Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population

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Objective: To determine reference values for urinary phosphate/creatinine (Cr) concentration ratios and to complete reference values for urinary calcium/creatinine and magnesium/creatinine ratios in the second morning urine sample of healthy infants, children, and adolescents.

Design: Urinary P/Cr, Ca/Cr, and Mg/Cr ratios were determined from the second morning urine sample. Two urine samples were obtained 1 week apart from most subjects to assess reproducibility.

Setting: Kindergartens and schools of Lausanne, Switzerland.

Participants: A total of 410 healthy children aged 1 month to 17 years (197 girls and 213 boys) participated in the study.

Results: The 5th and 95th percentiles were estimated from 664 urine samples. There were no differences related to sex. A nonlinear regression in terms of age was used to smooth the estimated percentiles yielding reference curves from which critical values may be obtained for any given age. The 95th percentile for urinary Ca/Cr and Mg/Cr agreed with previously reported values in children older than 7 years. The upper limit of the three solute/creatinine ratios decreased significantly with age: for urinary P/Cr from 19.0 mol/mol at 1 month to 2.7 at 14 years; for urinary Ca/Cr from 2.2 to 0.7 mol/mol, and for urinary Mg/Cr from 2.2 to 0.6 mol/mol. Lower limits varied little. Interindividual and intraindividual variations decreased with age.

Conclusions: Urinary P/Cr, Ca/Cr, and Mg/Cr ratios vary strongly with age. We provide reference values, expressed both in SI and in mass units, for urinary P/Cr, Ca/Cr, and Mg/Cr in children aged one month to 17 years. (J Pediatr 1997;131:252-7)

Pediatricians are often confronted with the lack of reference values for urinary phosphate excretion when treating patients with renal tubular disorders, metabolic acidosis, hyperparathyroidism, vitamin D intoxication, urolithiasis, or nephrocalcinosis. Few studies have been published on phosphate excretion in children,[1-3] and subjects participating in those studies were either from a population of hospitalized children[1] or not representative of all pediatric ages.[2,3]

Cr Creatinine

In a study on calcium excretion, Nordin[4] first demonstrated the usefulness of the solute/creatinine concentration ratio in random urine samples in adults. Since then, several authors have examined the calcium/creatinine and magnesium/creatinine concentration ratios in children because this constitutes an easier and probably more reliable way than a 24-hour urine collection to evaluate mineral excretion in this population. Although the influence of calcium intake and voiding time on urinary calcium excretion has been thoroughly investigated,[3, 5-11] there is still some controversy concerning the effect of age on the excretion of these solutes. In addition, the groups studied were often too small to allow a precise determination of reference values per age class,[12,13] lacked representation of certain ages,[2,3,5,6,8,10,11] and included subjects from inpatient or outpatient clinics.[5,10] Furthermore, in most reports results were given as the mean ± SD, which is not an appropriate approach, because the urinary excretion of a given solute does not follow a gaussian distribution.[14,15]

The purpose of this study was to determine age-related reference values for urinary phosphate, calcium, and magnesium to creatinine concentration ratios in the second morning urine samples for chil-

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dren older than 1 month. Parents were asked not to change their children's eating habits because we wished to determine the reference data of urinary mineral excretion under everyday life conditions.

METHODS

Study Protocol

Children were told not to change their eating habits or physical activity, and a questionnaire relative to the family's medical history was completed by the parents.

The second morning urine sample was collected between 8 and 11 AM. For children who were not toilet-trained, a random urine sample was collected between 6 and 11 AM. Adhesive urine collection bags were used to collect urine from infants. Whenever possible, two urine samples were collected under the same conditions at a 1-week interval. Only children without a personal or family history of kidney or metabolic disease, who were not currently ill, and not taking any medicines participated in the study.

In the second part of the questionnaire, the parents/child were asked to note all foods and drinks ingested during the 24-hour preceding urine collection, with the aim of studying the relation between the amounts of ingested calcium, magnesium, and phosphate and their urinary excretion. Only some of the returned questionnaires were precise enough to allow the quantitative analysis of mineral ingestion during this period. Written informed consent was given by all parents. This study was approved by the ethics committee of the Lausanne University Medical School.

Population

A total of 410 infants, children, and adolescents, aged 1 month to 17 years (median age 6.4 years; 197 girls and 213 boys), from 7 kindergartens and nurseries and 4 schools participated in the study (Table I). Kindergartens and schools were selected from different areas of the town so that the proportions of the different ethnic and socioeconomic groups observed in the study corresponded to those in the overall local population[13] of 200,000 inhabitants.

Table I. Study population and urine samples

Age class (yr)	No. of children	Children with two urine samples	Number of urine samples			
			Girls	Boys	Total	Fasting samples
1/12-1	79	34 (43%)	54	59	113	0
1-2	48	23 (48%)	29	42	71	0
2-3	41	19 (46%)	26	34	60	0
3-5	54	38 (70%)	54	38	92	4
5-7	40	30 (75%)	35	35	70	6
7-10	50	39 (78%)	37	52	89	3
10-14	51	30 (59%)	51	30	81	4
14-17	47	41 (87%)	38	50	88	23
TOTAL	410	254 (62%)	324	340	664	40

Four pediatricians collected urine samples from healthy infants who were seen for routine health supervision.

Sample Analysis

Urine samples were collected in chemically clean bottles and were brought to the laboratory, where samples were analyzed 3 to 4 hours after sampling. Solute concentrations were measured as follows: phosphate by the ammonium molybdate reduction method (interassay coefficient of variation <2% at values <15 mmol/L), magnesium by using a colorimetric reaction with xylidil blue (interassay coefficient of variation <2.5% at levels of 3 mmol/L), calcium by the o-cresolphthalein Complexone method (interassay coefficient of variation <2% at 3 mmol/L), and creatinine by a kinetic Jaffé method (interassay coefficient of variation <4% at 6 mmol/L). All tests were performed on a Hitachi 704 analyzer with reagents supplied by Boehringer (Rotkreuz, Switzerland).

Reference values are reported in SI units as well as in mass ratios. To convert from SI to mass units, the following multiplication factors were applied: 0.274 for urinary P/Cr, 0.354 for urinary Ca/Cr, and 0.215 for urinary Mg/Cr.

Statistical Analysis

All methods described herein were applied to the three urinary solute ratios. Two urine collections were obtained from 254 subjects, and the difference of the two measurements was expressed as a percentage of their sum. Because the distribution of these percentages was symmetric about zero (globally and for each sex separately), any possible systematic bias between first and second urine samples was ruled out. Sex differences were assessed by the Wilcoxon signed rank test for data of girls and boys paired by age. Because no significant sex differences were found, all further analyses were performed on the 664 available samples from children aged 1 month to 17 years. The subjects were subdivided into eight age classes (Table I), and results are reported by age class as well as for continuous age. At any given age the distributions of urinary P/Cr, Ca/Cr, and Mg/Cr were highly positively skewed. We used a quantile regression in terms of age to determine the running values of the 5th and 95th percentiles. Predicted values were obtained for each subject and reference values within each age class were calculated for the "average" child in the class and appear as step functions. The individual predicted values were then fitted by nonlinear regression (in terms of continuous age x) according to the following model:

$$y = C_0 + (B_0 + B_1x + B_2x^2) \cdot \exp(-A_0x)$$

In this model the constant C_0 represents the "adult" level to which children should

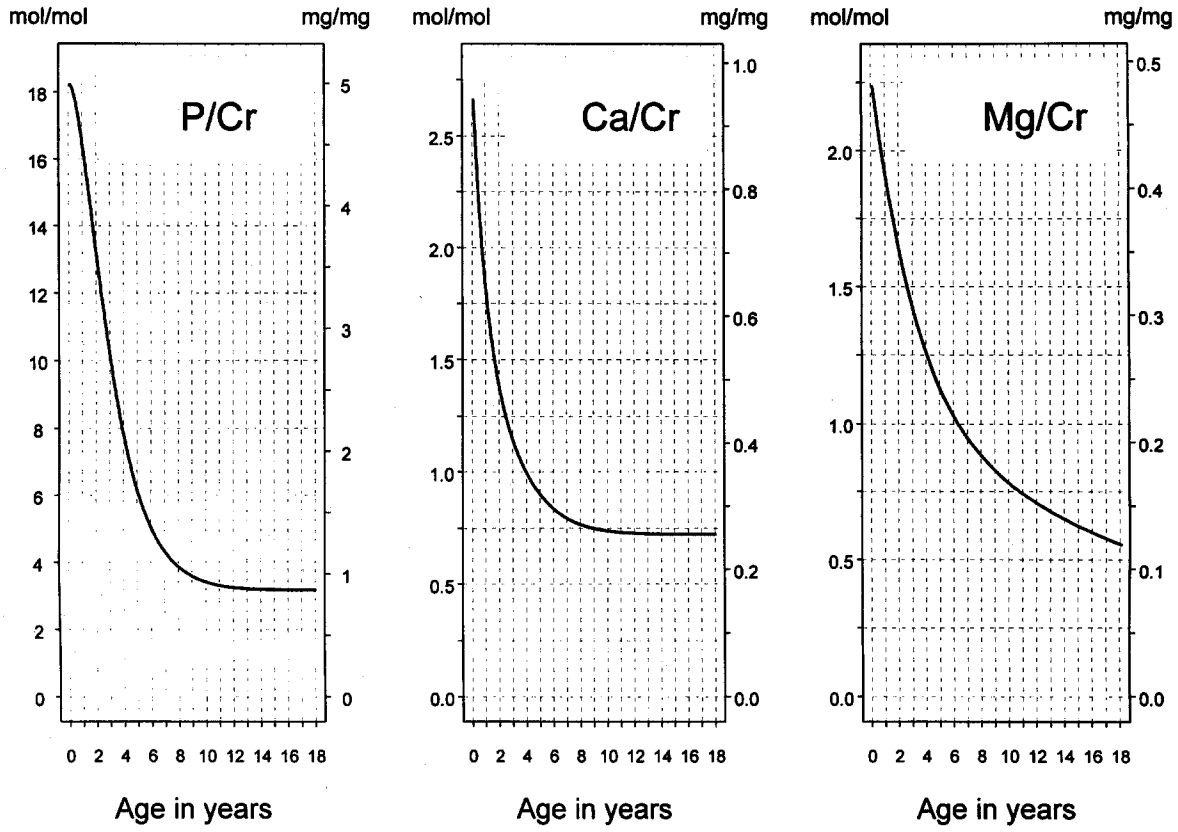

Figure. Estimated 95th percentiles for urinary P/Cr, Ca/Cr, and Mg/Cr ratios in relation to age.

converge, and the other term has the form of a "growth and decay" model that may be appropriate to describe the evolution of the urine ratios during maturation. The stability of the curves obtained from these estimated nonlinear regression coefficients is illustrated by a joint 95% confidence band that is based on the (approximate) asymptotic multivariate normality of the vector of coefficients and the resulting chi-square distribution derived in the usual way from the estimated covariance matrix of the coefficients.

Intraindividual variations were determined with the coefficient of variation of the two measurements obtained from the 254 subjects who had two urine collections (note that, up to a constant factor, the coefficient of variation is simply the absolute value of the difference divided by the mean as described above). Interindividual variations were determined, within each age category, by the standard deviation obtained with only the first urine sample of each subject. Analyses were performed on a personal computer with the statistical package STATA version 4.0 for Windows (Stata Corporation (1995); College Station, Texas).

RESULTS

On the basis of the following results, we decided not to segregate data and to determine reference values by age class according to the 664 available urine samples. First, there were no sex-related differences in the three solute/creatinine ratios. Second, two urine collections were obtained from 62% of subjects (Table I), and an order effect (systematic bias) between the first and the second urine samples could be excluded. Third, the number of urine samples collected from children who had not eaten their breakfast could be determined from the questionnaire (Table I). The possible influence of these urine samples after fasting on the determination of reference values was negligible in the lower age groups because of very small numbers, whereas in the older group, the results obtained for fasting and nonfasting subjects were very similar as shown by the small interindividual variations. Finally, because there were only five black children (1.2%) and four Asians (1%) and because these children did not yield either very high or very low values, racial effects were considered to be negligible for this population.

The 95th percentiles for urinary P/Cr, Ca/Cr, and Mg/Cr decreased with age: from 19.0 mol/mol at 1 month to 2.7 mol/mol at 17 years for urinary P/Cr, from 2.2 to 0.7 mol/mol for urinary Ca/Cr, and from 2.2 to 0.6 mol/mol for urinary Mg/Cr (Table II). Not surprisingly, the 5th percentiles varied little with age and were very low over the entire age range.

The curves obtained after smoothing of the 95th percentiles are shown in the Figure, where the left axis indicates values in moles per mole, and the right axis

indicates values in milligrams per milligram.

The stability of the mathematical model used in the smoothing is very satisfactory, because the 95% confidence bands for the 95th percentile for the three solute/creatinine ratios are remarkably narrow over the entire age range. Upper reference limits for the urinary P/Cr, Ca/Cr, and Mg/Cr ratios can thus be read at any age from these smoothed curves. The coefficients of the curves found for the 95th percentiles, as described in the Methods section, are as follows:

1. For urinary P/Cr: C_0 = 3.159, B_0 = 15.0768, B_1 = 9.2882, B_2 = –0.00015, and A_0 = 0.6048

2. For urinary Ca/Cr: C_0 = 0.7206, B_0 = 2.0840, B_1 = –0.017, B_2 = 0.1583, and A_0 = 0.6998

3. For urinary Mg/Cr: C_0 = 0.2995, B_0 = 1.9778, B_1 = –0.0895, B_2 = 0.0136, and A_0 = 0.1622

Intraindividual and interindividual variations for all three solute/creatinine ratios decreased steadily with age (Table III).

Table II. Urinary references limits (5th and 95th percentiles) for urinary P/Cr, Ca/Cr, and Mg/Cr by age class

Age class (yr)	Urinary P/Cr mol/mol (mg/mg)*		Urinary Ca/Cr mol/mol (mg/mg)*		Urinary Mg/Cr mol/mol (mg/mg)*	
	5th	95th	5th	95th	5th	95th
1/12-1	1.2 (0.34)	19.0 (5.24)	0.09 (0.03)	2.2 (0.81)	0.4 (0.10)	2.2 (0.48)
1-2	1.2 (0.34)	14.0 (3.95)	0.07 (0.03)	1.5 (0.56)	0.4 (0.09)	1.7 (0.37)
2-3	1.2 (0.34)	12.0 (3.13)	0.06 (0.02)	1.4 (0.50)	0.3 (0.07)	1.6 (0.34)
3-5	1.2 (0.33)	8.0 (2.17)	0.05 (0.02)	1.1 (0.41)	0.3 (0.07)	1.3 (0.29)
5-7	1.2 (0.33)	5.0 (1.49)	0.04 (0.01)	0.8 (0.30)	0.3 (0.06)	1.0 (0.21)
7-10	1.2 (0.32)	3.6 (0.97)	0.04 (0.01)	0.7 (0.25)	0.3 (0.05)	0.9 (0.18)
10-14	0.8 (0.22)	3.2 (0.86)	0.04 (0.01)	0.7 (0.24)	0.2 (0.05)	0.7 (0.15)
14-17	0.8 (0.21)	2.7 (0.75)	0.04 (0.01)	0.7 (0.24)	0.2 (0.05)	0.6 (0.13)

*Conversions have been performed with higher precision, then rounded for this presentation.

DISCUSSION

The reference values proposed in this study were calculated for children older than 1 month. The mathematical model used to smooth the step function of the 95th percentiles makes possible an easy determination of usable upper limits for urinary P/Cr, Ca/Cr, and Mg/Cr at any given age. Few authors propose reference limits for mineral/creatinine ratios as percentiles, although this is an appropriate approach for asymmetric distributions.[14, 15] Because the interindividual and intraindividual variations of urinary analytes are greater than those in serum or plasma,[16, 17] calculating the 3rd and 97th percentiles would require a much larger sample for acceptable confidence levels. In addition, the 5th and 95th percentiles are adequate for the diagnostic discrimination of urinary analytes.

The creatinine excretion rate is relatively constant. It is related to lean body mass, perhaps to skeletal mass, and therefore yields a good "unit" to standardize solute excretion in a urine sample. Measurements in a random urine sample are particularly interesting for pediatricians because timed urine collections are difficult to obtain and are often incomplete in small children and thus prone to gross errors. Ghazali and Barrat[5] first found that mineral/creatinine ratios in the second morning urine sample best represented the 24-hour mineral excretion related to body weight in children older than 1 year.

The upper reference values of the three analytes are discussed in detail below; the lower values are not discussed except to note that the 5th percentiles barely changed with age.

Phosphate

As shown in Table II, the 95th percentile decreased sharply during the first year of life from 19 mol/mol to stabilize around 2.7 mol/mol at 14 to 17 years. The latter value is very close to that reported for adults[18] (2.92 mol/mol), which was obtained as the mean +2 SD, and would represent the 97.5th percentile in a gaussian distribution.

In contrast to our study, Malone et al.[8] and Paunier et al.[1] did not observe an age effect on the 24-hour phosphate excretion in children. The fact that these authors do not report an age effect may be attributed to (1) the small number of subjects, (2) a restricted age range of the children studied, (3) the selection of the participating subjects, and (4) nutritional habits. In the study of Malone et al., the sample size was very small (n = 37) and the subjects were studied at an age when urinary P/Cr values were found to stabilize in our study (7 to 8 years), whereas Paunier et al. drew their sample population from an inpatient unit of a university hospital, thus making it difficult to consider this sample as representative of a normal population. Chen et al.,[3] who used the same laboratory technique as we did, also found that the urinary P/Cr ratio decreased with age and that there were no sex differences. They obtained lower values for the 95th percentile of urinary P/Cr in a Taiwanese school population (2.81 mol/mol at 7 to 10 years, 2.23 mol/mol at 10 to 14 years, and 1.42 mol/mol for children older than 14 years). However, urine samples were collected in the morning while children were fasting, which may explain lower values for phosphate excretion, in addition to the fact that Chinese children have a lower intake of milk products than Western Europeans.

Calcium

Several factors are thought to influence urinary calcium excretion: diet, physical activity, race, and (subject to some controversy) age. In our study, the 95th percentile decreased progressively to a value of 0.7 mol/mol by 8 years of age. Intraindividual and interindividual varia-

Table III. Interindividual and intraindividual variations of urinary P/Cr, Ca/Cr, and Mg/Cr by age class

Age class (yr)	Interindividual variation (SD in mol/mol)			Intraindividual variation (median CV in %)		
	Urinary P/Cr	Urinary Ca/Cr	Urinary Mg/Cr	Urinary P/Cr	Urinary Ca/Cr	Urinary Mg/Cr
1/12-1	5.4	0.7	0.5	17.5	19.0	18.0
1-2	3.9	0.4	0.4	23.3	14.0	37.3
2-3	2.6	0.3	0.3	17.4	12.0	32.3
3-5	1.9	0.2	0.3	21.5	8.0	20.4
5-7	1.0	0.2	0.2	19.0	5.0	12.5
7-10	1.0	0.2	0.2	26.6	3.6	14.0
10-14	0.7	0.1	0.1	15.7	3.2	12.9
14-17	0.7	0.1	0.1	15.6	2.7	14.0

tions of urinary Ca/Cr also decreased markedly with age. This decrease in interindividual variation has already been reported by Sargent et al.,[10] who also found an age-related decrease in urinary Ca/Cr in children younger than 6 years but did not specify the age at which urinary Ca/Cr values stabilized. Esbjörner and Jones[11] found "a weak but significant negative correlation" between postprandial urinary Ca/Cr values and age in a group of children aged 2 to 18 years (n = 153); these results are in agreement with our findings. The influence of age on urinary Ca/Cr ratio was not observed in other previous studies.[5-7,19] We believe that the effect of age was not observed in those studies because (1) the age of the study populations coincided with the ages at which, in our study, the urinary Ca/Cr value is constant (children older than 7 years, Figure and Table I), and (2) even though infants and young children were included in some of those studies, their results were not analyzed separately. The difference in diet may have contributed to the higher values of urinary Ca/Cr found in infants and young children, especially in European and in North American children.

In our study, most urine samples were collected after breakfast except in the group of adolescents (14 to 17 years), for whom approximately one fourth of the urine samples came from individuals who were fasting. Because the time of urine sampling in relation to meals influences urinary Ca/Cr,[6,7,9,11] a decrease in urinary Ca/Cr might be expected in this age group; however, the ratio was stable from about the age of 8 years and thereafter, and the interindividual variability was lowest in the group of adolescents.

The stabilized 95th percentile value of urinary Ca/Cr in adolescents (0.7 mol/mol) is in agreement with the upper values of urinary Ca/Cr determined by Sargent et al.[10] in healthy adults (0.61 mol/mol) and by Nordin[4] in hospitalized adults (0.28 mg/mg, [0.78 mol/mol]). Both studies were based on random urine samples and, as in our study, the o-cresolphthalein Complexone method was used to determine the urinary calcium concentration. In the former study, the authors describe values for the 95th percentile of urinary Ca/Cr in children younger than 6 years very similar to ours (2.24, 1.69, and 1.18 mol/mol at 7 months, 7 to 18 months, and 19 months to 6 years, respectively). Ghazali and Barrat,[5] who used the same analytical method as we did, also reported upper limits for urinary Ca/Cr in the second morning urine sample close to ours (0.25 mg/mg [0.7 mol/mol]).

The interest in determining upper limits for urinary Ca/Cr ratio in a random urine sample is derived from the need for an easy screening for hypercalciuria. Hypercalciuria is often divided in two main pathophysiologic entities with different therapeutic approaches.[20-22] Renal hypercalciuria is defined by an elevated urinary Ca/Cr in urine samples after fasting and after an oral calcium load (indicating a deficiency in renal tubular reabsorption of Ca), whereas the absorptive type of hypercalciuria is characterized by a normal urinary Ca/Cr ratio in the fasting state and an abnormally high urinary Ca/Cr value after an oral calcium load or a meal (consistent with a gastrointestinal hyperabsorption of dietary Ca).

The effect of calcium intake on the urinary Ca/Cr ratio in children has been widely studied (either as a meal or a calcium load),[6,7,11] and upper limits were determined in urine samples obtained after fasting and after a standardized calcium load. We believe that age-related upper limits of urinary Ca/Cr in the second morning urine sample provide values for a first screening for hypercalciuria.

Magnesium

Renal magnesium wasting is found in congenital renal tubular defects (Bartter and Gitelman syndromes) and in endocrine disorders (hypercalcemia, hyperthyroidism, hyperaldosteronism, and diabetes mellitus).[23] It may also be related to drug toxicity (*cis*-platinum, aminoglycosides, cyclosporine, and pentamidine[24]) and has been reported after renal transplantation or failure.[23]

Upper limits for magnesium excretion have not yet been determined for all ages. In our study the 95th percentile for urinary Mg/Cr in the second morning urine sample was age dependent and decreased steadily from 2.2 mol/mol during the first year of life to 0.6 mol/mol at adolescence. The course and values were very similar to those obtained for calcium (Figure). An upper limit of urinary Mg/Cr in a random urine sample was first proposed by Ghazali and Barrat[5] (who also used a colorimetric reaction with xylidil blue to determine urinary magnesium concentration) in 29 British children aged 1 to 15 years; the mean ± SD for urinary Mg/Cr was 0.31 mg/mg (1.44 mol/mol). There

was no age discrimination on their results, thus making a comparison with our findings difficult. Chen et al.[3] reported 95th percentiles for Mg/Cr in children older than 7 years. They found a similar decrease of urinary Mg/Cr values with age but their values were considerably lower than ours (0.24 mol/mol for 7 to 10 years; 0.19 mol/mol for 11 to 14 years, and 0.14 mol/mol for 15 to 18 years). However, they determined urinary magnesium concentration by atomic absorption spectrophotometry. Differences in the analytic methods used, as well as lower intake of milk products, as mentioned for urinary P/Cr, could account for the lower values of urinary Mg/Cr found by these authors.

In conclusion, this study provides age-related 5th and 95th percentiles for urinary P/Cr, Ca/Cr, and Mg/Cr determined by standard automated analytic chemical methods and analyzed by robust statistical methods. The calculated 5th percentiles for all three solute/creatinine ratios were nearly constant, whereas the 95th percentiles decreased markedly during the first 6 to 8 years of life. Interindividual and intraindividual variations also decreased significantly with age. Both facts are in agreement with complete maturation of the urinary excretion of these solutes by the age of 8 years.

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