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State of the gut microbiota in oxalate nephrolithiasis

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ABSTRACT

The gut microbiota (GM) is currently considered as a pathogenic factor in a number of diseases. It is known that some gastrointestinal diseases cause a high risk of developing urolithiasis. The study gives modern data demonstrating the influence of the GM, in particular *Oxalobacter formigenes,* on the formation of oxalate kidney stones. The relationship between the presence of inflammatory bowel diseases and the use of antimicrobial drugs with oxalate homeostasis was demonstrated, methods for correcting the GM in patients with urolithiasis, including the use of probiotics and diet therapy, were analyzed. The studies presented in the article demonstrate that the correction of the GM can be considered as a therapeutic goal and be an actual component of the complex treatment and metaphylaxis of nephrolithiasis.

Review

Implication for health policy/practice/research/medical education:
Urolithiasis is a common disease that affects patients of all ages and significantly reduces the quality of life. With technological advancements and growing expertise, nephrolithiasis can be diagnosed more easily than before. A better understanding of the relationship of this disease with the intestinal microbiota discussed in this study will lead to improved metaphylaxis and proper treatment of nephrolithiasis. This, in turn, will reduce the prevalence of kidney stones.

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Introduction

Urolithiasis is a chronic disease with a high prevalence in the general population and a tendency to relapse. According to the study by Gadzhiev et al, the incidence of urolithiasis in the Russian Federation was 176 773 in 2005, while 205 414 new urolithiasis cases were recorded in 2019. It was marked an annual uniform increase in patients with a diagnosis of urolithiasis, which amounted to 16.2% by 2019 (1). Approximately 10.6% of the male and 7.1% of the female population in the United States suffer from this disease (2). The manifestation of urolithiasis falls on the age of 25 to 40 years and after 50–55 years, and the tendency to increase the incidence is more pronounced in women (3).

In addition to the rapid increase in the incidence, the dependence of the stone formation on the eating habits of patients testifies to the relevance of the problem. Ziemba and Matlaga determined that an increase in dietary calcium intake and a decrease in fluid intake is associated with an increased risk of nephrolithiasis in both men and women (3). According to the study by Ferraro et al such modifiable risk factors as body mass index, fluid intake, DASH diet (Dietary Approaches to Stop Hypertension for weight loss and lowering blood pressure), intake of calcium and sugar-sweetened beverages cause a 50% increase in the risk of urolithiasis (4). Moreover Ferraro et al following the results of a prospective cohort study found that the intake of antimicrobials for more than 2 months at 40-59 years of age increases the risk of urolithiasis in older age groups (5). According to data provided by Penniston et al, it was found that patients with urolithiasis, regardless of symptoms, have a lower quality of life (6).

Calcium oxalate is the main component of most Randall's plaque stones on the surface of the renal papillae. The recurrence rate of oxalate nephrolithiasis reaches 50% during the first 5 years after the first episode of stone formation. Most often (in 80% of cases), stones consist of calcium oxalate or calcium phosphate, less often of urates (uric acid) or may be of a mixed composition (uric acid + calcium oxalate/phosphate <80%).

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It has been established that *Oxalobacter formigenes* is a representative of the gut microbiome, a bacterium that destroys oxalates in the gastrointestinal tract, promotes oxalic acid homeostasis and, as a result, reduces urinary oxalate excretion. Determining the role of *O. formigenes* in the pathogenesis of nephrolithiasis may contribute to a change in ideas about the possibilities of preventing stone formation.

Given the above data, it is clear that the gut microbiota (GM) influences the formation of kidney stones. Correction of intestinal dysbiosis may lead to improved treatment outcomes and metaphylaxis of urolithiasis. This review study will consider the state of GM in urolithiasis and the effect of antimicrobials on the intestinal oxalobiome.

Study of the role of *Oxalobacter formigenes* in oxalate metabolism

The pathophysiology of stone formation is largely related to the function of the gastrointestinal tract, since the concentration in urine of two main prolithogenic factors, calcium and oxalate, mainly depends on the degree of their intestinal absorption. It can be assumed that the microbiota plays a role in the metabolism of these substances in the intestinal lumen and, therefore, can influence their absorption. A number of studies have determined that, oxalate is broken down by microbes in human feces, although little is known about the nature of the microbes responsible for this activity. Oxalate is a compound found in plants consumed by humans (e.g., rhubarb, spinach, and beets).

In 1980, a group of American microbiologists led by Milton Ellison isolated from the material obtained from the rumen of some mammals a bacterial strain that was characterized by a pronounced metabolic activity in the decomposition of oxalates. Later, this bacterium was isolated from the intestines of other mammals, including the domestic guinea pig *(Cavia porcellus*). The results of these studies allowed to develop the methods for cultivating the bacterial strain, which was subsequently classified taxonomically as a new species, named *O. formigenes* due to its metabolic activity. Later, the biological and metabolic characteristics of this species were studied using more advanced methods.

Oxalobacter formigenes is a gram-negative obligate anaerobic bacterium that obtains energy from the fermentation of oxalate. The enzymes involved in this process are oxalyl-CoA decarboxylase and formyl-CoA transferase, which genes are highly expressed by Oxalobacter that makes the bacterium the most efficient biological system for oxalate degradation. An analysis of the Oxalobacter genome made it possible to isolate two different strains (group 1 and group 2), which metabolic differences have not been fully studied.

Medical interest in *O. formigenes* increased after its isolation from human faecal samples using culture methods. It was determined that the bacterial load of oxalobacter was significantly lower in the group of patients who underwent bariatric surgery - gastric bypass and, therefore, more prone to the development of hyperoxaluria (7). This observation led to the suggestion that this bacterium is involved in the pathophysiological process of calcium oxalate stone formation. Back in the late 1980s, Argenzio et al demonstrated that intestinal absorption of oxalate in domestic animals is inversely proportional to the bacterial load of *O. formigenes* (8). Since *Oxalobacter* is present in human GM in small quantities and, therefore, is a "minor factor" in such a complex ecosystem, its isolation using classical microbiological methods is difficult. In 1985, a group of American microbiologists developed a method for the identification and quantification of Oxalobacter in human faecal samples using the polymerase chain reaction (PCR) of the oxc gene (oxalyl-CoA decarboxylase) (9). This species-specific method has given new impetus to the studies of Oxalobacter and renewed interest in the medical community, especially for its potential value in the treatment of urolithiasis. An important factor in the breakdown of oxalates in the intestine is not only the direct presence of Oxalobacter, but also its quantity. The presence of *O. formigenes* is not constant in human GM and is, according to various estimates, from 30% to 70% in adults. However, when *Oxalobacter* is present, it tends to persist for a long time. Factors affecting intestinal colonization by this bacterium are still unknown.

Sidhu et al in a clinical study of 145 patients who were confirmed to have idiopathic oxalate stones, showed an inverse correlation between the level of colonization of *O. formigenes* in the intestine and the number of episodes of renal colic. In the group of patients colonized by *O. formigenes*, urinary oxalate excretion was higher (10). According to the data of Kaufman et al, obtained in a study involving 247 patients with oxalate stones and 259 people without urolithiasis, the prevalence of *O. formigenes* colonization was higher in the control group (38% versus 17%). In addition, according to the results of this study, it was revealed that colonization with *O. formigenes* reduces the risk of recurrent stone formation by 70% (11). Siener et al published the results of a study on the relationship between the presence of *O. formigenes* in faecal samples and the excretion of oxalates in the urine when following a special diet. The study involved 37 patients, including 26 men and 11 women aged 19 to 77 years. Siener et al showed that GM colonization by *O. formigenes* does not affect intestinal absorption of oxalates. At the same time, plasma oxalate concentration was significantly higher in patients without *O. formigenes* in GM (in the ratio of 5.79 µmol/L to 1.70 µmol/L). In patients with GM colonization by *O. formigenes*, the number of stone formation episodes was lower (12).

Antimicrobials and the oxalobiome

There is a hypothesis that antimicrobial therapy may contribute to the disappearance of Oxalobacter from GM in people previously colonized with this bacterium. In an observational prospective controlled study, Kharlamb et al found that in patients with a history of *H. pylori*, the colonization of *O. formigenes* is reduced against the background of antimicrobial therapy with amoxicillin, clarithromycin (13). The number of *Oxalobacter* in GM usually increases after the consumption of foods high in oxalates, since the growth of these bacteria depends on the presence of an energy substrate. On the other hand, the presence of *Oxalobacter* in the microbiota can reduce the fractional absorption of oxalate ingested with food. Therefore, potentially this bacterium is a very important factor in the regulation of oxalate metabolism in the body and the pathophysiology of hyperoxaluria. In their turn, PeBenito et al in 2019 revealed a significant effect of antimicrobials on the colonization of *O. formigenes* and the level of electrolytes in the urine and showed that the overall structure of the gut microbiome differed depending on the presence of this bacterium (14). A prospective "case-control" study examined the effect of antimicrobials (particularly fluoroquinolones and cephalosporins) on colonization of the GM by *Oxalobacter*. The study results showed that the administration of antimicrobials can contribute to the emergence of resistance of oxalotrophic bacteria in the gut microbiome (15). Meanwhile, Joshi and Goldfarb found that *O. formigenes* degrades oxalate in the gut and its presence is associated with lower urinary oxalate levels, which confer protection against oxalate stone formation (16). In addition, in a recent analysis of the Health Improvement Network (THIN) database in children and adults in the UK, which included 25 981 patients with nephrolithiasis and 259 797 healthy individuals, it was shown that the use of antimicrobials increases the likelihood of developing urolithiasis. Twelve classes of oral antimicrobials were evaluated for their potential to cause stone formation. Use of any of five different classes of antimicrobials (sulfonamides, cephalosporins, fluoroquinolones, nitrofurantoin, and broad-spectrum penicillin) 3 to 12 months prior to diagnosis of nephrolithiasis has been associated with stone formation. At the same time, the risk of urolithiasis was highest in young patients, as well as in those who took antimicrobial drugs 3-6 months before they were diagnosed (17). The probability of developing urolithiasis, depending on the duration of the use of antimicrobials, according to the study results, is shown in Table 1.

Recently Liu et al found that patients with inflammatory bowel disease often have disturbances in oxalate homeostasis and, as a result, urolithiasis (more often oxalate nephrolithiasis). Gut oxalate levels have been shown to be elevated in patients with inflammatory bowel disease, with the highest levels observed in patients with Crohn's disease affecting both the ileum and colon (18). Due to the fact that it is not possible to completely abandon antimicrobial therapy currently, its administration should be justified, and also accompanied by an increase in fluid intake or a diet low in oxalates or the prescription of a probiotic after its use.

Particular interest in the therapeutic use of *O. formigenes* is due to the insufficient number of drugs that can affect the regulation of oxalate metabolism and, consequently, the lack of an alternative to the diet for hyperoxaluria. In a study on male Sprague-Dawley rats, which were induced with severe hyperoxaluria when supplemented with ammonium oxalate, were treated with a probiotic

Table 1. The likelihood of developing urolithiasis depending on the prescription of oral antimicrobials (17)

Class of antibiotics	3 to <6 months		6 to <12 months		1 to <3 years		3-5 years	
	HR (95% CI)	R	HR (95% CI)	R	HR (95% CI)	R	HR (95% CI)	R
Sulfonamides	2.63 (2.42 to 2.85)	<0.001	2.06 (1.92 to 2.22)	<0.001	1.46 (1.38 to 1.55)	0.001	1.55 (1.48 to 1.62)	<0.001
Cephalosporins	2.26 (2.06 to 2.48)	<0.001	1.7 (1.57 to 1.84)	<0.001	1.32 (1.25 to 1.4)	0.001	1.33 (1.26 to 1.4)	<0.001
Fluoroquinolones	1.98 (1.77 to 2.22)	<0.001	1.59 (1.44 to 1.75)	<0.001	1.3 (1.22 to 1.39)	0.001	1.27 (1.2 to 1.34)	<0.001
Nitrofurans	2.16 (1.9 to 2.46)	<0.001	1.69 (1.51 to 1.9)	<0.001	1.44 (1.31 to 1.58)	0.001	1.59 (1.46 to 1.72)	<0.001
Broad spectrum penicillins	1.44 (1.29 to 1.61)	<0.001	1.21 (1.11 to 1.32)	<0.001	1.1 (1.03 to 1.16)	0.002	0.002 1.06 (1.01 to 1.12)	0.02
Metronidazole	1.16 (0.96 to 1.39)	0.12	1.04 (0.9 to 1.2)	0.57	1.03 (0.95 to 1.13)	0.46	0.99 (0.92 to 1.06)	0.69
Macrolides	1.04 (0.95 to 1.14)	0.40	1.06 (0.99 to 1.13)	0.11	1.05 (1 to 1.1)	0.04	1.01 (0.97 to 1.05)	0.77
H. pylori treatment	1.68 (0.81 to 3.49)	0.17	1.76 (1.12 to 2.76)	0.01	0.86 (0.63 to 1.17)	0.33	0.92 (0.74 to 1.14)	0.45
Tetracyclines	0.98 (0.88 to 1.08)	0.66	0.97 (0.89 to 1.06)	0.51	1.01 (0.96 to 1.07)	0.69	1.01 (0.96 to 1.06)	0.71
TB drugs	1.39 (0.74 to 2.62)	0.30	1.49 (0.85 to 2.59)	0.16	0.87 (0.53 to 1.42)	0.56	0.76 (0.51 to 1.14)	0.18
Lincosamides	0.87 (0.36 to 2.14)	0.76	0.73 (0.36 to 1.45)	0.36	0.92 (0.59 to 1.42)	0.71	0.98 (0.69 to 1.4)	0.91
Penicillins	0.99 (0.94 to 1.05)	0.83	0.97 (0.93 to 1.01)	0.18	0.98 (0.95 to 1.01)	0.30	0.99 (0.96 to 1.02)	0.61

containing *O. formigenes*. As a result, a decrease in the concentration of oxalates in the urine was found 2 days after the start of taking the probiotic. This probiotic also demonstrated good safety (19). After the use of the same probiotic by healthy volunteers, a stable decrease in oxaluria and a constant colonization of faeces by it were noted (20). The use of the probiotic *O. formigenes* has found its place in pediatric practice in the treatment of primary hyperoxaluria, a genetic disease characterized by a defect in the kidneys in the metabolism of oxalates and leading to a severe form of secondary calcification and nephropathy in childhood. As a result of a randomized, double-blind, placebo-controlled multicenter study of children with a confirmed diagnosis of primary hyperoxaluria, oral administration of *O. formigenes* (Oxabact®) had no significant effect on oxaluria (21). Jairath et al in a study of the effectiveness of the probiotic Oxalobacter in patients with kidney stones (mainly calcium oxalate), found a tendency to decrease the frequency of hyperoxaluria (82.5% versus 15%, $P<0.0001$) (22). The results of a recent placebo-controlled randomized clinical study showed that limiting oxalates with food reduced their excretion in urine. At the same time, the probiotic Oxadrop and the synbiotic Agri-King did not affect the level of oxalate in urine in patients on a diet with a limited intake of oxalate compounds (23). At the same time, the results of the study by Okombo and Liebman showed that the intake of VSL#3® probiotic by healthy patients for 4 weeks reduces the absorption of oxalates in the gastrointestinal tract, which can slow down the formation of kidney stones (24). The scientific community is also interested in the use of other probiotic drugs that have, at least theoretically, oxalate-degrading activity. Indeed, some bacteria of the genera *Bifidobacterium*, *Lactobacillus* (in particular, *Lactobacillus animalis, Lactobacillus murinus, Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus plantarum*) have demonstrated oxalate-degrading activity in vitro. For example, Campieri et al reported six patients with idiopathic calcium oxalate urolithiasis and hyperoxaluria treated with a mixture of lyophilized lactic acid bacteria (*L. acidophilus, L. plantarum, L. brevis., S. thermophilus, B. infantis*) for four weeks. As a result, it was noted a decrease in daily oxalate excretion in all patients (25). In addition, the results of some studies suggest that one of the important directions in the treatment of nephrolithiasis will not be the use of probiotics with oxalate-degrading activity, but the use of drugs containing the enzyme oxalyl-CoA decarboxylase, which reduce both the intestinal absorption of oxalate and the size of existing stones.

Thus, the gut microbiome plays a role in changing the absorption of lithogenic substances in the gastrointestinal tract and, consequently, affects the risk of urinary stones formation. It can be assumed that the study of the GM state in urolithiasis will contribute to the development of new methods of its correction, and therefore improve the results of both treatment and metaphylaxis of stone formation.

Conclusion

The GM is a complex, metabolically active ecological system, the composition of which depends on many factors, both internal and external. A number of clinical studies have demonstrated a violation of the GM state in oxalate nephrolithiasis. At the same time, the assumptions about the leading role of *O. formigenes* in the process of oxalate metabolism in the intestine in urolithiasis are confirmed. Considering the decrease in the age of primary patients with signs of urolithiasis, as well as the annual increase in the incidence of nephrolithiasis, we can conclude that this problem is relevant. The currently available data suggest that GM correction may lead to a change in therapeutic approaches and be an important component of the complex treatment and metaphylaxis of nephrolithiasis.

Authors' contribution

NVS, SVP and ZAI developed the conceptualization and methodology of the study. NVS and SVP validated this study. NVS, SVP, ZAI, EIR and GNK were involved in formal analysis, resource search. NVS, SVP and ZAI were the main investigators of the study. SVP and ZAI have prepared the original draft of the study. NVS, EIR and GNK carried out the review and editing. NVS provided project supervision and administration. NWS was responsible for funding acquisition. All authors have read and approved the contents of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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