Review

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Impact of the Human Microbiome on Nephrolithiasis

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Nephrolithiasis has many causes, and its prevalence is increasing worldwide. The interest in the human microbiome is growing because of the advance of new diagnostic techniques, and recent studies have suggested a link between the microbiome and nephrolithiasis. This paper reviewed the role of the microbiome in nephrolithiasis. The absence of *Oxalobacter formigenes* induces hyperoxaluria, which promotes calcium oxalate stone (CaOx) formation. *Escherichia coli* promote CaOx supersaturation through hypocitraturia caused by the bacterial production of citrate lyase. Infection stones are associated with urea-splitting organisms, particularly *Proteus mirabilis*, and the stones themselves contain many species of bacteria.

Keywords: Microbiota; Nephrolithiasis; Gastrointestinal microbiome

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INTRODUCTION

Nephrolithiasis is one of the most frequently encountered urologic diseases, and its incidence and prevalence are increasing worldwide. The prevention of nephrolithiasis is essential, but its etiology is variable and complex, involving geographical, climatic, ethnic, dietary, and genetic factors [1].

Attention to the contributions of the gastrointestinal and urinary microbiome in nephrolithiasis has increased recently [2]. Lederberg and McCray [3] first defined the microbiome as the ecological community of commensal, symbiotic, and pathogenic microorganisms sharing the body space. Advances in molecular techniques have enabled a more comprehensive assessment of the microorganisms present in urine [4]. 16S ribosomal RNA (rRNA) gene sequencing can identify bacteria in healthy urine [5-8]. Expanded quantitative urine culture (EQUC) resolves the discrepancies between cultures and molecular assays. EQUC can also determine if the bacteria in urine are alive [5].

The Human Microbiome Project (HMP) was launched in 2008 to explore microbial communities and their connections with their human hosts [9]. On the other hand, the bladder was not included in the HMP initially. Samples were collected from the airways, skin, oral cavity, gut, and vagina [9]. Urine has historically been considered sterile in healthy individuals, but urine contains a variety of bacteria. These bacteria are not routinely cultivated but can be identified by 16S rRNA gene sequencing [10-12]. This paper reviewed the role of the microbiome in nephrolithiasis.

MAIN BODY

1. Pathophysiology of Urinary Stone Formation

The stone formation process involves precipitation, nucleation, crystal growth, and crystal aggregation [13]. Urinary supersaturation and crystallization cause intrarenal

crystal precipitation [14]. Calcium, oxalate, urate, and phosphate ions promote crystallization, and magnesium, citrate, pyrophosphate inhibit crystallization [15-17]. There are three hypotheses regarding the mechanisms of lithogenesis.

1) Randall's plaque hypothesis

In 1937, Randall described [18] crystal growth from calcium phosphate plaques (Randall's plaques) in the interstitium within the renal papilla at the base of the calyx in the kidney. Randall's plaques are the first step toward calcium oxalate (CaOx) stone formation [14]. Damage to the renal tubular epithelium exposes the plaque to supersaturated urine, allowing CaOx stones to grow [19].

2) The free particle theory

In 1994, Kok and Khan [20] reported that large free crystalline particles could form in the long loop of Henle during normal transit time through the kidney. These particles obstruct the collecting ducts and form the nidus of a stone.

3) The fixed particle theory

Crystals attach to the renal tubular epithelium, leading to epithelial damage, nucleation, contact of nuclei with supersaturated urine, and crystal development. Brushite, cystine, and carbonate apatite crystals obstruct the inner medullary collecting ducts and ducts of Bellini, causing epithelial cell damage, inflammation, and focal interstitial fibrosis [21-23].

2. The Human Microbiome Project

The human body contains at least ten times more bacteria than human cells, and most bacteria are found in the human gut [24]. The HMP Consortium, which is an alliance of a broad collection of scientific experts funded by the US National Institutes of Health (NIH), was set up to study the relationship between the microbiome and human hosts [9]. The goals of the HMP are to form standardized resources for microbiome analysis, provide microbiome data to the scientific community for disease research, and promote the development of new technologies for microbiome analysis [25]. The project's initial data contained 4,788 samples from 242 screened and phenotyped adults (129 males, 113 females). 16S rRNA gene sequencing and whole-genome shotgun sequencing were used for analysis [26]. Microbiome samples were collected from 15 distinct body sites in both men and women. Three additional sites in the vagina were included for females [26]. The specimens included the oral cavity and oropharynx, skin, and stool [26]. The HMP currently aims to sequence at least 3,000 reference microbial genomes relevant to the human body and make them available from the National Center for Biotechnology Information and the Data Analysis and Coordination Center (http://hmpdacc.org/HMRGD) [9]. It will also offer a database to support future research [25].

3. Gut Microbiome and Urolithiasis

1) Bacteria that degrade oxalate

Oxalobacter formigenes rely on oxalate in the intestines as a carbon source for energy and growth [27]. In the US, *O. formigenes* colonizes 38-62% of adults. In India and Korea, the colonization percentage in adults is approximately 60% and 77%, respectively [28,29]. Dawson et al. [30] isolated anaerobic bacteria from sheep rumen, later defined as *O. formigenes* that relied on oxalate for energy. Allison et al. [31] described the same bacteria from human feces. The clinical results indicated a direct connection between the organism's absence, hyperoxaluria, and the formation of oxalate stones. Numerous oxalate-degrading bacteria exist, such as *Lactobacillus, Bifidobacterium, Enterococcus, Clostridium, Eggerthella, Providencia, Streptococcus*, and *Leuconostoc genera* [32]. Increased oxalate degradation by the gastrointestinal microbiome may decrease oxalate absorption and reduce urinary oxalate excretion [33].

Siener et al. [34] suggested that the absence of *O. formigenes* induces hyperoxaluria, which may cause the formation of CaOx stones. Of 37 idiopathic CaOx stone patients, only 11 (30%) tested positive for *O. formigenes*, while 26 (70%) were negative in the stool culture and stool polymerase chain reaction. Moreover, 60-80% of patients who formed multiple stones were negative for *O. formigenes*. On the other hand, there were no differences in 24-hour urine oxalate between *O. formigenes*-negative and *O. formigenes*-positive. This result contradicts the previously assumed mechanism through which the absence of *O. formigenes*, as described previously, causes hyperoxaluria. Ticinesi et al. [35] analyzed the microbiome composition through 16S rRNA microbial profiling and shotgun metagenomics analysis of fecal samples from 52 idiopathic

calcium stone formers and 48 controls. Three taxa (*Dorea, Enterobacter,* and *Faecalibacterium*) were underrepresented in stone formers ($p<0.05$). Very few *O. formigenes* were detected in analyzed fecal samples (<0.001% in all samples), and the average relative abundance of *O. formigenes* was similar between stone formers and controls. The relative abundances of five taxa (*Defluviitaleaceae, Catabacter, Anaerofilum, Sutterella,* and *Peptococcus*) were significantly associated with the 24-hour urinary oxalate excretion in both stone formers and controls. *Defluviitaleaceae, Sutterella,* and *Peptococcus* showed a positive association, while *Catabacter* and *Anaerofilum* showed a negative association. *Bacteroides, Actinobacteria, Alistipesindistinctus,* and *Odoribactersplanchnicus* were more abundant in nephrolithiasis patients than the healthy controls [36]. The fecal samples of stone formers had a significantly lower bacterial representation of genes related to oxalate degradation, and gene expression was inversely correlated with the 24-hour oxalate excretion ($r=-0.87$, $p=0.002$). Oxalate-degrading genes were expressed in several bacterial species, and gene expression was inversely correlated with oxaluria ($r=-0.85$, $p=0.02$). *Faecalibacterium* produces short-chain fatty acids that attenuate inflammation and oxidative stress associated with kidney stone formation [37].

Batagello et al. [38] performed a meta-analysis of the gut microbiome in nephrolithiasis. They concluded that *O. formigenes* was not a good predictor of the nephrolithiasis risk. Although studies consistently reported a higher level of colonized *O. formigenes* in healthy controls than urinary stone patients, six out of 14 studies reported no significant impact of *O. formigenes* on the urinary oxalate levels. *O. formigenes* colonization ranged from 11% to 100% in healthy controls and 0% to 100% in urinary stone patients. They concluded that targeting a broad diversity of bacteria is necessary for microbiome analysis rather than focusing on a few species.

4. Urinary Microbiome and Stones

1) *Escherichia coli*

High-throughput sequencing has shown that nephrolithiasis involves the *Enterobacteriaceae* genus in the urinary microbiome, including *E. coli* species [39]. Barr-Beare et al. [40] reported associations between *E. coli* and renal CaOx deposits. Mice with uropathogenic *E. coli* inoculation had a 2.7 times higher rate of calcium deposition. Several theories can explain the association between urinary bacteria and nephrolithiasis. The bacteria may adhere to CaOx crystals and cause pyelonephritis, and the resulting biofilm may promote crystal agglomerations. In addition, CaOx supersaturation in hypocitraturia caused by the bacterial production of citrate lyase may encourage stone formation [40-42].

2) Urea-splitting organisms

Organisms, including *Proteus, Staphylococcus, Klebsiella,* and *Pseudomonas,* decompose urea in urine. The decomposition generates ammonia, bicarbonate, and carbonate, alkalizing the urine. These decomposition products form crystals with calcium, magnesium, and phosphoric acid in the urine that form infection stones (struvite or carbonate apatite) [43,44]. The bacterium most commonly associated with infection stones is *Proteus mirabilis* [45].

5. Microbiome in Stones

Bacteria can be isolated from approximately 15-70% of stones [46-48]. CaOx stones contained positive cultures in 13% to 44% of samples. *E. coli* (15-35%) was the most common bacteria identified from stone cultures, followed by *Pseudomonas* spp. and *Proteus* (urease-producing bacteria), which are typically associated with the formation of struvite stones [46,47].

Dornbier et al. [49] analyzed the microbiome of calcium-based urinary stones. They identified the urine and stone microbiota of nephrolithiasis patients using 16S rRNA gene sequencing and EQUC. Bacteria were identified in 29/52 (55.8%) of stones. *Enterobacteriaceae* (including the genera *Escherichia* and *Klebsiella*), *Staphylococcus, Veillonella, Streptococcus, Corynebacterium, Haemophilus, Proteus, Lactobacillus,* and *Bifidobacterium* were dominant the bacterial taxa. Twelve stones contained dominant bacterial taxa, and 5/12 (41.7%) of these were CaOx stones. In contrast, 36/40 (90%) of stones without dominant taxa were CaOx. EQUC and 16S-rRNA gene sequencing identified multiple enriched bacterial species, including *Staphylococcus epidermidis, Enterobacter cloacae, Escherichia coli* (a member of the family *Enterobacteriaceae*), and *Lactobacillus gasseri*. Dornbier et al. [49] developed a methodology to detect bacteria in stones and estimate whether they are more abundant in the urine than other species. Table 1 lists the microbiome associated with nephrolithiasis.

Table 1. Microbiome associated with nephrolithiasis

Gut microbiome	Urinary microbiome	Stone microbiome
Known oxalate-degrading bacteria	*Escherichia coli*	*Staphylococcus, Veillonella, Streptococcus*
Oxalobacter formigenes	Urea-splitting organisms (*Proteus, Staphylococcus, Klebsiella, Pseudomonas*)	*Corynebacterium, Haemophilus, Proteus*
Lactobacillus		*Lactobacillus, Bifidobacterium, Enterobacteriaceae*
Bifidobacterium		
Enterococcus		
Clostridium		
Eggerthella		
Providencia		
Streptococcus		
Leuconostoc		
Related to 24-hour urine oxalate excretion		
Defluviitaleaceae		
Catabacter		
Anaerofilum		
Sutterella		
Peptococcus		
Lower in stone formers		
Dorea		
Faecalibacterium		
Enterobacter		
Higher in stone formers		
Bacteroidetes		
Acinobacteria		
Alistipesindistinctus		
Odoribactersplanchnicus		

6. Standardization of Microbiome Studies for Nephrolithiasis

Kachroo et al. [2] developed MICROCOSM (MICRObiome contributions on the Complexity Of the Stone Matrix), which focused on the relationship between the microbiome and urolithiasis. The goal of MICROCOSM was to standardize the protocol for microbiome research within the field of urolithiasis to minimize the technical biases and barriers related to microbiome studies. Similar results were found in studies comparing the microbiomes of patients with stones with the microbiomes of healthy controls. On the other hand, despite some apparent differences between patients with stones and healthy controls [38], there were inconsistencies in the compositions of the microbiomes correlating with the disease [2]. MICROCOSM was developed to minimize the discrepancies in microbiome research resulting from experimental factors, such as sample collection, storage, DNA extraction, sequencing, or data analysis.

7. Probiotics for Prevention of Nephrolithiasis

The endogenous digestive microbiome, which utilizes oxalate, potentially prevents oxalate absorption [50]. On the other hand, studies with probiotics, including *Oxalobacter*, *Lactobacillus*, and *Bifidobacterium*, showed disappointing results [33].

1) Probiotics containing *Lactobacillus*

A pilot study with Oxadrop® reduced urine oxalate excretion by 40% in mildly hyperoxaluric CaOx stone patients [51]. In subsequent research, 10 patients with enteric hyperoxaluria were treated daily with Oxadrop® and received 4 g, 8 g, and 12 g each month for three months [52]. This study showed a dose-dependent effect until the second month. The patients administered 4 g and 8 g exhibited a 19% and 24% decrease in urine oxalate excretion, respectively. On the other hand, during the third month, at 12 g per day, urine oxalate excretion increased in four out of 10 patients, which was close to the baseline established without treatment. No effects on urinary oxalate excretion were observed in a randomized, placebo-controlled study [53].

2) Probiotics containing *Oxalobacter*

Research in a mouse model of type 1 primary hyperoxaluria demonstrated that oral administration of *O. formigenes* might decrease urinary oxalate excretion [54].

In a pilot study of nine patients (five with normal renal function, four with primary hyperoxaluria), urine oxalate excretion was reduced by 50% for four weeks by administering an oral preparation of *O. formigenes* in four with primary hyperoxaluria patients [55]. In this study, three out of five patients with normal renal function exhibited a 22-48% decrease in urinary oxalate excretion while taking the first oral formulation of *O. formigenes*. Moreover, *O. formigenes* did not establish persistent gut colonies, so the beneficial effects depended on the continual administration of probiotics. Despite the hopeful preliminary data, there was no follow-up controlled trial using *O. formigenes* in patients with enteric or idiopathic hyperoxaluria. Therefore, the effect of probiotics containing *O. formigenes* on urinary oxalate excretion requires more investigation [33].

CONCLUSIONS

The absence of *O. formigenes* may cause enteric hyperoxaluria, but the colonization rate of *O. formigenes* varies in healthy people and urinary stone patients. Furthermore, the presence of *Faecalibacterium, Enterobacter,* and *Dorea* in stone formers may reduce the likelihood that CaOx stones will form. *Faecalibacterium* may attenuate the inflammation and oxidative stress associated with stone formation. In mice, urine *E. coli* could promote CaOx stone formation. On the other hand, CaOx stones do not contain large amounts of microorganisms, and no organisms were present in uric acid and cystine stones. A standardized study on the correlation between the stool and urine microbiome and stone formation is currently ongoing, and the effects of probiotics on oxalate degradation require more research. The microbiome likely plays a role in forming nephrolithiasis, but more research will be needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

H.D.J. and J.Y.L. participated in data collection, designed the study, and wrote the manuscript. Both authors read and approved the final manuscript.

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