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ORIGINAL ARTICLE

Oxalobacter formigenes: Opening the door to probiotic therapy for the treatment of hyperoxaluria

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Abstract

Objective. The aim of this study was to determine the early effect of the administration of *Oxalobacter formigenes* on the metabolic pattern of patients with calcium oxalate stones, comparing it with potassium magnesium citrate (KMgCit). *Materials and methods.* Eighty patients were randomized to receive either 30 mEq of KMgCit or 700 million *O. formigenes,* both twice a day. Serum creatinine, serum urate, serum calcium and phosphorus, serum intact parathyroid hormone (if serum calcium >10.5 mg/dl) and 24 h urine metabolic evaluation for various metabolites (e.g. oxalate, calcium, phosphorus, citrate, magnesium, urate and creatinine) were evaluated at baseline and 1 month after starting the treatment. *Results.* In both groups hyperoxaluria was the most common abnormality, followed by hypercalciuria. The incidence of hyperoxaluria decreased at 1 month compared to baseline in both KMgCit (77.5% vs 37.5%, $p = 0.0006$) and *O. formigenes* preparation (82.5% vs 15%, $p < 0.0001$) groups, while other urinary metabolic abnormalities were similar at baseline and 1 month in both groups. Three patients in the KMgCit had mild self-limiting secondary symptoms. *Conclusion.* Compared with KMgCit, *O. formigenes* preparation is more effective in decreasing the incidence of hyperoxaluria, opening the door to probiotic therapy as a potential new weapon against hyperoxaluria.

Key Words:

Hyperoxaluria, Oxalobacter formigenes, probiotic therapy, urolithiasis

History

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Introduction

Calcium stones represent 80% of urinary lithiasis cases, either as calcium oxalate or as calcium phosphate [1]. Hypercalciuria is identified worldwide as the main predisposing factor in calcium oxalate stones; nevertheless, in the eastern hemisphere, hypocitraturia has been recognized as the most important cause [2]. Dietary and environmental factors are crucial in urolithiasis and general measures can prevent recurrence in the majority of patients.

Pharmacological prophylaxis is necessary in patients who are at high risk for repeated stone formation; without it, recurrence rates of urolithiasis can reach 50% within 10 years of an initial stone event [3]. The ideal drug should halt stone formation, have no side-effects and be easy to administer to achieve good compliance and optimal results.

Although the role of oxalate-degrading bacteria in calcium oxalate stone development is not clear, *Oxalobacter formigenes* has been discovered to colonize the bowel of non-stone-forming individuals and decrease intestinal oxalate. The absence of these bacteria has been linked to increased urinary oxalate levels and higher rates of stone formation in recurrent stone formers [4,5].

The aim of this study was to determine the early effect of the administration of *O. formigenes* in the metabolic pattern of patients with calcium oxalate stones, comparing it with potassium magnesium citrate (KMgCit), which has a known beneficial effect on stone recurrence.

Materials and methods

A prospective randomized controlled study was conducted from May 2011 to May 2013, after approval from the ethics committee and written informed consent had been obtained from the patients. All adult patients with calcium oxalate stones were included except for those with inflammatory intestinal disease or urinary tract infection, and those undergoing antibiotic treatment.

In total, 80 patients were included in the study and randomized by a computerized block randomization table to KMgCit preparation or *O. formigenes* preparation (40 patients in each group). KMgCit was given in a dose of 30 mEq twice a day and *O. formigenes* preparation was given in one capsule twice a day (Ochek®, *Oxalobacter formigenes* 700 million, *Lactobacillus acidophilus* 400 million, *Lactobacillus rhamnosus* 300 million, *Bifidobacterium lactis* 300 million; La Renon Healthcare, Gujarat, India).

The parameters considered were serum creatinine, serum urate, serum calcium and phosphorus, serum intact parathyroid hormone (if serum calcium >10.5 mg/dl) and 24 h urine metabolic evaluation for various metabolites including oxalate, calcium, citrate, magnesium, urate and creatinine for baseline evaluation and at 1 month after starting the drug.

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Table 1. Patients' baseline characteristics.

Parameter	Group I: KMgCit (n = 40)	Group II: *O. formigenes* (n = 40)	p
Age (years)	40.5 ± 16	42.6 ± 12.14	0.341
BMI (kg/m^2)	23.45 ± 3.06	24.38 ± 3.06	0.177
Gender			
Male	31	28	0.306
Female	9	12	0.306
Comorbidity			
Diabetes mellitus	4	5	0.500
Hypertension	8	7	0.500
Past history			
Lithuria	11	10	0.500
PCNL	5	4	0.500
ESWL	6	5	0.500
URS	5	4	0.500
RIRS	1	1	0.753
Open stone surgery	3	6	0.241
Stone size (mm)	19.65 ± 9.7	20.45 ± 8.8	0.702
Hounsfield unit (HU)	1249 ± 244	1315 ± 153	0.153
Serum creatinine (mg/dl)	0.95 ± 0.27	0.90 ± 0.23	0.492
Serum urate (mg/dl)	5.90 ± 1.38	6.25 ± 1.59	0.351
Serum calcium (mg/dl)	9.12 ± 0.47	9.30 ± 0.71	0.182
Serum phosphorus (mg/dl)	3.60 ± 0.73	3.50 ± 0.61	0.095
Urine pH	6.09 ± 0.40	6.15 ± 0.54	0.057
24 h urine creatinine (mg/day)	827 ± 305	855 ± 266	0.602

Data are shown as mean ± SD.
O. formigenes = *Oxalobacter formigenes*; KMgCit = potassium magnesium citrate; BMI = body mass index; PCNL = percutaneous nephrolithotomy; ESWL = extracorporeal shock-wave lithotripsy; URS = ureterorenoscopy; RIRS = retrograde intrarenal surgery.

During the study period all patients were kept on a normal diet without any restrictions, and all were followed up regarding their drug intake and any side-effects affecting compliance.

Sample size calculation was not attempted since this was a pilot study and no prior hypothesis on between-group differences could be made. Group sizes were chosen to ensure a sufficient statistical basis to assess efficacy results in each group. Parameters in both groups were assessed and analysed by SPSS version 15.0 software by Student's paired t test and the chi-squared test. All treatment comparisons were two-sided tests conducted at the 0.05 significance level.

Results

As shown in Table 1, the two groups were comparable in terms of age, gender, body mass index, comorbidities, history, and serum and urinary metabolic abnormalities. In both groups hyperoxaluria (>44 mg/day or >0.49 mmol/day) was the most common abnormality, presenting in 64 of the 80 patients, making a global incidence of 80% in the present series.

Although all the patients completed the treatment course with full compliance, three patients in the KMgCit group had self-limiting transient gastrointestinal disturbances at 2 weeks. Antacid was prescribed for these patients and they were advised to stop their medication for 3 days and then restart the drug gradually. None of the patients in the *O. formigenes* group complained of any adverse effects.

The incidence of hyperoxaluria decreased at 1 month compared to baseline in both KMgCit (77.5% vs 37.5%, p = 0.0006) and *O. formigenes* preparation (82.5% vs 15%, p < 0.0001) groups, while other urinary metabolic abnormalities were similar at baseline and 1 month in both groups (Table 2). The absolute values of urinary oxalate decreased significantly in both groups until reaching normal

Table 2. Incidence of urinary metabolic abnormalities at baseline and 1 month after treatment in the two groups.

Parameter	Group I: KMgCit Baseline	Group I: KMgCit 1 month	p	Group II: *O. formigenes* Baseline	Group II: *O. formigenes* 1 month	p
Hyperoxaluria (>44 mg/day or >0.49 mmol/day)	31 (77.5)	15 (37.5)	0.0006*	33 (82.5)	6 (15)	< 0.0001*
Hypercalciuria (>150 mg/day or >37.5 mmol/day)	17 (42.5)	18 (45)	1	21 (52.5)	18 (45)	0.655
Hypocitraturia (< 114 mg/day or < 0.59 mmol/day)	3 (7.5)	3 (7.5)	1	2 (5)	1 (2.5)	1
Hypomagnesuria (< 75 mg/day or < 3.1 mmol/day)	15 (37.5)	12 (30)	0.637	17 (42.5)	8 (20)	0.053
Hyperuricosuria (>750 mg/day or >4.5 mmol/day)	3 (7.5)	2 (5)	1	3 (7.5)	1 (2.5)	0.615

Data are shown as n (%).
O. formigenes = *Oxalobacter formigenes*; KMgCit = potassium magnesium citrate.

Table 3. Comparison between the absolute values of urinary metabolic parameters at baseline and 1 month after treatment in the two groups.

	Group I: KMgCit			Group II: *O. formigenes*		
Parameter	Baseline	1 month	*p*	Baseline	1 month	*p*
Oxalate						
(mg/24 h)	51.3 ± 12.5	41.3 ± 9.6	0.0001*	52.7 ± 11.9	38.0 ± 8.5	< 0.0001*
(mmol/24 h)	0.57 ± 0.14	0.46 ± 0.11		0.58 ± 0.13	0.42 ± 0.09	
Calcium						
(mg/24 h)	162.4 ± 89.9	152.5 ± 95.1	0.449	155.6 ± 52.9	152.9 ± 61.3	0.832
(mmol/24 h)	4.06 ± 2.24	3.8 ± 2.4		3.9 ± 1.3	3.8 ± 1.5	
Citrate						
(mg/24 h)	212.9 ± 79.1	221.9 ± 104.1	0.668	218.2 ± 66.6	229.2 ± 82.8	0.513
(mmol/24 h)	1.11 ± 0.41	1.2 ± 0.54		1.14 ± 0.35	1.2 ± 0.43	
Magnesium						
(mg/24 h)	84.1 ± 50.2	98.1 ± 52.2	0.313	91.6 ± 47.9	104.9 ± 44.7	0.211
(mmol/24 h)	3.5 ± 2.06	4.03 ± 2.14		3.76 ± 1.97	4.3 ± 1.83	
Uric acid						
(mg/24 h)	418.6 ± 194.9	421.5 ± 188.5	0.946	459.4 ± 159.4	457.6 ± 152.5	0.959
(mmol/24 h)	2.5 ± 1.2	2.5 ± 1.12		2.7 ± 0.95	2.72 ± 0.90	

Data are shown as mean ± SD.
O. formigenes = *Oxalobacter formigenes*; KMgCit = potassium magnesium citrate.
*Statistically significant ($p < 0.05$).

levels (Table 3), with the highest decrease observed in the *O. formigenes* group.

Discussion

Hypercalciuria is recognized worldwide as the most frequent underlying factor in calcium oxalate stones; however, increased urinary oxalate excretion may be underestimated may might even be a more prevalent risk factor than hypercalciuria for stone disease in some populations [6,7]. In the present study population, hyperoxaluria was the most frequent metabolic abnormality, probably because of the diet of the Indian population. It is clear that the treatment of hyperoxaluria is important to prevent stone recurrence, but the ideal management option for this condition has not been found.

Dietary restriction of oxalate intake alone may not be a reliable approach to prevent stone recurrence, as oxalate is derived from both endogenous and exogenous sources, with absorbed dietary oxalate rapidly excreted by the kidney [8].

Potassium magnesium citrate prevents repeated calcium oxalate stones, and is proven to reduce the risk of recurrence by 85% when given for up to 3 years [9]. The protective effect of citrate is based on its buffering capacity, its ability to complex with calcium in solution and its inhibitory activity. Citrate forms a soluble complex with calcium, reducing the ionic activity of calcium and decreasing the urinary saturation of calcium oxalate and calcium phosphate. Urinary magnesium, by complex formation with oxalate, decreases the availability of oxalate to form complexes with calcium. Therefore, the relative supersaturation with calcium oxalate and the risk of calcium oxalate nucleation are reduced [10,11]. The most direct way to increase urinary magnesium excretion is to give oral magnesium supplementation. However, the limitation of KMgCit is its contraindication in patients with renal failure and chronic diarrhoea, as potassium increment can lead to hyperkalaemia in renal failure and magnesium supplements can increase diarrhoea in patients with chronic diseases such as inflammatory bowel disease.

Oxalobacter formigenes is a Gram-negative anaerobic bacterium that can establish in the human colon and depends on oxalate for its main energy source [5,12,13]. When indicated therapeutically, *O. formigenes* colonizes the gut and reduces the urinary oxalate concentration, decreasing the risk of calcium oxalate stone formation. Kaufman et al. found that individuals who are colonized with *O. formigenes* have a 70% lower risk of becoming recurrent calcium oxalate stone formers [12].

In the present study, both KMgCit and *O. formigenes* preparation significantly reduced the incidence of hyperoxaluria after 1 month of treatment. When comparing the two drugs, the *O. formigenes* group had a greater reduction in the incidence of hyperoxaluria, suggesting that this agent may provide a superior therapeutic approach for hyperoxaluria.

In this study, no significant changes in other metabolic abnormalities were seen during the study period. This could have been due to the low dose in the KMgCit group, the relatively low number of patients studied and the short duration of treatment, as well as the absence of dietary modifications that constitute one of the bases of the medical treatment of urolithiasis.

The absence of adverse secondary effects and the good tolerance profile of the drug make *O. formigenes* a safe treatment alternative. The main limitation of this agent is that its effect remains only as long as the preparation is taken; therefore, long treatment periods are needed and in some cases could be indicated for life.

Something that is yet to be determined is whether *O. formigenes* and KMgCit have an additive effect in reducing hyperoxaluria; since they have different mechanisms of action, the combination of both agents could result in even better outcomes. Further studies are needed to clarify this issue.

In conclusion, when compared to KMgCit, *O. formigenes* preparation is more effective in decreasing the incidence of hyperoxaluria, opening the door to probiotic therapy as a potential new weapon against hyperoxaluria.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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