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Urinary calcium excretion in healthy Turkish children

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Abstract The aim of this study was to establish the age related reference percentile values for urinary calcium excretion in healthy Turkish children, and to determine the frequency of hypercalciuria and also the factors affecting urinary calcium excretion. A cross-sectional study was performed in Aydın, in western Turkey during winter. Study population was constituted from seventeen districts of this region (sample size was calculated from a formula using the results of the last population census) by stratified and random sampling methods. Urinary calcium excretion was measured as the calcium/creatinine concentration ratio in the second non-fasting urine samples. A total of 2252 children (1132 male) with a mean age of 8.57 ± 4.44 years (ranged from 15 days to 15 years) were studied. The mean of urinary calcium/creatinine concentration ratio was calculated as 0.092 ± 0.123. The percentile values between 3rd and 97th for urinary calcium/creatinine concentration ratio according to age were calculated and shown as multiple line graphs. Hypercalciuria prevalence was found as 9.6% when the upper limit of urinary calcium/creatinine concentration ratio was accepted as 0.21. Urinary calcium/creatinine concentration ratio of the children from different districts, altitudes, and ethnic origins were statistically different. Poor negative correlations were found between urinary calcium/creatinine concentration ratio and age and weight. No differences in urinary calcium/creatinine concentration ratios were observed in terms of sexes, diet, physical activity, urolithiasis in the family, symptoms related to hypercalciuria, amount of calcium in drinking water, and urine strip analysis. In conclusion, reference values for urinary calcium/creatinine concentration ratios should be established for children in each country and also in each geographic region.

Keywords Children · Idiopatic hypercalciuria · Normal values · Urinary calcium excretion · Urinary creatinine

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Introduction

Hypercalciuria is defined as >4 mg/kg/24 h (0.1 mmol/kg/day) urinary excretion of calcium during childhood [1–5]. Due to the difficulties of obtaining 24-h urine collection in children, the ratio of urinary calcium to creatinine (UCa/UCr) is routinely used in clinical practice to diagnose hypercalciuria as it has a good correlation with daily calcium excretion [1, 6].

A definitive upper value has not been accepted for hypercalciuria. Generally, UCa/UCr ratio of >0.21 has been regarded as abnormal and accepted as hypercalciuria [3,6,7]. However, hypercalciuria has been accepted as the values ranging between 0.17 and 0.37 in different studies [6, 8–14]. Unfortunately, the available data on normal values for urinary calcium excretion in children were controversial, due to differences in study populations, age, and variations in dietary intake in these studies. In addition, some authors showed that urinary UCa/UCr ratio was higher in the younger age groups [7, 15]. Therefore, there has not been an accepted value for the reference of normal urinary UCa/UCr ratio.

Recent studies have shown that there have been variations in UCa/UCr ratio and frequency of hypercalciuria and these variations were believed to result from differences in age, genetics, race, mineral composition of drinking water, nutritional habits, and geographical variations [2, 7, 10, 12, 13].

It is important to determine and treat hypercalciuria in children in our country, which is in the stone belt. In this way, urinary calculi formation in adult age, osteopenia, and growth retardation can be prevented.

The aim of this study was to investigate UCa/UCr values in healthy children between the ages of 0 and 15 years, to establish the age related reference percentile values for UCa/UCr, to determine the frequency of hypercalciuria and to investigate the factors affecting urinary Ca excretion.

Material and method

According to the results from the last population census obtained from Government Statistics Institute, the number of children aged between 0 and 15 years was determined to be 265,893 in Aydın. Detailed information about their age groups and gender was also taken. The sample number of children in our study has been determined by the formula which has been given below and known as ''to calculate the sample number, if the population number in universe is known'' and also by using program of Epi. Info 2002.

$$n = \frac{N(t_{1-\alpha})2 \times (p \times q)}{S^2(N-1) + (t_{1-\alpha})^2(p \times q)}$$

p = prevalence, $q = 1–p$, S = standard deviation, N = total number of children in Aydın, $(t_{1-\alpha})$ = the degree of freedom at a determinate confidence interval (t-value is 1.96 according to 95% confidence interval).

In this cross-sectional investigation, study group was determined as 2,149 children by using 95% confidence interval, 1% error. The study region was accepted as center and 16 districts of Aydın city. Children included to the study were chosen as proportional to the total number of children with the age between 15 days and 15 years according to their age and sex from 17 different study regions by using stratified and random sampling methods. The sample number was calculated by the proportion given below.

$$\text{The number of urinary sample which had to be taken according to the age and sex from one region} = \frac{\text{total sample number}}{\text{total number of 0–15 aged children in the region}} \times \text{number of children at the same age and sex}$$

Children who do not use any medications except vitamins, fluorine, and iron, and who are not acutely or chronically ill were accepted to the study. The urinary samples were obtained from children between November 2002 and April 2003.

The procedures followed were in accordance with the Helsinki Declaration of World Medical Association and the ethical standards. Approval forms were signed and questionnaire-providing information about the children was answered by the parents and the family. Second urine samples obtained at 2.2 ± 1.0 h after breakfast were taken and frozen at –85 C. Drinking water samples were also frozen at –85 C, Urinary strip examinations were performed in all urines.

Urinary calcium, creatinine, and drinking water calcium values were examined on I Lab 1800 autoanalyser with photometric method by using commercial ILAB kits (182503-40 lot number for calcium and 18255-40 lot number for creatinine). Calcium values were studied without dilution and creatinine values were studied by diluting at 1/10 ratio. Results were given as ''mg/dl.''

Statistical analyses were performed by using one-way anova, Dunnett C, χ^2, Pearson correlation, pair-wise comparison, and student *t*-tests. The results were expressed as mean ± SD and $P < 0.05$ was regarded as statistically significant.

Results

Second morning urine samples were obtained from 2,252 children (1,132 males and 1,120 females). The mean age of the children was 8.57 ± 4.44 years (14 days–15 years). The mean age of girls (8.58 ± 4.43 years) and boys (8.56 ± 4.45 years) were similar.

The mean urinary UCa/UCr ratio was determined as 0.092 ± 0.123 mg/mg (0.003–1.6) for the whole group. Mean UCa/UCr values and reference percentiles of all age groups were calculated and graphics were performed (Table 1 and Fig. 1).

In Aydın, hypercalciuria prevalence was calculated as 9.6% when the upper limit of UCa/UCr was accepted as 0.21. Poor negative correlations were found between UCa/UCr and age and weight, respectively ($r = –0.101$, $r = –0.090$). Significant differences were found in UCa/UCr ratio of different districts ($F = 3.714$, $P < 0.001$). Covariance analysis was performed and it was found that this difference was independent of age effects ($F = 3.64$, $P < 0.001$). A positive and good correlation was found in the altitudes of districts and UCa/UCr values ($r = 0.551$, $P = 0.022$). The mean value of UCa/UCr, prevalence of hypercalcuria and the altitudes of all regions are shown in Fig. 2.

Table 1 Reference percentile values of the UCa/UCr(mg/mg) of all age groups

Age group (year)	3%	5%	25%	50%	75%	90%	95%	97%
0–11 month	0.010	0.010	0.020	0.100	0.200	0.460	0.640	1.010
1	0.008	0.009	0.013	0.070	0.177	0.250	0.309	0.394
2	0.004	0.005	0.016	0.045	0.100	0.196	0.256	0.550
3	0.002	0.004	0.014	0.040	0.095	0.198	0.319	0.373
4	0.004	0.007	0.021	0.057	0.110	0.191	0.296	0.407
5	0.002	0.004	0.023	0.066	0.120	0.203	0.280	0.350
6	0.003	0.005	0.023	0.059	0.127	0.227	0.283	0.398
7	0.003	0.006	0.022	0.056	0.141	0.230	0.370	0.424
8	0.005	0.007	0.030	0.060	0.126	0.204	0.295	0.315
9	0.003	0.010	0.026	0.070	0.126	0.192	0.258	0.298
10	0.004	0.009	0.024	0.055	0.132	0.205	0.299	0.350
11	0.004	0.005	0.023	0.048	0.126	0.248	0.280	0.375
12	0.005	0.004	0.017	0.040	0.097	0.180	0.248	0.307
13	0.002	0.007	0.012	0.027	0.081	0.164	0.268	0.370
14	0.004	0.004	0.020	0.047	0.11	0.175	0.240	0.285
15	0.004	0.005	0.023	0.052	0.145	0.217	0.258	0.325
Total	0.004	0.006	0.021	0.052	0.122	0.206	0.283	0.398

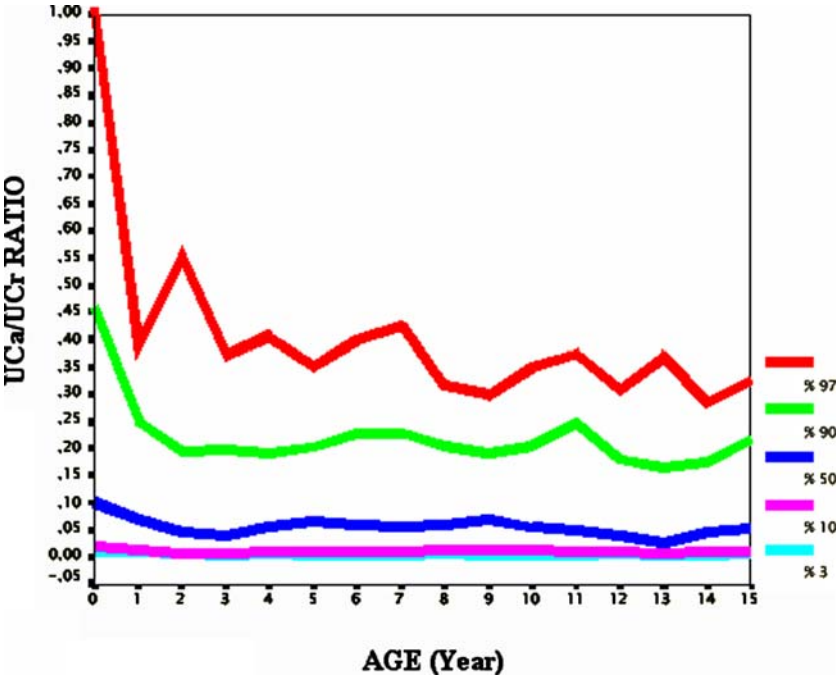

Fig. 1 The reference values of 3, 10, 50, 90 and 97th percentiles of UCa/UCr

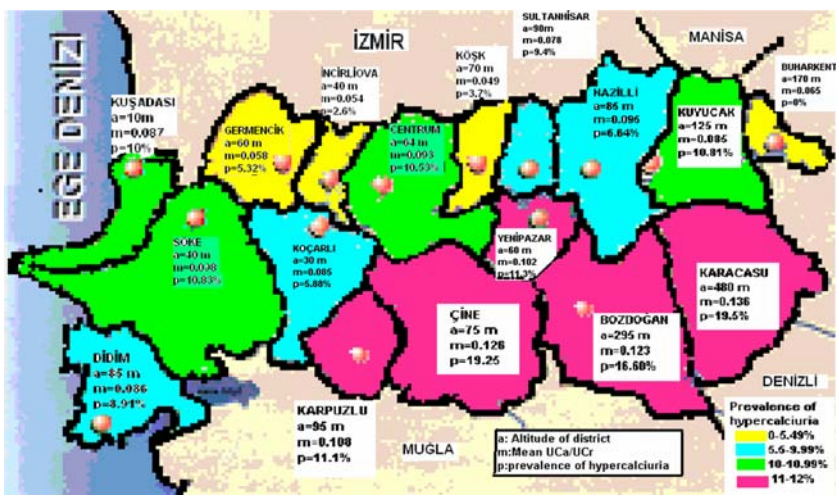

Fig. 2 The mean UCa/UCr, prevalence of hypercalciuria and altitude of each district

When the children who immigrated from other regions and whose parents were from the same city were grouped, statistically significant differences were found in these groups ($F = 2.592$, $P = 0.035$). UCa/UCr ratio of children from one ethnic group called as Acarlar was lower than other groups. Skin color of the children from Acarlar was darker and they were immigrated from Afghanistan.

No differences in UCa/UCr ratios were observed between sexes, vitamin and flour intake, diet, physical activity, stone formation history in the family, signs or symptoms related to hypercalciuria, amount of calcium in drinking water and results of urine strip analysis.

Discussion

Hypercalciuria, especially idiopatic hypercalciuria, has been interestingly noticed as a cause of urinary tract complaints in children. Hypercalciuria is one of the important risk factors for stone disease in

adults and children; however, data on normal values of urinary calcium excretion and incidence are controversial. In the textbooks of pediatric nephrology and urology [1–4, 9], the upper limit for urinary calcium excretion was given as 4–5 mg/kg/day and 0.20–0.24 as the calcium creatinine concentration ratio. The characteristics of the study groups in the references [7, 10, 11, 13, 16–19] cited in these books were different. Not all of the study groups consisted of only healthy children, but some authors studied the children from day care centers admitting for minor complaints [6, 10, 11]. Some studied the schoolchildren aged between 6 and 17 years [7,16,17,20], some between 2 and 17 years [10, 13, 18, 19], and some also infants [6, 8, 14]. Multiple studies have shown that the urinary calcium creatinine ratio varies not only with age but also with geographic area [6, 7, 13, 17, 20, 21]. Therefore, the results of these studies were controversial and did not reflect the given characteristics of society. Different upper limits ranging between 0.17 and 0.37 for hypercalciuria were also started to be used by different countries [6–8, 10, 12–14, 20, 22, 23]. We believe that it is important to have accurate normal reference values of urinary calcium excretion for children at different ages in a given geographic area. A true hypercalciuria definition is important for preventing unnecessary treatment. On the other hand, the risk of urinary stone formation and other complications will be higher if these cases are unrecognized.

In this study, the mean UCa/UCr ratio was found as 0.092 ± 0.123; this ratio was higher than that in the results of the investigations performed in United States, Japan, Iran, and China [10, 20, 21, 24]. However, the mean UCa/UCr ratio was found to be lower in Argentina, India, Hungary, and Sweden [7, 13, 14, 22]. In the studies from Turkey, the prevalence of hypercalciuria in children was found between 2.8% and 12.5% [25–27]. There are many factors affecting urinary excretion of calcium. Many authors suggested that variations in calcium excretions in different communities might occur due to differences in age, sex, the nutritional habits, mineral composition of drinking water, race, geographic area, and climate [4].

In the studies carried out in other countries, the prevalence of hypercalciuria frequency varies between 0.6% and 12.7% [7, 10, 12]. As the accepted upper limit of UCa/UCr ratio was 0.21 mg/mg for hypercalciuria, the prevalence of hypercalciuria was established as 9.6% in our region. In other words, the value of 0.21 used for hypercalciuria limit in many studies was seen to be similar to the 90th percentile in our study (0.206 mg/mg).

A weak but significant negative correlation between UCa/UCr and age was found in different studies [7, 8, 13, 14, 21]. Some authors found no correlation between UCa/UCr and age [11, 17, 20, 22]. In our study, UCa/UCr was significantly higher in younger children than older groups like other studies. This result may be explained by lower excretion of creatinine for the body weight in the younger group or by increasing amount of calcium absorption in the infants.

Other studies showed that the urine UCa/UCr ratios in African-American children were lower than Caucasian children [4, 6]. The urine UCa/UCr ratio of children having black skin whose families immigrated from Afghanistan to Aydın was also lower than the children whose families immigrated from other places. This result might show that there is a correlation between UCa/UCr and vitamin D metabolism.

As the altitude of the district increased, the mean urinary UCa/UCr ratio was also found to statistically increase.

In this study, no difference in UCa/UCr ratios were observed in sexes, vitamin administration, physical activity, history of nephrolithiasis in the family, signs or symptoms related to the hypercalciuria, amount of calcium in drinking water and results of urine strip analysis.

As a summary in this study, normal values of the calcium excretion were determined for each age groups and different regions and also reference percentiles were constituted. The prevalence of hypercalciuria was found as 9.6%. This value was equal to the 90th percent in Aydın. Our data showed that there were correlations between urinary UCa/UCr ratios and age, weight, race, geographic location, and altitude.

In conclusion, reference values for urinary UCa/UCr ratios should be established for children in each country and also in each geographic region. In the future, we are planning to evaluate hypercalciuric children by using these percentile values in our region and to determine risk ratios

for the urinary stone formation according to these percentile values.

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