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Evaluating the associations between urinary excretion of magnesium and that of other components in calcium stone-forming patients

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Abstract

Purpose Magnesium plays numerous vital roles in human's body. It is known as a protective factor in stone formation by binding to oxalate in the intestinal and urinary system, and decreasing its absorption and crystallization, respectively. Due to controversies about the association between the 24-h urine magnesium and other urine metabolites in different studies, this study was designed to find a clear answer to this question.

Methods In this retrospective cross-sectional study, data from 24-h urinalysis of the calcium stone-forming (CSF) patients were assessed. The correlation between 24-h urine (24-U) magnesium to creatinine ratio (Mg/Cr) with other 24-U metabolites to creatinine ratio was assessed, using Spearman correlation test. The association between 24-U magnesium and 24-U oxalate was also studied in a multivariate logistic regression model.

Results Among 965 patients, the level of Mg/Cr showed a direct association with all other 24-U metabolite to Cr ratio (p-value < 0.001 for all analyses). The result of multivariate regression analysis showed that the higher quartile of 24-U oxalate (> 47 mg/24 h) increased the odds of 24-U magnesium more than 75 mg/24 h (data median) (OR 1.89, 95% CI 1.14–3.13) comparing with the lower quartile of 24-U oxalate (≤ 26 mg/24 h).

Conclusions In a routine dietary habit, since rich sources of magnesium contain a high amount of oxalate at the same time, it is not surprising that magnesium level in 24-h urinalysis showed a direct association with 24-h urine oxalate.

Keywords Association · Calcium stones · Magnesium · Oxalate · Urine metabolites

Introduction

Magnesium is considered the fourth most abundant cation in the human's body, and the second most plentiful intracellular cation [1]. Magnesium plays an essential role in more than 300 fundamental metabolic reactions [2]. Hence, its deficiency leads to a variety of chronic and inflammatory diseases, such as insulin resistance, type-2 diabetes mellitus, hypertension, cardiovascular disease (e.g., stroke), migraine headaches, and osteoporosis [3].

The role of urinary magnesium in the prevention of renal stone formation has been discussed for decades. Although studies consider hypomagnesuria a rare risk factor for stone formation (affecting $< 1\%$ of stone formers as an isolated factor), it accompanies other abnormalities in 6–11% of cases suffering from renal stone [4, 5]. Magnesium is one of the stone formation inhibitors that compete with calcium in binding to oxalate which results in magnesium oxalate (MgOx) formation, a more soluble complex in urine. In addition, magnesium may reduce the risk of calcium oxalate (CaOx) stone formation through its effect on oxalate absorption both in the gastrointestinal tract and urinary system [6], as the association between magnesium and citrate which has been shown in some studies [5, 7].

Prevention is of utmost importance in the appropriate management of patients with urolithiasis; however, some controversies have been shown in different studies in regards to the association between 24-h urinary magnesium and oxalate [5, 8]. We aimed to evaluate the 24-h urine magnesium level and other metabolites, especially oxalate in patients

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with calcium urolithiasis in order to find the relationship between the urinary level of this cation and other metabolites in patients suffering from calcium stone disease.

Methods

Study design and population

A retrospective cross-sectional study was performed on the medical database of patients with urolithiasis referred to the stone prevention clinic, Labbafinejad Hospital, Shahid Beheshti University of medical sciences, from its establishment date (November 2010) until June 2017. The institutional review board of the Urology and Nephrology Research Center (UNRC) approved the study protocols.

The inclusion criteria for the patients to participate in this study were as follow; patients ≥ 18 years old who had undergone metabolic workup for kidney stone with well-documented personal history of calcium urolithiasis (radio-opaque images at plain abdomen X-ray, or stone analysis that showed more than 50% calcium) [9], and valid 24-h urine analysis results. To avoid any possible confounders, patients with following characteristics were excluded from the study population: past medical history of primary hyperoxaluria (24-h urine oxalate > 80 mg), chronic bowel inflammatory diseases or malabsorption syndromes, autoimmune diseases, previous gastrointestinal surgery, and finally patients who were taking calcium, magnesium, or vitamin B6 supplements.

Data collection

Two well-trained physicians gathered all needed information in software designed specifically for this purpose. The information included demographic data, medical and drug history, anthropometric measurements [body weight, height, and body mass index (BMI)], serum blood urea nitrogen (BUN) and creatinine (Cr), and the 24-h urinalysis that had been collected before we started any intervention, while patients had their routine dietary habits and physical activity. In cases with more than one 24-h urinalysis, we analyzed the first sample's information. With regard to proper 24-h urine collection, patients whose 24-h urine collections were deemed to be inadequate (for men: 24-h urine Cr (24-U Cr) < 800 mg, for women: 24-U Cr < 600 mg [8]) were excluded from the study population. The 24-h urine samples were analyzed for volume, urea, creatinine, sodium, potassium, uric acid, phosphate, calcium, magnesium, citrate, and oxalate.

The prevalence of hypomagnesuria was assessed using two different cut-points: first, magnesium < 44 mg/24 h, which was used in previous studies [5]; and second, magnesium < 72 mg/24 h, which was approved by the European Association of Urology (EAU) guideline in urolithiasis [10]. The risk of CaOx stone formation was evaluated using activity product (AP) and supersaturation (SS) indices. AP (CaOx) index was calculated according to the formula described by Tiselius [11, 12], and CaOx SS was measured using the Lithorisk software [13].

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 22 (IBM Corp., NY, USA). The normality test was executed for all variables, and non-parametric analyses were performed for cases without normal variable distribution.

Before analyzing the association between 24-U magnesium and other 24-h urine metabolites, the ratio of all 24-h urine metabolites to 24-U creatinine were calculated and used in the analyses, in order to adjust for the effect of urine collection and body size. The correlation between 24-U magnesium to creatinine and other 24-h urine metabolites to creatinine ratio were assessed, using Spearman correlation test. The Spearman coefficients (r) and 95% confidence intervals were calculated using bias-corrected and accelerated bootstrap. To assess the levels of CaOx stone formation risk indices according to the 24-U magnesium, the level of AP (CaOx) index and CaOx SS were compared between patients with 24-U magnesium above and below the median value, using Mann–Whitney U test.

The association between 24-U magnesium and 24-U oxalate was also studied in a multivariate logistic regression model. The 24-U magnesium was transformed into two categorical variables according to data median and considered as the dependent variable. The 24-U oxalate was transformed to a four categorical variable, according to quartiles. Demographic characteristics, anthropometric data, serum BUN and creatinine, and all 24-U metabolites, including 24-U creatinine, were considered as potential confounders. All confounders were transformed to categorical variables according to data median, and analyzed in a univariate regression model in order to find out whether they are eligible for entering into the multivariate model. Variables with p-value < 0.15 were considered as eligible confounders, and entered the multivariate model. Backward logistic regression (LR) method was used in multivariate analyses. The level of significance was set at p-value < 0.05.

Results

From November 2010 to June 2017, 1973 patients were referred to our tertiary stone preventive clinic. To avoid possible confounders, patients younger than 18 years of old

($n=125$), non-calcium based stone ($n=173$), associated medical diseases ($n=52$), those who were under treatment with vitamin B6 or calcium, magnesium containing supplements ($n=33$), patients with under collected 24-U urine ($n=73$), missing data regard to the 24-U oxalate or magnesium ($n=54$), and those who didn't have 24-U analysis ($n=498$) were excluded from the study. During the defined time span, 965 patients met the inclusion criteria; 673 (69.7%) men, and 292 (30.3%) women.

The patients' demographic and anthropometric data and the mean values of serum and urine information are listed in Table 1. The prevalence of hypomagnesuria was 10.7%, using magnesium < 44 mg/24 h cut-point [5], and 45.8%, using magnesium < 72 mg/24 h cut-point [10].

The correlation of magnesium to creatinine ratio with other 24-h urine metabolites to creatinine ratio is demonstrated in Table 2. As seen in Table 2, the level of magnesium to creatinine ratio showed a direct association with all 24-h urine metabolites to creatinine ratio (p-value < 0.001 for all analyses). Considering CaOx stone formation as a risk index, although the level of CaOx SS was not different between the patients with 24-U magnesium above and below the median value, the level of AP (CaOx) was significantly higher in patients with 24-U magnesium above the median value ($p < 0.001$) as shown in Fig. 1a, b.

Using multivariate logistic regression model to determine the association between 24-U magnesium and 24-U oxalate (Table 3), the following variables were entitled as confounders: gender, serum creatinine and all 24-h urine metabolites namely volume, urea, creatinine, calcium, sodium, potassium, citrate, uric acid, and phosphate. The result of multivariate regression analysis showed that only the fourth quartile of 24-U oxalate (24-U oxalate > 47 mg), in comparison with 24-U oxalate ≤ 26 mg, increased the odds of 24-U magnesium more than 75 mg (data median) (OR 1.89, 95% CI 1.14–3.13).

Table 1 Characteristics of study participants [the values are mean (standard deviation), unless mentioned otherwise]

Variable	$N=965$
Age (years)	46.90 (12.09)
Gender [*N* (%)]	
Female	292 (30.3)
Male	673 (69.7)
Weight (kg)	80.00 (14.72)
BMI (kg/m^2)	28.70 (4.86)
Serum BUN (mg/dL)	16.03 (6.68)
Serum creatinine (mg/dL)	1.15 (0.25)
24-h urine volume (mL)	1668.6 (646.7)
24-h urine urea (g/24 h)	23.10 (8.63)
24-h urine creatinine (g/24 h)	1.32 (0.42)
24-h urine calcium (mg/24 h)	163.78 (84.15)
24-h urine sodium (mEq/24 h)	157.72 (71.88)
24-h urine potassium (mEq/24 h)	47.7 (20.64)
24-h urine magnesium (mg/24 h)	79.75 (33.85)
24-h urine citrate (mg/24 h)	457.45 (263.67)
24-h urine oxalate (mg/24 h)	37.24 (15.26)
24-h urine phosphorus (g/24 h)	0.74 (0.29)
24-h urine uric acid (mg/24 h)	405.13 (212.11)
AP (CaOx) index	1.17 (0.63)
CaOxSS index	6.15 (3.19)

AP (CaOx) index: ion-activity product index for calcium oxalate; CaOxSS index: calcium oxalate supersaturation index

Table 2 The correlation of 24-h urine magnesium to creatinine ratio with the ratio of 24-h urine metabolites to 24-h urine creatinine

	24 h urine magnesium to creatinine ratio		
	Spearman coefficient	95% CI	*p*-value
Volume (mL)	0.217	0.1320–0.299	< 0.001***
Urea/creatinine (g/g)	0.348	0.269–0.426	< 0.001***
Calcium/creatinine (mg/g)	0.334	0.254–0.410	< 0.001***
Oxalate/creatinine (mg/g)	0.345	0.264–0.417	< 0.001***
Sodium/creatinine (mEq/g)	0.300	0.222–0.376	< 0.001***
Potassium/creatinine (mEq/g)	0.429	0.354–0.501	< 0.001***
Citrate/creatinine (mg/g)	0.304	0.229–0.376	< 0.001***
Phosphorus/creatinine (g/g)	0.314	0.237–0.388	< 0.001***
Uric acid/creatinine (mg/g)	0.304	0.224–0.378	< 0.001***

95% CI 95% confidence interval

****p*-value < 0.001

Discussion

Low urinary magnesium is recognized as one of the risk factors for CaOx crystallization. Different studies choose dissimilar cut-points to discrete normal urine magnesium levels from hypomagnesuria, which results in different statistics in regards to the prevalence of hypomagnesuria in their populations. Preminger et al. [7] reported 4.3% as the prevalence of hypomagnesuria among 1116 subjects in whom he studied their 24 h urine (magnesium < 50 mg/24 h). In another report from Asplin et al. on 31,300 24-h urine of adults older than 18 years, the fifth percentile of the normal population (magnesium < 44 mg/24 h) was considered a cut-point for hypomagnesuria. Using this criterion, hypomagnesuria was detected in only 4.6% of the cases [6]. However, Schwartz et al. in his study on 2147 patients during 8 years, by choosing magnesium < 44 mg/24 h as a

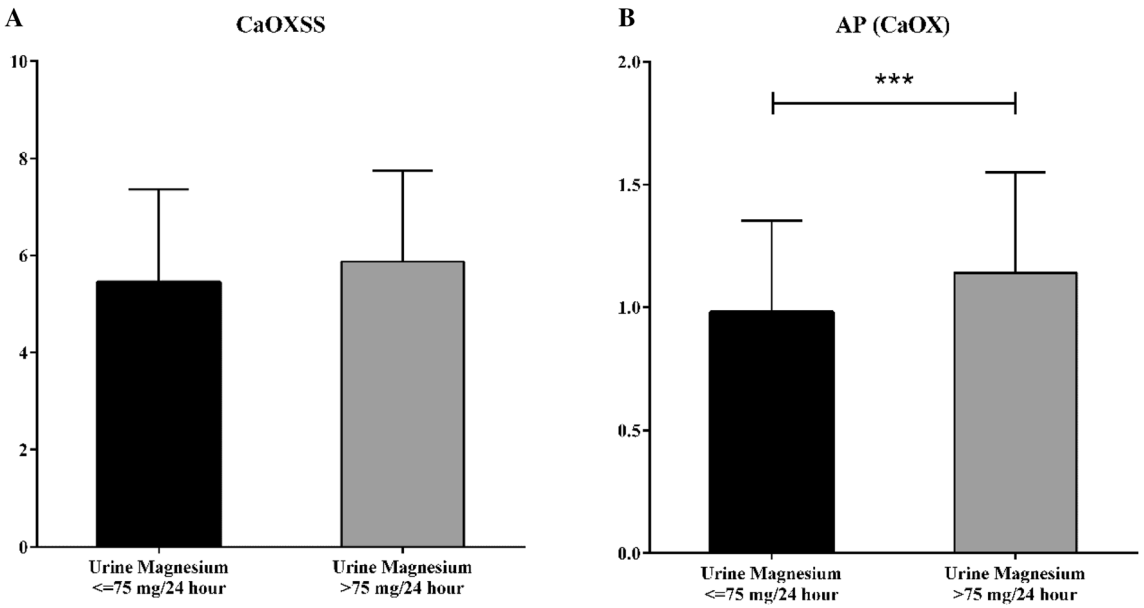

Fig. 1 The relationship between calcium oxalate stone formation risk indices according to 24-h urine magnesium level, **a** CaOx SS: calcium oxalate supersaturation index, **b** AP (CaOx) index: ion-activity product index for calcium oxalate

Table 3 Multivariate logistic regression analysis of association between 24 h urine magnesium and oxalate

Variable	Categories	Multivariate analysis		
		N (%)	Adjusted OR (95% CI)	*p*-value
Oxalate	≤ 26 mg/24 h	248 (25.7)	1 (Reference)	–
	26–37 mg/24 h	247 (25.6)	1.12 (0.71–1.76)	0.620
	37–47 mg/24 h	241 (25.0)	1.06 (0.66–1.69)	0.817
	> 47 mg/24 h	229 (23.7)	1.89 (1.14–3.13)	0.013*

Multivariate model was adjusted for gender, serum Cr, and all 24-h urine metabolites including volume, urea, creatinine, calcium, sodium, potassium, citrate, uric acid, and phosphate

OR odds ratio, *95% CI* 95% Confidence Interval

*p-value < 0.05

definition of hypomagnesuria, reported 11% as the rate of hypomagnesuria among his patients [5]. In our cross-sectional study, since the normal range of 24-U magnesium is not available in Iranian healthy population, we chose magnesium < 72 mg/24 h as a cut-point for hypomagnesuria based on EAU guideline in urolithiasis [10]. Using this guideline, the rate of hypomagnesuria was 45.8% in our study. Using magnesium < 44 mg/24 h as a cut-point for hypomagnesuria, the prevalence of hypomagnesuric patients decreased from 45.8 to 10.7% which is nearly consistent with Schwartz's study results (11%) with 2147 patients. It is noteworthy that the reported prevalence of hypomagnesuria in Preminger's, Schwartz's and Asplin's studies were published before the time of cut-point definition for hypomagnesuria in the American and European textbook and guidelines in urolithiasis [14, 15]. Therefore, changing the magnesium cut-point in 24-h urine has remarkably affected not only the prevalence of hypomagnesuria, but also the preventive and medical modalities. This difference can be seen in our study, since our findings confirmed that the AP (CaOx) index was significantly high even in the patients in whom the 24-U magnesium was above the median value.

While the role of certain urine metabolites such as calcium, oxalate, citrate, and uric acid is well established, the part of magnesium in urine is yet to be well-understood [8]. From the theoretical standpoint, magnesium acts as a competitor to calcium in oxalate binding. Therefore, its presence in the gastrointestinal system and urinary tract may reduce the oxalate absorption by binding to it. In addition, in urine, the combination of magnesium with oxalate makes it more soluble than calcium oxalate molecule [6]. It has been shown that magnesium may also play a role in renal citrate metabolism, since the low urinary magnesium level is shown to be associated with reduced urinary citrate levels [5, 7].

In the last three decades, the association between the amount of magnesium in diet and oxalate absorption has been tested in different studies. Although some studies show that magnesium prevents hyperoxaluria by mentioned mechanism, other investigations do not support this finding [5, 8]. Our data showed that after adjustment for 24-U creatinine, patients with higher urinary magnesium also excreted significantly high urinary oxalate, calcium, sodium, potassium, uric acid, phosphate, and urea. On the contrary with our results,

Eisner et al. in his study based on the 24-U analysis of 311 patients, by dividing the level of 24-U magnesium into five quintiles [8], found out that the rate of hyperoxaluria was decreased in higher quintiles of urine magnesium. While in the study by Schwartz et al. [5], retrospective review of 2147 patients with pure CaOx stone to show the relationship between urinary magnesium and other urinary metabolites, revealed that patients with hypomagnesuria (urine magnesium < 43 mg/24 h) excreted significantly less oxalate, citrate, calcium, uric acid, and sodium in their urine, which is consistent with our finding. Since the distribution of the patients in our study was relatively similar to Schwartz's and Eisner's study population, more investigation should be done to find factors that cause different results in similarly designed studies. It is noteworthy that we gathered our patient's data while they were on their routine diet and before changing their dietary habits to the stone preventive clinic protocols (general or specific recommendation diet according to full metabolic evaluation). On the other hand, the direct association between the urine magnesium level and oxalate could be discussed by the fact that urine magnesium level is highly dependent on the patient's diet [16]. A case control study by Siener et al. [17] in recurrent CaOx stone patients with or without hyperoxaluria revealed that the patients with hyperoxaluria had significantly higher magnesium intake.

It is important to know that only 10% of the magnesium is supplied by water and 35–40% of ingested magnesium is absorbed from the diet. Therefore, the direct relationship between the urine levels of magnesium and oxalate in this study showed that most of the magnesium diet sources of our patients contain a high amount of oxalate at the same time. According to the literature, green leafy vegetables containing chlorophyll (such as spinach) are the richest source of magnesium. Nuts and whole grains should be mentioned as other rich sources of magnesium. Interestingly, all these sources contain a high amount of oxalate, simultaneously. Due to this fact, it seems that the supplement of magnesium may be recommended for therapeutic attempts.

Choosing a cross-sectional design for our study was the most important limitation. Therefore, it is implausible to collect information about the dietary habits of the patients. In addition, our study design (cross-sectional) can only assess the correlation between the 24-U metabolites and, other randomized clinical trials in order to assess the effect of oral magnesium supplements on hyperoxaluria and CaOx supersaturation are needed.

Conclusion

In this study, the 24-h urine magnesium level showed a direct association with other urine metabolites even with 24-h urine oxalate. The fact that most magnesium sources in normal diet contain a high amount of oxalate at the same time gives grounds for our findings. Therefore, in patients with calcium lithiasis who are not undergoing any kind of treatment, the assessment of dietary nutrient is suggested.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Urology Nephrology Research Center institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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