RENAL FAILURE, 2017
VOL. 39, NO. 1, 146–152
http://dx.doi.org/10.1080/0886022X.2016.1256308

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CLINICAL STUDY

OPEN ACCESS

Urinary oxalate to creatinine ratios in healthy Turkish schoolchildren

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ABSTRACT

Aim: we aimed to establish reference values for urinary oxalate to creatinine ratios in healthy children aged 6–15 years and to investigate the relationship between their nutritional habits and oxalate excretion.

Materials and methods: Random urine specimens from 953 healthy children aged 6–15 years were obtained and analyzed for oxalate and creatinine. Additionally, a 24-h dietary recall form was prepared and given to them. The ingredient composition of the diet was calculated. The children were divided into three groups according to age: Group I (69 years, $n = 353$), Group II (10–12 years, $n = 335$), and Group III (13–15 years, $n = 265$).

Results: The 95th percentile of the oxalate to creatinine ratio for subjects aged 6–9, 10–12, and 13–15 years were 0.048, 0.042, and 0.042 mg/mg, respectively. The oxalate to creatinine ratio was significantly higher in Group 1 than in Group 2 and Group 3. Urinary oxalate excretion was positively correlated with increased protein intake and negatively correlated with age. A significant positive correlation was determined between urinary oxalate excretion and the proline, serine, protein, and glycine content of diet. Dietary proline intake showed a positive correlation with the urine oxalate to creatinine ratio and was found to be an independent predictor for urinary oxalate.

Conclusions: These data lend support to the idea that every country should have its own normal reference values to determine the underlying metabolic risk factor for kidney stone disease since regional variation in the dietary intake of proteins and other nutrients can affect normal urinary excretion of oxalate.

ARTICLE HISTORY
Received 23 April 2016
Revised 15 September 2016
Accepted 27 October 2016

KEYWORDS
Urine oxalate; reference value; Turkish children; diet; hyperoxaluria

Introduction

Oxalate is a highly insoluble end product of vitamin C and amino acids, such as glycine, serine, and hydroxyproline in humans. The main excretion route is the kidney, particularly in the form of calcium salt, which has a tendency to crystallize in the renal tubules. The overproduction of oxalate in the liver because of the enzymatic defect results in increased excretion by the kidney which can lead to urolithiasis, nephrocalcinosis, and even chronic kidney disease.[1,2] Hyperoxaluria (HO) is defined as a urinary oxalate excretion which exceeds 95% of the normal values and is an important lithogenic factor. It has been shown that 27–32% of stone formers have urine oxalate values above the 95% reference range.[3,4]

The diagnosis of HO in children with urolithiasis can be made using 24-h urine collection, which is the gold standard method for assessing urinary oxalate excretion in individuals and in populations. When applied to population studies, however, this method may place a high burden on participants especially for risk of low-participation rates. Therefore, determining the oxalate to creatinine ratio in random urine samples may be an alternative method in an attempt to overcome this concern.[5,6]

Oxalate excretion is affected by certain factors, such as age, fluid intake and urine output, dietary pyridoxine, dietary oxalate, and endogenous production of oxalate.[7,8] It has been shown that urinary oxalate excretion varies with age and dietary oxalate.[5,8]

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Although the main source of oxalate excreted in the urine in both normal individuals and primary HO patients is endogenous in origin,[9,10] it has been shown that dietary oxalate load has a much greater contribution to urinary oxalate excretion than previously recognized.[11] About 10–20% of urinary oxalate results from dietary oxalate, such as from tea, chocolate, and spinach.[12] Lieske et al.[13] demonstrated that stone formers with HO had a 36% reduction in urinary oxalate excretion when they consumed a low oxalate and normal calcium diet. The main precursor of oxalate in humans is glyoxylate. Interestingly, it was shown that there is a clear correlation between diet and intracellular compartmentalization of glyoxylate detoxification in different mammalian species.[9] Urinary oxalate reference values can show variability in different populations based on nutritional habits. For these reasons, it is important to establish accurate reference values for oxalic acid excretion from different populations. The aim of this study was to establish reference values for urinary oxalate to creatinine ratios in healthy schoolchildren aged 6–15 years in Turkey and to investigate the relationship between their nutritional habits and oxalate excretion.

Patients and methods

In this study, random urine specimens from 953 healthy children aged 6–15 years were obtained and analyzed for oxalate and creatinine. Then, the urinary oxalate to creatinine ratio was determined from each sample. The children, who were aged 6–15 years, were selected from different elementary and high schools, and different socioeconomic groups. All parents and children were informed about the study procedures and informed consent was obtained from the families. The children and parents were questioned about the children's health status and the anthropometric measurements of children were performed by a pediatrician. This study was approved by The Ethics Committee of Erciyes University, Faculty of Medicine (approval date 03/01/2012, number 2012/63). The inclusion criteria were: (1) no use of drugs, such as diuretics or anti-epileptics; (2) no symptoms of acute or chronic diseases; (3) no history of stone formation. The children were divided into three groups according to age: Group I (6–9 years, $n = 353$), Group II (10–12 years, $n = 335$), and Group III (13–15 years, $n = 265$). This classification was based on the new education system put into practice in March 2012. It is usually termed as "4 + 4 + 4" (4 years primary education: first level, 4 years primary education: second level, and 4 years secondary education).

To collect urine samples, the second non-fasting morning urine was collected from all the children and only a single specimen of urine from each child was examined. A mid-stream urine specimen was obtained. Then, the samples were immediately acidified by adding 0.1 mL of 6 mol/L hydrochloric acid to 5 mL aliquots and stored at $-20\,^{\circ}C$ until analysis.[14] After thawing at room temperature, the urine samples were analyzed for oxalate by the enzymatic method using an analytical procedure on a manual spectrophotometer (Biochemical Enterprise) and for creatinine by the Jaffe reaction.

A 24-h dietary recall form was prepared and given to either the children themselves or to their parents to document food consumption and its ingredients in children for 3 d before urine sampling. We asked them to write down all the foods and beverages they had consumed and record all vitamin, mineral, and herbal supplements. We also asked them to document the time the meal was consumed and place where it was consumed (home, school, restaurant, etc.), and the type of eating occasion or meal (breakfast, lunch, dinner, snack, or other). The amount of each food or beverage consumed was recorded as grams, volume in cups, tablespoons, teaspoons or fraction of the whole depending on the type of food, or beverage. The questionnaire was filled in at home the day before the urine sample was obtained. Later, it was analyzed by a dietitian. The ingredient composition of the diet was calculated using the BeBIS software system version 7 (Pacific Company, Stuttgart, Germany).

All statistical tests were performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL). First, the distributions of all parameters were determined using the Kolmogorov–Smirnov test. The parameters with normal distribution were expressed as mean ± SD and the parameters with abnormal distribution were expressed as median (range). The comparisons among the three groups for the parameters with normal distribution were done using ANOVA with the *post hoc* Turkey procedure, and those for the parameters with abnormal distribution were done using the Kruskal–Wallis H-test. Correlations were calculated with the Pearson product moment or Spearman rank order, as determined by the normality of data distribution. $p < .05$ was accepted as statistically significant. Multiple regression analyses were performed using a stepwise method in the study group. Urine oxalate was used as a dependent variable and proline, phosphate, serine, protein, and glycine were used as independent variables. A p value of $<.05$ was accepted as statistically significant.

Table 1. Urinary oxalate and creatinine levels and oxalate to creatinine ratios in study groups based on gender and age.

Age groups and gender	*n*	Oxalate (mean ± SD) (mg/L)	Creatinine (mean ± SD) (mg/dL)	Oxalate (mean ± SD)	To creatinine ratio (mg/mg) range	5th–95th percentile
6–9 years	353	13.89 ± 8.38	68.5 ± 33.3	0.023 ± 0.015	0.001–0.095	0.0039–0.048
Boys	177	14.61 ± 8.35	68.2 ± 34.1	0.024 ± 0.015	0.002–0.095	0.0039–0.048
Girls	176	13.17 ± 8.36	68.8 ± 32.6	0.022 ± 0.015	0.001–0.089	0.0038–0.048
10–12 years	335	13.35 ± 8.61	84.0 ± 33.7	0.018 ± 0.012	0.001–0.062	0.0026–0.042
Boys	175	13.35 ± 8.56	84.9 ± 39.9	0.018 ± 0.012	0.001–0.062	0.0025–0.041
Girls	160	13.35 ± 8.67	83.05 ± 39.4	0.018 ± 0.011	0.001–0.062	0.0030–0.045
13–15 years	265	13.67 ± 8.01	98.0 ± 40.8	0.016 ± 0.011	0.001–0.053	0.0029–0.042
Boys	148	13.75 ± 8.13	97.6 ± 38.5	0.016 ± 0.012	0.001–0.053	0.0026–0.039
Girls	117	13.57 ± 7.89	98.5 ± 43.6	0.016 ± 0.012	0.001–0.050	0.0034–0.044

Table 2. Gender, urinary oxalate and creatinine levels, and oxalate to creatinine ratios in groups.

Variables	Group 1 (*n* = 353)	Group 2 (*n* = 335)	Group 3 (*n* = 265)	*p*
Gender (F/M)	176/177	160/175	117/148	>.05
Oxalate (mg/L)[a]	13.89 ± 8.38	13.35 ± 8.61	13.67 ± 8.01	>.05
Creatinine (mg/L)[a]	68.5 ± 33.3	84.0 ± 33.7	98.0 ± 40.8	.001
Oxalate/creatinine (mg/mg)[a]	0.023 ± 0.015[b,c]	0.018 ± 0.012	0.016 ± 0.011	.001

[a]mean ± SD.
[b]Group 1 vs. Group 2.
[c]Group 1 vs. Group 3.

Table 3. Univariate correlations of urinary oxalate and urine oxalate to creatinine ration in study population.

	Urine oxalate		Urine oxalate to creatinine ratio	
Dietary contents	*r*	*p*	*r*	*p*
Protein	.087	.007	.045	.16
Phosphate	.090	.005	.06	.06
Glycine	.07	.02	.027	.4
Proline	.090	.006	.064	.047
Serine	.087	.007	.054	.09

Table 4. Predictors of urinary oxalate identified by a multiple regression analysis in children.

	Dependent variable = urine oxalate	
Independent variables	β	*p* values
Proline	.087	.007
Phosphate	.023	.681
Serine	.04	.568
Protein	.058	.092
Glycine	.004	.935

Results

Urinary oxalate and creatinine levels are listed according to age group and gender in Table 1. There was no difference in urinary oxalate excretion between the age groups and genders (Tables 1 and 2). The mean ± SD, range and 5th–95th percentiles of urinary oxalate to creatinine ratios are listed in Table 1. The 95th percentile of the oxalate to creatinine ratio for subjects aged 6–9, 10–12, and 13–15 years were 0.048, 0.042, and 0.042 mg/mg, respectively. The oxalate to creatinine ratios were significantly higher in Group 1 than in Group 2 and Group 3 ($p = .000$, Table 2).

A significant positive correlation was determined between urinary oxalate excretion and the proline, phosphate, serine, protein, and glycine content of diet (Table 3). There was no correlation between the vitamin C content of diet and urine oxalate excretion. Dietary proline intake showed a positive correlation with the urine oxalate to creatinine ratio (Table 3). There was no relationship between the urine oxalate to creatinine ratio and diet content of vitamin C, glycine, and serine (Table 3). The urine oxalate to creatinine ratio showed a negative correlation with age ($r = -.225$, $p = .001$). Factors independently associated with urinary oxalate excretion were examined by multiple regression analysis and the results are presented in Table 4. Dietary proline was found to be an independent predictor for urinary oxalate ($R^2 = .008$, $p = .007$). We determined no significant changes in urinary oxalate excretion from 6 to 15 years; However, urinary creatinine levels showed a significant increase with age, as expected.

Discussion

In this study, we obtained reference values for the oxalate to creatinine ratio in healthy Turkish children aged 6–15 years. We showed that there was an inverse relationship between the oxalate/creatinine ratio and age, from 6 to 9 years and urinary oxalate excretion was associated with some oxalate precursors, such as glycine, proline, and serine. In addition, the dietary intake of proline was found to be an independent predictor for urinary oxalate.

Determination of the urinary excretion rate of some solutes, such as calcium, uric acid, and oxalate is usually performed to investigate the underlying causes in children who are kidney stone formers.[3,4] Although a few

studies investigating the urinary oxalate to creatinine ratio in healthy children have been published in the literature (Table 5),[6,14–18] their results showed different values for the normal ranges of oxalate to creatinine ratio based on age and gender in different countries. For this reason, it is recommended that countries establish their own normal reference values for the urinary oxalate to creatinine ratio for use in their region.[19]

In our study, we obtained the reference values for the oxalate to creatinine ratio in healthy Turkish schoolchildren. The study showed that the oxalate to creatinine ratio had a tendency to decrease with age. This result is similar to those in some previous reports.[6,5,17] In the study by Matos et al.,[6] the authors evaluated the urinary oxalate to creatinine ratio in 384 children aged 1 month to 17 years. They measured urinary oxalate excretion by the enzymatic method using oxalate oxidase and found that the 95th percentile of this ratio was quite close between subjects aged 5–7 and 7–17 years (0.056 and 0.048 mg/mg, respectively). Sikora et al.[15] obtained the 95th percentile for the urinary oxalate to creatinine ratio in 109 children aged 6–16 years. They found that children aged over 12 years had a lower urinary oxalate to creatinine ratio than those under 12 years. Barratt et al.[17] showed that the mean urinary oxalate to creatinine ratio decreased from 0.030 in those aged 5–12 years to 0.013 in those aged over 12 years. In this study, the 95th percentile of the oxalate to creatinine ratio was 0.048 in the 6–9 year old age group and 0.042 in both the 10–12 and 13–15 year old age groups.

The influences of the dietary intake of various nutrients on urinary oxalate excretion in calcium oxalate stone formers were evaluated by Naya et al.[20,21] They examined the associations between urinary oxalate excretion and the dietary contents of animal fat, animal protein, and various fatty acids and found that the intake of animal fat was correlated with urinary oxalate excretion univariate analysis, but that of total protein, animal protein, calcium, and carbohydrate were not. In multivariate analysis, the intake of animal fat was correlated with urinary oxalate excretion and the intake of calcium was inversely correlated with urinary oxalate excretion. They also detected that the dietary content of arachidonic acid was positively correlated with urinary oxalate excretion. They thought that arachidonic acid increases the intestinal absorption of oxalate and increases the clearance of oxalate in the kidneys.[20] This study showed both a significant positive correlation between urinary oxalate excretion and glycine, proline and serine, and a significant positive correlation between the urinary oxalate to creatinine ratio, and dietary intake of proline. Proline and its major metabolite (hydroxyproline) are amino acids which have key roles in collagen integrity especially in the connective tissues.[22] The degradation of hydroxyproline by different enzymes in the liver gives rise to oxalate.

High-animal protein intake is thought to be a risk factor for calcium oxalate stone disease. The effect of dietary protein on the urinary excretion of calcium, acid, and citrate is well established. However, its effect on oxalate excretion is not well known. Some studies showed that urinary oxalate excretion increased with increased protein intake and decreased with protein restriction.[22–24] This relationship, however, between urinary oxalate excretion and dairy protein intake was not found in other studies.[25,26] In our study, we detected a positive correlation between urinary oxalate excretion and increased protein intake.

Urinary oxalate was shown to increase with ascorbic acid (AA) supplementation, which is converted *in vivo* to oxalate and excreted without further metabolism quantitatively in the urine.[27] Traxer et al. [28] found that the intake of 2 g AA daily resulted in a statistically significant increase in urinary oxalate in both healthy subjects and stone formers and there was not a different response to AA intake between stone formers and normal subjects. We could not show any correlation between urinary oxalate excretion and AA intake. In a healthy population, the kidneys can eliminate large ingested amounts of vitamin C via urine, which prevents secondary HO. However, excessive vitamin C intake can be a serious problem in some individuals, especially in those with underlying kidney disease.[29] We especially selected healthy children for the design used in our study. This might be a reason for the lack of correlation between urinary oxalate excretion and AA intake.

The strengths of this study include the following: (1) participants were selected from different socioeconomic groups; (2) it is one of the largest studies to assess the urinary oxalate to creatinine ratio and give its percentile in children so far.

The study also has important limitations: (1) a major limitation of this article is that only a single urine specimen was obtained after a single day of standard diet; (2) children under six years of age were not included in this study because of the problems involved in collecting urine samples from the local health centers; therefore, we were not able to give a reference value for children under 6 years of age; (3) as mentioned above, urine samples were taken at any time from 8.00 am to 3.00 pm. Consequently, we had to disregard the effect of hydration on solute excretion in urine; (4) we could not calculate the amount of oxalate in diet because of

Table 5. Summary of studies about urinary oxalate excretion.

Country	*n*	Age	Urine sample	Method	Results	Comment
Spain[18]	112	5–12 years	12 h	Oxalate oxidase/peroxidase method	Ox/Cr (mmol/mol) 29.4 (95th percentile for children with FH) 34.5 (95th percentile for children without FH) 5–6 years 39.4 (97.5th percentile) 7–8 years 32.4 (97.5th percentile) 9–10 years 32.6 (97.5th percentile) 11–12 years 25.6 (97.5th percentile)	No differences between boys and girls Urine Ox/Cr was lower aged 11–12 years than 5–10 years.
Poland[15]	109	6–16 years	The second morning urine sample	ND	Ox/Cr (mmol/mmol) <12 years 0.076 (95th percentile) >12 years 0.051 (95th percentile)	The values of Ox/Cr ratios are decreased in older children and there was significant difference between children under and above 12 years of age.
India[16]	208	8–15 years	24 h	Chromotropic acid reaction	0.7 mg/kg (median) 1.5 mg/kg (95th percentile) of 24-h oxalate. Ox/Cr 0.01 (median) 0.06 (95th percentile)	Oxalate excretion was similar in boys and girls, but reduced significantly with increasing age.
Germany[14]	169	1 d–13 years	Pre-noon spot urines	Ion-chromatography	Ox/Cr (mmol/mol) (mean ±2 SD) <1 month 131(75–188) 16–30 months 84 (29–139) 31–50 months 70 (20–121) 51–70 months 56 (20–91) 71–100 months 52 (22–83) 101–130 months 44 (18–71) 131–161 months 42 (12–73)	There is an inverse relationship between the oxalate/creatinine ratio and age. This finding was explained by the gain of muscle mass and hence increased creatinine production with increasing age.
Switzerland[6]	384	1 month–17 years	Second morning urine sample	Enzymatic using oxalate oxidase	95th percentile for Ox/Cr (mg/mg) 0–0.5 years <0.175 0.5–1 years <0.139 1–2 years <0.103 2–3 years <0.08 3–5 years <0.064 5–7 years <0.056 7–17 years <0.048	The 95th percentiles decreased with age: for UOx/Cr from 0.175 mg/mg (0.22 mol/mol) at 1 to 6 months to 0.048 mg/mg (0.06 mol/mol) from 7 years and beyond.
England[17]	137	0.1–17.0 years	Second morning urine sample	Enzymatically with immobilized oxalate oxidase	UOx/UCr (mmol/mmol) <1 year 0.061 (mean) 1–5 years 0.036 5–12 years 0.030 >12 years 0.013	The urine oxalate:creatinine molar ratio (UOx/UCr) decreased with age.
This study	953	6–15 years	Non-fasting random urine	Enzymatic method using analytical procedure on manual spectrophotometer	Ox/Cr (mg/mg) (mean ± SD) 6–9 years 0.023 ± 0.015 0.048 (95th percentile) 10–12 years 0.018 ± 0.012 0.042 (95th percentile) 13–15 years 0.016 ± 0.011 0.042 (95th percentile)	There is an inverse relationship between the oxalate/creatinine ratio and age, from 6 to 9 years.

the technical limitations of BeBIS. We sent a questionnaire to the families of subjects to obtain information about dietary intake for 3 d. There is a possibility that incomplete information was given; (5) we could not determine any family history of urolithiasis from the questionnaire. It was shown that the urinary excretion of solutes caused an increased risk of lithiasis in children with a family history of urolithiasis. Therefore, it is advised that children with a family history of urolithiasis should be excluded from population studies aimed at setting reference values, such as this study[18]; (6) there were no data on 24-h urine oxalate excretions, thus this may limit the ability to make meaningful correlations with diet; (7) we could not collect urine samples from patients with primary HO to confirm thresholds where disorders of oxalate metabolism, such as primary HO, might be more likely, and to determine the appropriate cut offs. Despite all these limitations, we think that a good data set of a reference range for morning urine oxalate creatinine ratios was provided with this study. This could be useful for identifying patients with hyperoxaluric conditions. The urinary oxalate to creatinine ratio declines with age and shows variability according to geographic area. Using different laboratory or urine collection methods may be a reason for the variations in urinary oxalate excretion in different studies. Based on our study findings, we think that every country should have its own normal reference values to determine the underlying metabolic risk factor for kidney stone disease since regional variation in the dietary intake of proteins and other nutrients can affect normal urinary excretion of oxalate.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure statement

The authors declare that they have no conflicts of interest.

Funding

This work was supported by the Erciyes University Scientific Research Center [TSU-12-3903].

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