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Evaluation of the effects of magnesium supplement in primary and secondary preventions of nephrolithiasis: a systematic review

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ABSTRACT

Introduction: The role of magnesium supplement to prevent primary and/or secondary kidney stones has not been fully determined. The aim of this study is to evaluate the effects of magnesium supplement in modifying urinary risk factors of recurrent kidney stones.
Method: We searched MEDLINE, Scopus, and Google Scholar databases on December 7, 2014 and reference lists of systematic reviews and randomized, controlled trials. Among the initial 282 articles found by our search strategy and hand searching, we found eight English-language studies were eligible for our study.
Result: Magnesium supplementation could be beneficial in nephrolithiasis prevention through increasing urinary magnesium, citrate, and calcium while declining urinary oxalate. In pediatric patients, the results were more prominent and could decline urinary oxalate up to 90% of the baseline.
Conclusions: Magnesium supplementation could be beneficial, especially with potassium-citrate combination. However, due to the low number of well-designed randomized controlled trials, especially in pediatrics, the conclusions of this study need further confirmation.

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Introduction

Nephrolithiasis is a relatively common disease with an estimated lifetime prevalence of 7-13% (1,2). Additionally, in untreated patients, a 5-year recurrence rate is between 35 to 50% (3). The main compositions of kidney stones are calcium oxalate, calcium phosphate, and less commonly uric acid and struvite. Although kidney stone formation is a multifactorial process, it could be explained simply as an imbalance between supersaturating and inhibitory factors in urine. Citrate and magnesium are two prominent components of the inhibitory system of urine (4).

Magnesium seems to inhibit kidney stone formation by several mechanisms. Firstly, it binds with oxalate in the intestine, and consequently decreases oxalate absorption and the urinary concentration of oxalate. Secondly, it competes with calcium ions to make a complex with oxalate ions and forms magnesium oxalate, which is more soluble than calcium oxalate, 0.07 g/100 ml versus

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0.0007 g/100 ml respectively (5,6). Moreover, in vitro studies showed that magnesium could slow the crystallization process by directly decreasing the nucleation rate and supersaturation. (5,6).

Although systematic reviews implicate the effectiveness of citrate (7,8), thiazides (8-10) and increased fluid intake (11) in reducing nephrolithiasis recurrence, it is uncertain whether magnesium could be an added benefit. Some studies have reported the protective effects of magnesium, while others could not demonstrate its preventive benefits in formation and/or recurrence of kidney stones.

Methods

Literature search strategy

We searched MEDLINE, Scopus, and Google Scholar on December 7, 2014 and we reviewed reference lists of eligible randomized controlled trials (RCTs) and articles suggested by experts. Our literature search strategy was [magnesium AND ("urinary stone" OR "renal stone" OR "kidney stone" OR nephrolith* OR urolith*) AND oxal* AND citrate AND calcium].

Study selection

We included all English-language RCTs, case-controls, and cohort studies that involved assessing the prevention of primary (new) and/or secondary (recurrent) urolithiasis using magnesium treatment alone and/or with other pharmacologic treatments and included at least a 24-hour or spot urinary collection report on the levels of calcium, magnesium, oxalate, and citrate.

Results

We found 281 articles using our search strategy in the MEDLINE electronic database. According to the title and abstracts, we found 230 articles that did not fulfill our inclusion criteria. We could not access five articles because their publication dates were too old, and two articles were not in English. We further evaluated the full text of the remaining articles and we excluded an additional 36 articles due to the insufficient outcome data and/or unsuitable intervention. We found another eligible study by hand search after reviewing the article reference list. Finally, eight articles fulfilled our inclusion criteria with adequate outcomes and appropriate interventions and so were included in this systematic review (Figure 1).

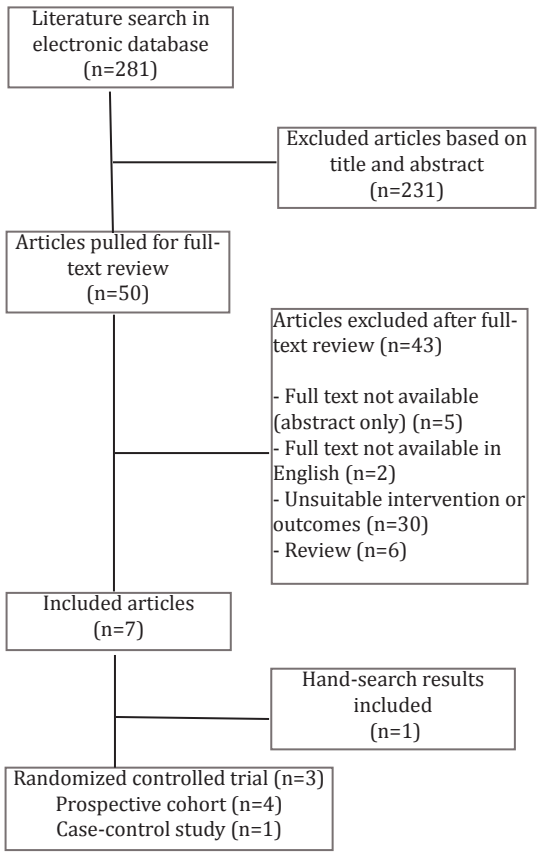
Study characteristics

Almost all studies excluded patients with comorbidities related to nephrolithiasis. Except for one study (12), the outcome measured in order to assess urinary risk factors for nephrolithiasis was a 24-hour urine test. In two studies, the primary prevention was assessed in healthy participants (13,14); while secondary prevention was evaluated in four studies (12, 15-17), in which three of them included recurrent calcium oxalate stone formers (15-17) and the other did not mention stone composition (12). In the other two studies, both healthy volunteers and recurrent stone formers were included (18,19). However only in Kato et al.'s (18) study, urinary risk factors were reported in separate tables.

We included three randomized controlled trials in which two of them included adults (13,15) and the last included pediatric patients. In the pediatric field, we could only find one RCT eligible based on our inclusion criteria (12). Unfortunately in this trial, only the spot urine test was used, which made it difficult to interpret and compare their results with the adult studies.

Most compounds of magnesium that were used in these studies included: magnesium-oxide (MgO) and potassium-magnesium-citrate (K-Mg-Cit). However, in a more recent RCT (12), magnesium-chloride ($MgCl_2$) was also used. Furthermore, only in three studies, magnesium combination treatment was compared with the standard treatment (K-Cit).

Figure 1. PRISMA flowchart of the study



Discussion

In various studies, it is recommended that a comprehensive urinary and serum evaluation should be performed in order to identify probable risk factors for nephrolithiasis and to prevent further recurrence (20-22).

In our systematic review, magnesium therapy in addition to standard therapy with potassium citrate was found to be efficient in decreasing urinary risk factors. Ignoring the exceptions, after treatment with combinations, containing magnesium, urine magnesium, calcium, citrate, and potassium increased while urine oxalate decreased (Table 1).

Table 1. The extracted data of included studies

Author Year Reference	Article type	Nephrolithiasis history	No. of patients (mean age±SD)	Mg treatment duration	Treatment dose	Outcome measure	urine Mg, Ca, Citrate, Oxalate, K before Mg treatment	Urine Mg, Ca, Citrate, Oxalate, K after Mg treatment	Change (%) in urine Mg, Ca, Citrate, Oxalate, K (after-before)	urine Mg, Ca, Citrate, Oxalate, K after standard treatment (without Mg)	Change (%) in urine Mg, Ca, Citrate, Oxalate, K (after-standard)
Gheissari 2012 (12)	RCT	Yes (proven by ultrasound)	24; 12M,12F (6.46±2.7)	28	1 mEq K ion/kg/d of K-Citrate solution ±3mg/kg/day $MgCl_2$ for children less than 10 kg up to 10mg/kg/day in adolescents weighted 40 kg (3 times a day)	spot urine	5.7, 6.6, 1.74, 3.2, 51.6 (mg/dl, mg/dl, U/L, mg/dl, mEq/l)	6.6, 7.5, 2.6, 0.29, 52	15.79, 13.64, 49.43, -90.94, 0.77	6.4, 6.7, 2.5, 0.31, 49.7	3.12, 11.94, 4, -6.45, 4.63
Zerwekh 2007 (13)	RCT	No	Intervention: 11; 7M, 4F (36) Placebo: 9; 5M, 4F (36)	35	21 mEq Mg, 42 mEq K, 63 mEq citrate (per day)	24-h urine	99, 116, 554, 28, 43 (mg, mg, mg, mg, mEq)	165, 222, 976, 31, 82	66.67, 91.38, 76.17, 10.71, 90.70	-	-
Allie 2003 (14)		No	8; 8M, 0F	56 days	300 mg MgO±800 mg Ca± 4604 mg citrate (per day)	24-h urine	4.71, 3.09, 3.16, 0.2, 58.7 (mmol, mmol, mmol, mmol, mmol)	5.8, 3.45, 3.12, 0.2, 66.7	23.14, 11.65, -1.26, 0, 13.63	-	-
Ettinger 1997 (15)	RCT	Yes (active and recurrent calculous disease)	Intervention: 31; 22M, 9F (47.45) Placebo: 33; 28M, 5F (46.8)	3 years	21 mEq. Mg, 42 mEq. K and 63 mEq. Citrate (3 times a day)	24-h urine	116 237, 587, 37, 58 (mg, mg, mg, mg, mEq)	142, 225, 769, 44, 89	22.41, -5.06, 31.01, 18.92, 53.45	-	-
Rattan 1994 (16)		Yes (recurrent calcium oxalate (CaOx) stone formers)	16; 10M,6F (37)	3 months	300 mg MgO + 10mg Vit B6 (per day)	24-h urine	1.7, 6.43, 1.52, 0.68, 36.79 (mmol, mmol, mmol, mmol, mmol)	3.21, 8.23, 2.01, 0.37, 45.36	88.82, 27.99, 32.24, -45.59, 23.29	-	-
Gershoff 1967 (17)		Yes (recurrent calcium oxalate (CaOx) stone formers)	36	5 years	100 mg MgO+ 10mg Vit B6 (per day)	24-h urine	79, 218, 435, 33.9, - (mg, mg, mg, mg, mEq)	87, 276, 531, 34.5, -	10.13, 26.61, 22.07, 1.77, -	-	-
Kato 2004 (18)	Uncontrolled clinical trial	No	Healthy: 25; 25 M (31)	7	13.7 mEq K, 13.7 mEq Na, and 34.0 mEq citrate (3 times a day) ±24.8 meq MgO (2 times a day)	24-h urine	82.7, 163.8, 343.7, 23.1, 42.8 (mg, mg, mg, mg, mEq)	119.3, 160, 584.5, 21.6, 64.6	44.26, -2.32, 70.06, -6.49, 50.93	91.9, 161.8, 494.9, 22, 58	29.82, -1.11, 18.1, -1.82, 11.38
		Yes (at least 1 calculus within previous 2 years)	Nephrolith Hx: 14; 10M, 4F (52.9)				87.7, 221.5, 241.5, 29, 40.6 (mg, mg, mg, mg, mEq)	143.2, 250.4, 391.5, 19.3, 50.9	63.28, 13.05, 62.1, -33.45, 25.37		
Pak 1992 (19)	Case series	Yes	Healthy: 5; 4M,1F (32) Nephrolith Hx: 5; 4M, 1F (65)	27	12.3 mEq Mg +24.5 mEq K + 37 mEq citrate (2 times a day) OR 25 mEq K-citrate (2 times a day)	24-h urine	102, 179, 638, 67, 46 (mg, mg, mg, mg, mEq)	146, 161, 1027, 63, 97	43.14, -10.06, 60.97, -5.97, 110.87	108, 150, 932, 73, 97	35.19, 7.33, 10.19, -13.70, 0

Among the studies that used MgO, only Rattan et al. (16) reported a decrease in urine oxalate and in the other two studies, no difference (14), or even increase (17) in urine oxalate level after treatment with magnesium were observed. Although the results of Rattan et al.'s (16) study are suggestive of the benefits of MgO treatment in nephrolithiasis prevention, it should be mentioned that magnesium oxide and magnesium hydroxide have poor gastrointestinal absorption, and therefore they are inappropriate treatments in kidney calcium calculi, especially when used alone (23). Additionally, the bioavailability of these forms is less than other magnesium salts, including magnesium compound with chloride, citrate, gluconate, and aspartate (15).

In relation to Mg-K-Cit treatment, it is generally observed that urine citrate increases between 31 to 76%. Although urine oxalate increased up to about 19% after Mg treatment in two of these studies (13,15), it decreased up to 34% of the baseline level in the other two studies (18,19). Hyperoxaluria and consequently renal stones could be due to increased oxalate intake, increased intestinal absorption of oxalate, or inborn errors of metabolism (4).

Although the incidence of urolithiasis in children seems to be lower than adults, its incidence is increasing globally, which is partly due to the extensive use of diagnostic tools including sonography in the presence of urinary symptoms among children (24-26).

In the most recent RCT that included children with nephrolithiasis and used magnesium chloride in combination with K-Cit, hopeful results were seen. We observed the most prominent decrease in urine oxalate (90% decline in relation to the baseline) among the literature studied in this systematic review. Recent literature have emphasized on metabolic abnormalities as the leading cause of pediatric urolithiasis (40-84% of cases) (27-29). Therefore, urolithiasis in children is more likely to recur and any treatment protocol should include treatment of both the stone and its underlying disorder, especially metabolic disorders.

It is reported in Turkey that hypomagnesuria is more common in children with nephrolithiasis than in adults, and this could be the reason why children response better to magnesium treatment (30).

The last question that we would like to address through this systematic review is whether adding magnesium to standard nephrolithiasis treatment with K-Cit could add benefit in lowering urinary risk factors. We found that only in three studies the standard treatment was compared with the Mg combination treatment. In all of these studies, urinary magnesium and citrate increased, whereas urinary oxalate decreased and this could be in favor of magnesium in nephrolithiasis prevention.

Conclusion

We found that magnesium treatment could be beneficial in declining urinary risk factors in both healthy and recurrent kidney stone formers. Additionally, it was observed that children responded dramatically to a combination therapy of magnesium with the standard treatment of potassium-citrate.

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Conflict of Interest

The authors declare no conflict of interest.

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