1097/MNH.0b013e32836214b9
32 Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(4):804–11. https://doi.org/10.2215/CJN.05811108
33 Ferraro PM, Taylor EN, Eisner BH, Gambaro G, Rimm EB, Mukamal KJ, et al. History of kidney stones and the risk of coronary heart disease. JAMA. 2013;310(4):408–15. https://doi.org/10.1001/jama.2013.8780
34 Rule AD, Roger VL, Melton LJ 3rd, Bergstralh EJ, Li X, Peyser PA, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol. 2010;21(10):1641–4. https://doi.org/10.1681/ASN.2010030253
35 Fouts DE, Pieper R, Szpakowski S, Pohl H, Knoblach S, Suh M-J, et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. J Transl Med. 2012;10(1):174. https://doi.org/10.1186/1479-5876-10-174
36 Nelson DE, Van Der Pol B, Dong Q, Revanna KV, Fan B, Easwaran S, et al. Characteristic male urine microbiomes associate with asymptomatic sexually transmitted infection. PLoS One. 2010;5(11):e14116. https://doi.org/10.1371/journal.pone.0014116
37 Woo PCY, Lau SKP, Teng JLL, Tse H, Yuen KY, Yuen K-Y. Then and now: use of 16S rDNA gene sequencing for bacterial identification and discovery of novel bacteria in clinical microbiology laboratories. Clin Microbiol Infect. 2008;14(10): 908–34. https://doi.org/10.1111/j.1469-0691.2008.02070.x
38 Vaughan MH, Zemtsov GE, Dahl EM, Karstens L, Ma L, Siddiqui NY. Concordance of urinary microbiota detected by 16S ribosomal RNA amplicon sequencing vs expanded quantitative urine culture. Am J Obstet Gynecol. 2022;227(5):773–5. https://doi.org/10.1016/j.ajog.2022.06.031
39 Meštrović T, Matijašić M, Perić M, Čipčić Paljetak H, Barešić A, Verbanac D. The role of gut, vaginal, and urinary microbiome in urinary tract infections: from bench to bedside. Diagnostics. 2020;11(1):7. https://doi.org/10.3390/diagnostics11010007
40 Evenepoel P, Poesen R, Meijers B, Meijers B. The gut-kidney axis. Pediatr Nephrol. 2017; 32(11):2005–14. https://doi.org/10.1007/s00467-016-3527-x
41 Jiang S, Xie S, Lv D, Wang P, He H, Zhang T, et al. Alteration of the gut microbiota in Chinese population with chronic kidney disease. Sci Rep. 2017;7(1):2870. https://doi.org/10.1038/s41598-017-02989-2
42 Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346(2):77–84. https://doi.org/10.1056/NEJMoa010369
43 Allison MJ, Dawson KA, Mayberry WR, Foss JG. Oxalobacter formigenes gen. nov., sp. nov.: oxalate-degrading anaerobes that inhabit the gastrointestinal tract. Arch Microbiol. 1985;141(1):1–7. https://doi.org/10.1007/BF00446731
44 Arvans D, Jung Y-C, Antonopoulos D, Koval J, Granja I, Bashir M, et al. Oxalobacter formigenes–derived bioactive factors stimulate oxalate transport by intestinal epithelial cells. J Am Soc Nephrol. 2017;28(3):876–87. https://doi.org/10.1681/ASN.2016020132
45 Siener R, von Unruh G, Hesse A, Bangen U, SidhuHönow HR. The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int. 2013;83(6):1144–9. https://doi.org/10.1038/ki.2013.104
46 Stern JM, Chen Z, Agalliu I, MoazamiQiu SY, Kurland IJ, et al. Evidence for a distinct gut microbiome in kidney stone formers compared to non-stone formers. Urolithiasis. 2016;44(5):399–407. https://doi.org/10.1007/s00240-016-0882-9
47 Deng Q, Liang H, Wang Z, Wang J, Zhang J, Zhang Y. 16S rRNA gene sequencing reveals altered composition of gut microbiota in postoperative individuals with renal stones. Lett Appl Microbiol. 2022; 75(2):271–80. https://doi.org/10.1111/lam.13701

48 Yuan C, He Y, Jin X, Liu Y, Xiang L, Wang K, et al. Association of dietary patterns with gut microbiota in kidney stone and non-kidney stone individuals. Urolithiasis. 2022;50(4):389–99. https://doi.org/10.1007/s00240-022-01325-2
49 Xiang L, Jin X, Liu Y, Ma Y, Jian Z, Wei Z, et al. Prediction of the occurrence of calcium oxalate kidney stones based on clinical and gut microbiota characteristics. World J Urol. 2021;40:221–7. https://doi.org/10.1007/s00345-021-03801-7
50 Bichler K-H, Eipper E, Braun V, Naber K, Zimmermann R, Lahme S. Urinary infection stones. Int J Antimicrob Agents. 2002;19(6):488–98. https://doi.org/10.1016/s0924-8579(02)00088-2
51 Braude AI, Siemienski J. Role of bacterial urease in experimental pyelonephritis. J Bacteriol. 1960;80(2):171–9. https://doi.org/10.1128/jb.80.2.171-179.1960
52 Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol. 1973;1(3):132–41.
53 Johnson DE, Russell RG, Lockatell CV, Zulty JC, Warren JW, Mobley HL. Contribution of Proteus mirabilis urease to persistence, urolithiasis, and acute pyelonephritis in a mouse model of ascending urinary tract infection. Infect Immun. 1993;61(7):2748–54. https://doi.org/10.1128/iai.61.7.2748-2754.1993
54 Jung HD, Cho S, Lee JY. Update on the effect of the urinary microbiome on urolithiasis. Diagnostics. 2023;13(5):951. https://doi.org/10.3390/diagnostics13050951
55 Barr-Beare E, Saxena V, Hilt EE, Thomas-White K, Schober M, Li B, et al. The interaction between Enterobacteriaceae and calcium oxalate deposits. PLoS One. 2015;10(10):e0139575. https://doi.org/10.1371/journal.pone.0139575
56 Hirano S, Ohkawa M, Nakajima T, Orito M, Sugata T, Hisazumi H. Renal infections and implicated urinary stone formation. Hinyokika kiyo. 1985;31(8):1387–91.
57 Venkatesan N, Shroff S, Jeyachandran K, Doble M. Effect of uropathogens on in vitro encrustation of polyurethane double J ureteral stents. Urol Res. 2011;39(1):29–37. https://doi.org/10.1007/s00240-010-0280-7
58 Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, et al. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70(7):1305–11. https://doi.org/10.1038/sj.ki.5001707
59 Wigner P, Bijak M, Saluk-Bijak J. Probiotics in the prevention of the calcium oxalate urolithiasis. Cells. 2022;11(2):284. https://doi.org/10.3390/cells11020284
60 Turroni S, Vitali B, Bendazzoli C, Candela M, Gotti R, Federici F, et al. Oxalate consumption by lactobacilli: evaluation of oxalyl-CoA decarboxylase and formyl-CoA transferase activity in Lactobacillus acidophilus. J Appl Microbiol. 2007;103(5):1600–9. https://doi.org/10.1111/j.1365-2672.2007.03388.x
61 Campieri C, Campieri M, Bertuzzi V, Swennen E, Matteuzzi D, Stefoni S, et al. Reduction of oxaluria after an oral course of lactic acid bacteria at high concentration. Kidney Int. 2001;60(3):1097–105. https://doi.org/10.1046/j.1523-1755.2001.0600031097.x
62 Chapman CMC, Gibson GR, Rowland I. Health benefits of probiotics: are mixtures more effective than single strains? Eur J Nutr. 2011;50(1):1–17. https://doi.org/10.1007/s00394-010-0166-z
63 Moustafa A, Li W, Singh H, Moncera KJ, Torralba MG, Yu Y, et al. Microbial metagenome of urinary tract infection. Sci Rep. 2018;8(1):4333. https://doi.org/10.1038/s41598-018-22660-8
64 Gao H, Lin J, Xiong F, Yu Z, Pan S, Huang Y. Urinary microbial and metabolomic profiles in kidney stone disease. Front Cell Infect Microbiol. 2022;12:953392. https://doi.org/10.3389/fcimb.2022.953392
65 Kim H-N, Kim JH, Chang Y, Yang D, Joo KJ, Cho Y-S, et al. Gut microbiota and the prevalence and incidence of renal stones. Sci Rep. 2022;12(1):3732. https://doi.org/10.1038/s41598-022-07796-y
66 Denburg MR, Koepsell K, Lee J-J, Gerber J, Bittinger K, Tasian GE. Perturbations of the gut microbiome and metabolome in children with calcium oxalate kidney stone disease. J Am Soc Nephrol. 2020;31(6):1358–69. https://doi.org/10.1681/ASN.2019101131
67 Stepanova N, Akulenko I, Serhiichuk T, Dovbynchuk T, Savchenko S, Tolstanova G. Synbiotic supplementation and oxalate homeostasis in rats: focus on microbiota oxalate-degrading activity. Urolithiasis. 2022;50(3):249–58. https://doi.org/10.1007/s00240-022-01312-7
68 Martinez-Piñeiro JA, de Iriarte EG, Armero AH. The problem of recurrences and infection after surgical removal of staghorn calculi. Eur Urol. 1982;8(2):94–101. https://doi.org/10.1159/000473488