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Urinary excretion of calcium and phosphate in preterm infants

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Abstract The aims of this study were to determine reference ranges for the urinary calcium (UCa/Cr) and phosphate (UPO₄/Cr) creatinine ratios and to study factors influencing these ratios in a representative population of preterm infants managed according to current nutritional guidelines. Spot urine samples were obtained from 186

Editorial comment: this paper describing urinary excretion of calcium and phosphate in preterm infants elicited completely different reactions from the three referees selected to review the manuscript. It is important to establish reference ranges for urinary excretion of these minerals. Nevertheless, it is also important to understand the effect of dietary intake of both calcium and phosphate in defining normative data. It is essential that readers of this article also read the accompanying commentary by Professor Frank Pohlandt.

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preterm infants (gestation 24–34 weeks) for measurement of UCa/Cr and UPO₄/Cr ratios as part of a routine metabolic bone screening program, once every 2–4 weeks from the 3rd to the 18th week of life. Data were also collected on gender, appropriate or small for gestational age (SGA), nutrition [total parenteral nutrition (TPN), preterm or term formula, and breast milk], plasma Ca, PO₄, urea, and electrolytes and on the use of drugs (furosemide, dexamethasone, and theophylline). Data from infants treated with any of these three drugs were analysed separately and not included in establishing the reference ranges for UCa/Cr and UPO₄/Cr. The mean gestational age of the study population was 28 weeks (range 24–34 weeks). The 95th percentile for UCa/Cr at 3 weeks of age was 3.8 mmol/mmol and decreased significantly with increasing postnatal age ($P < 0.001$). The 95th percentile for UPO₄/Cr was 26.69 mmol/mmol at 3 weeks of age, but this did not change significantly with increasing postnatal age ($P = 0.296$). On univariate analysis there was no significant association of UCa/Cr and UPO₄/Cr with gender and type of enteral nutrition. The UCa/Cr was lower in infants who were SGA ($P = 0.013$) and with low plasma Ca ($P = 0.008$). Infants on TPN had significantly higher UCa/Cr ($P = 0.019$) and lower UPO₄/Cr ratios ($P \leq 0.001$). Multivariate analysis confirmed the decrease in UCa/Cr ratio with increasing postnatal age, but the SGA effect was eliminated. The use of furosemide ($P < 0.001$) and theophylline ($P = 0.003$) was associated with a significant increase in the UCa/Cr ratio. The use of dexamethasone was also associated with an increase in UCa/Cr ratio, but this did not achieve statistical significance ($P = 0.339$). The use of furosemide, theophylline, and dexamethasone had no effect on UPO₄/Cr. We report a reference range for UCa/Cr and UPO₄/Cr ratios and factors influencing these ratios in a representative population of preterm infants between 24 and 34 weeks gestation, managed according to current nutritional guidelines.

Keywords Urinary calcium · Urinary phosphate · Urinary creatinine · Nephrocalcinosis · Percentile

Introduction

The urinary excretion of calcium (UCa) and phosphate (UPO_4) in healthy children between 1 and 18 years [1, 2, 3, 4, 5] has been well documented, but studies on UCa and UPO_4 excretion in preterm infants are limited. Research on UCa and UPO_4 in preterm babies has used normal reference ranges for UCa and UPO_4 in term infants [6]. However, the normal UCa and UPO_4 might vary in preterm infants according to postnatal age (PNA). Reference data for UCa and UPO_4 in preterm babies would enable a more accurate study of the aetiology of nephrocalcinosis (NC) in this age group and would be useful in studies of Ca and PO_4 metabolism and in optimizing Ca and PO_4 supplementation. Karlen et al. [7] studied UCa and UPO_4 excretion in 51 stable preterm infants (mean gestation 32 weeks) who were fed predominantly on breast milk without PO_4 supplementation. However, it is recognised that extremely low birth weight infants fed on breast milk are depleted in PO_4 and Ca and are paradoxically hypercalciuric in relation to the degree of PO_4 deficiency [8, 9]. It is also likely that these data no longer reflect current nutritional practice.

Increased excretion of UCa and UPO_4 has been associated with the development of NC in preterm infants [10, 11, 12]. We and others have reported an incidence of NC of 16%–63% in preterm infants born before 32 weeks gestation or very low birth weight (VLBW) infants [10, 13, 14]. A recent retrospective study of babies born at <37 weeks gestation reported that the incidence of NC was 0.73% (1.7% for VLBW infants) [15]. Factors known to influence UCa excretion in the preterm infant include frusemide [16, 17], theophylline [18, 19], and dexamethasone [20]. Furosemide has also been shown to increase UPO_4 excretion in VLBW infants [17].

A close linear correlation has been established between 24-h UCa excretion and random UCa/Cr ratio in children [1, 3] and adults [21], but accurate timed collection of urine in preterm infants is difficult. The present study was conducted to determine reference ranges for UCa/Cr and UPO_4 /Cr ratios in a population of preterm infants born at 24–34 weeks gestation, who were managed according to current nutritional guidelines, and to study the effect of frusemide, theophylline, and dexamethasone.

Patients and methods

The study population was drawn from preterm babies born at The Queen Mother's Hospital, Glasgow, a tertiary neonatal unit. Urine and blood samples were obtained from 186 consecutive preterm infants (gestation 24–34 weeks) as part of a routine metabolic bone screening program performed every 2–4 weeks from the 3rd to 18th week of life. All infants were stable at the time of urine collection (60% required ventilation during the first 1–3 weeks of life and 25% were oxygen dependent at 36 weeks of post-conceptual age). All but 5 infants were Caucasians. Urine samples were collected either by clean catch or adhesive bag (Hollister U-Bag) between 0100 and 0800 hours and blood samples (for plasma urea and electrolytes, Ca, PO_4 , and alkaline phosphatase) between 0700 and 0900 hours. In total, 296 paired urine and plasma samples were

analysed. Data were collected on gender, whether the birth weight was appropriate (AGA) or small (SGA) for gestational age, nutritional details [total parental nutrition (TPN), preterm or term formula, and breast milk], and on the use of drugs (frusemide, dexamethasone, and theophylline). Data from infants treated with frusemide, dexamethasone, or theophylline (88 paired urine and plasma samples) were analysed separately and not used for establishing the reference ranges for UCa/Cr and UPO_4 /Cr ratios.

Nutrition and supplementation

The unit practice was to use a maximum of 150 ml/kg per day TPN, 170 ml/kg per day preterm formula (Ostoprem), or 200 ml/kg per day expressed breast milk (EBM)/term formula; 100 ml of TPN provided 1 mmol of Ca and PO_4 and 1.7 g of protein. TPN infusion commenced at 60 ml/kg per day, increased to a maximum of 150 ml/kg per day over 4 days, and continued at this rate until the baby tolerated oral feeding. The TPN PO_4 content was increased according to plasma PO_4 and tubular PO_4 reabsorption (TRP), and TPN protein content increased to 2.32 g/100 ml from day 8 onwards. No protein fortifier was added to EBM. All infants on enteral feeding received routine supplementation of vitamin D 800 IU (Mother's and Children's Vitamin Drops) and PO_4 1 mmol/kg per day (potassium acid phosphate). TPN-fed infants received vitamin D as ergocalciferol (Vitlipid N Infant, Fresenius Kabi, UK) at 160 units/kg per day up to a maximum of 400 units/day. One 32-week and 3 33-week gestation babies did not receive routine PO_4 supplementation. Oral supplementation of vitamin D and PO_4 was initiated when 50% of the enteral feed was tolerated and PO_4 supplementation was adjusted to maintain plasma $\text{PO}_4 > 1.8$ mmol/l and TRP < 85%. The sodium intake was adjusted according to the plasma and urinary sodium levels.

Sample analysis

Plasma Ca, PO_4 , urea, electrolytes, and alkaline phosphatase were analysed by dry slide technique using an Ortho Vitros 950 analyser. Urinary Ca, PO_4 , and creatinine were also analysed by dry slide technique using an Ortho Vitros 250 analyser. Urine was acidified to pH < 3 prior to analysis of PO_4 and Ca. The analyzer range for urine Ca is 0.12–4.49 mmol/l and for urine PO_4 0.13–6.46 mmol/l. It should be noted that the absolute value of UCa/Cr or UPO_4 /Cr will depend on the creatinine concentration of the urine specimen. As the urine in preterm infants is often extremely dilute, laboratory practice was to re-analyse urine creatinine specimens with a value less than 1.0 mmol/l, using plasma methodology that has a much lower limit of detection (around 12 $\mu\text{mol/l}$). UCa/Cr and UPO_4 /Cr ratios are reported as the molar ratios. TRP (ratio of the PO_4 clearance to the creatinine clearance) was calculated and expressed as a percentage.

Statistical analysis

The data were transformed by Box-Cox regression as they were positively skewed. Transformation used the parameter $\lambda = 0.3$ for the UCa/Cr ratio and $\lambda = 0.5$ for the UPO_4 /Cr ratio. We performed multivariate linear regression with the clustering option since more than one measurement was taken from the same individual at different times. The 5th and 95th percentiles for the UCa/Cr and UPO_4 /Cr ratios were calculated using the square root of the error mean square of the regression as an estimate of the standard deviation for the distribution. Univariate and multivariate analysis was performed to determine the factors influencing UCa/Cr and UPO_4 /Cr ratios.

Results

The mean gestational age was 28 weeks with lower and upper quartiles of 27 and 30 weeks, respectively. Plasma urea, creatinine, bicarbonate, PO₄, Ca, and alkaline phosphatase values are shown in Table 1. Since there was no significant difference on univariate analysis in UCa/Cr and UPO₄/Cr with gestation and gender, all data were grouped for further analysis (Table 2).

Urinary Ca/Cr

The percentile distribution of UCa/Cr is shown in Fig. 1, which shows a significant decrease with increasing PNA ($P<0.001$).

Univariate analysis

UCa/Cr was significantly lower in SGA babies and in babies with lower plasma Ca and higher in babies on TPN and with higher TRP. No significant association was found with gestation, gender, the type of enteral feed, plasma bicarbonate, PO₄, or alkaline phosphatase (Table 2).

Table 1 Plasma biochemistry results of preterm infants

Biochemical factor	Result	Result	Result
	(median)	(range)	(lower to upper quartile)
Urea (mmol/l)	1.40	0.4–7.7	0.86–2.80
Creatinine (μ mol/l)	33.00	16–108	28.00–38.50
Bicarbonate (mmol/l)	26	11–40	23–29
Alkaline phosphatase (U/l)	219	30–791	179–300
Calcium (mmol/l)	2.43	2.1–2.82	2.34–2.50
Phosphate (mmol/l)	1.98	1.06–4.29	1.79–2.24

Table 2 Factors affecting urinary calcium/creatinine (Ca/Cr) and phosphate/creatinine (PO₄/Cr) (univariate analyses) (CI confidence interval, TRP tubular reabsorption of phosphate, EBM expressed

Multivariate analysis

breast milk, OP Ostoprism milk, FF Farley's first milk, SGA small for gestational age, TPN total parenteral nutrition)

UCa/Cr was significantly lower in babies on EBM and in those with a low plasma PO₄, but the effect of SGA was eliminated. In addition, UCa/Cr was significantly higher in babies with higher plasma Ca and bicarbonate, and babies on TPN (Table 3).

Urinary PO₄/Cr

The percentile distribution of urinary UPO₄/Cr is shown in Fig. 2. By univariate analysis babies on TPN had significantly lower UPO₄/Cr ratio and those with lower plasma PO₄ and higher plasma Ca had lower and higher UPO₄/Cr ratios respectively; however this was not significant. In addition, there was no significant association between the UPO₄/Cr ratio and gestation, PNA, gender, SGA, type of enteral feed, plasma bicarbonate, and alkaline phosphatase (Table 2).

Multivariate analysis

Babies on TPN ($P<0.001$) and with lower gestational age (24–29 weeks) had a significantly lower UPO₄/Cr ratio ($P=0.03$). Babies with a higher plasma Ca had a significantly higher UPO₄/Cr ($P=0.04$) and there was a trend

Factor	Urinary Ca/Cr				Urinary PO ₄ /Cr			
	n	Coefficient	95% CI	P value	n	Coefficient	95% CI	P value
Group 1 and 2 ^a	204	0.022	-0.27 to 0.315	0.882	185	-0.41	-0.982 to 0.162	0.159
Gestation at birth	204	0.043	-0.027 to 0.113	0.227	185	-0.105	-0.268 to 0.059	0.207
Gender	204	-0.007	-0.327 to 0.312	0.964	185	0.251	-0.345 to 0.846	0.407
EBM	204	-0.168	-0.486 to 0.15	0.297	185	-0.164	-0.849 to 0.521	0.636
OP milk	204	-0.053	-0.346 to 0.24	0.722	185	0.278	-0.32 to 0.876	0.359
FF milk	204	-0.118	-0.393 to 0.157	0.399	185	0.413	-0.351 to 1.18	0.287
Postnatal age	204	-0.053	-0.082 to -0.024	<0.001	185	0.039	-0.034 to 0.112	0.296
SGA	204	-0.385	-0.689 to -0.081	0.013	185	-0.175	-0.843 to 0.493	0.605
TPN	204	1.25	0.204 to 2.29	0.019	185	-3.53	-4.8 to -2.27	<0.001
Plasma calcium	189	-0.576	-0.997 to -0.155	0.008	181	0.766	-0.145 to 1.68	0.099
Plasma phosphate	191	0.117	-1.2 to 1.43	0.861	183	-2.35	-5.21 to 0.5	0.105
Plasma bicarbonate	190	0.024	-0.007 to 0.055	0.127	182	-0.02	-0.082 to 0.043	0.531
Plasma alkaline phosphatase	165	-0.001	-0.002 to 0.001	0.333	162	0	-0.004 to 0.003	0.881
TRP	184	0.021	0.011 to 0.032	<0.001	184	-0.141	-0.155 to -0.128	<0.001

^a Divided into two groups, i.e., 24–29 and 30–34 week's gestation at birth

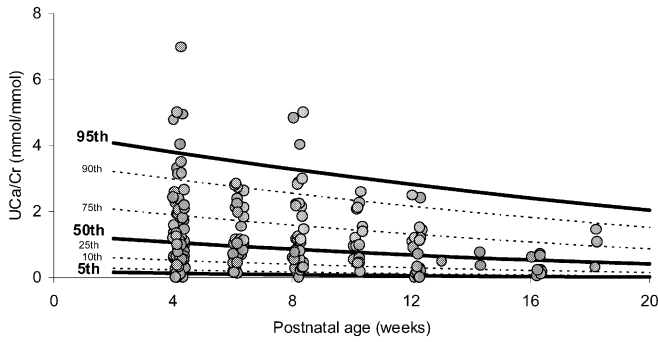


Fig. 1 Urinary calcium/creatinine (*UCa/Cr*) ratio percentile for 24- to 34-week preterm infants from 3 to 18 weeks of age. Conversion factor: 1 mmol/mmol=0.355 mg/mg

Table 3 Factors affecting urinary Ca/Cr (multivariate analyses)

Factor	Coefficient	<i>P</i> value
Postnatal age	-0.085	<0.001
TPN	0.732	0.014
EBM	-0.296	0.014
Plasma phosphate	-0.345	0.013
Plasma calcium	1	0.031
Plasma bicarbonate	0.031	0.023
TRP	0.013	0.003
SGA	-0.212	0.113

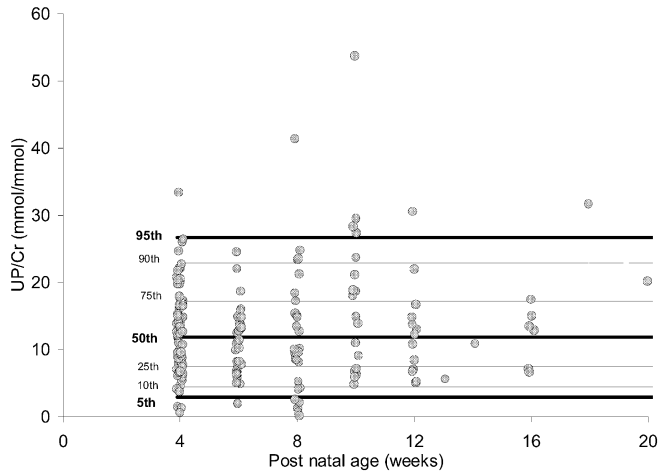


Fig. 2 Urinary phosphate/creatinine (*UPO₄/Cr*) ratio percentile for 24- to 34-week preterm infants from 3 to 18 weeks of age. Conversion factor: 1 mmol/mmol=2.74 mg/mg

towards a lower *UPO₄/Cr* in babies with lower plasma *PO₄* (*P*=0.06).

There was no change in the percentile reference ranges for *UCa/Cr* and *UPO₄/Cr* ratios when the data were re-analysed after excluding values from week 13–18 (Figs. 3 and 4).

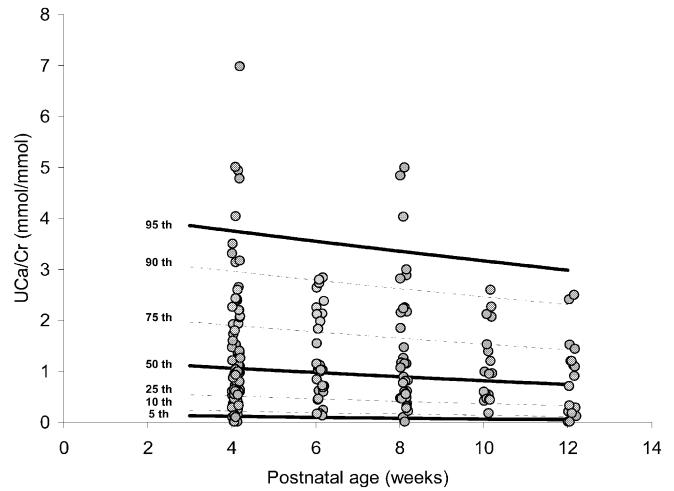


Fig. 3 *UCa/Cr* ratio percentile for 24- to 34-week preterm infants from 3 to 12 weeks of age (excluding values from weeks 13–18)

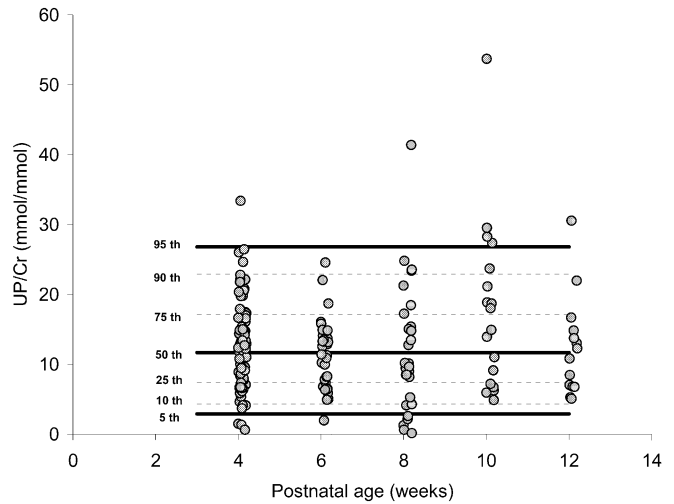


Fig. 4 *UPO₄/Cr* ratio percentile for 24- to 34-week preterm infants from 3 to 12 weeks of age (excluding values from week 13–18)

Drugs and urinary Ca and *PO₄*

Frusemide and theophylline (both loading and maintenance doses) significantly increased *UCa/Cr*. Babies who received postnatal dexamethasone also had higher *UCa/Cr*, but this was not significant (Table 4). There was no association between *UPO₄/Cr* and the use of frusemide, theophylline, or dexamethasone (Table 4).

Discussion

We report reference ranges for *UCa/Cr* and *UPO₄/Cr* ratios for a population of preterm infants (24–34 weeks gestation) who received *PO₄* supplementation and found a significant negative correlation between *UCa/Cr* and PNA. This age-related decrease in *UCa/Cr* is similar to that seen in term infants within the 1st year of life [22] as

Table 4 Urinary Ca/Cr and UPO₄/Cr ratios in babies receiving drugs

Drug	Urinary Ca/Cr	Urinary Ca/Cr	<i>P</i> value	Urinary PO ₄ /Cr	Urinary PO ₄ /Cr	<i>P</i> value
	with drug	without drug		with drug	without drug	
Frusemide	2.45 (<i>n</i> =25)	1.0 (<i>n</i> =267)	<0.001	11.0 (<i>n</i> =24)	12.7 (<i>n</i> =247)	0.32
Theophylline	1.35 (<i>n</i> =63)	0.92 (<i>n</i> =229)	0.003	13.1 (<i>n</i> =62)	12.4 (<i>n</i> =209)	0.3
Dexamethasone	1.29 (<i>n</i> =22)	1.02 (<i>n</i> =270)	0.399	11.7 (<i>n</i> =22)	12.7 (<i>n</i> =249)	0.69

Results are shown as median (*n*=sample size)

Urinary Ca/Cr and UPO₄/Cr ratios are in mmol/mmol

well as in older children [5, 23]. Our data differ from other studies [1, 2], including those of Karlen et al. [7] who found little or no correlation of UCa with PNA. However, this latter study was carried out in infants who did not receive PO₄ supplementation and as a result were likely to be hypercalciuric [8, 9].

We believe the decrease in UCa/Cr ratio with advancing PNA results from improved bone deposition of Ca [24, 25, 26]. The negative correlation could also be due to a decrease in urinary sodium excretion [27, 28], since Ca reabsorption in the proximal tubule (50%–55%) and loop of Henle (20%–30%) parallels sodium reabsorption [29]. The influence of PNA on urinary creatinine excretion is somewhat controversial. Al-dahhan et al. [30] and Coulthard et al. [31] found no relationship between urinary creatinine and PNA. However, others have reported that urinary creatinine excretion is positively correlated with PNA [28].

We used the type of nutrition as a proxy for Ca and PO₄ intake, and found no relationship between the type of milk ingested and UCa/Cr on univariate analysis. However, babies on breast milk had a significantly lower UCa/Cr ratio on multivariate analysis. These findings are similar to other reports in which no relationship was found between UCa/Cr and Ca intake [2, 22, 24, 32]. The likely explanation for this lack of correlation is that UCa in preterm infants originates mainly from bone turnover with a relatively small percentage (12%–27%) coming from oral intake [24]. Preterm infants fed unsupplemented breast milk tend to be hypercalciuric due to PO₄ deficiency [8, 9, 33] and our finding of a low UCa/Cr in infants given PO₄-supplemented EBM suggest improved bone deposition of Ca [9]. However, Schell-Feith et al. [6] found that a high Ca intake was associated with higher Ca excretion and an increased risk of NC. These authors also noted that the PO₄ intake was higher in the NC group, but found no difference in UPO₄ excretion, duration and volume of parenteral or enteral (breast or formula) nutrition between NC and non-NC infants. We found that infants with NC received smaller amount of Ca and PO₄ between 2 and 6 weeks of life compared with non-NC babies, and there was no difference in urinary excretion of Ca between the two groups. NC babies also received TPN for significantly longer [13]. Our finding of an increase in UCa/Cr in infants on TPN is in agreement with those of Vileisis [34] and Hoppe et al. [35]. Explanations for this finding include a relative PO₄ depletion [34], a higher sodium intake [35], and a lower protein intake [26] re-

sulting in hypercalciuria due to decreased utilisation of Ca for bone growth. Decreased bone mineralisation may result in metabolic bone disease of prematurity, abnormal growth, and fractures [36]. We did not measure direct bone mineral content in this study but the indirect measure of bone mineral content was within acceptable limits for preterm infants (Table 1). All our infants with a plasma alkaline phosphatase >500 U/l had a plasma PO₄>1.6 mmol/l, with the exception of 1 whose plasma PO₄ was 1.13 mmol/l. A recent study by Backstrom et al. [37] showed that a combination of plasma alkaline phosphatase activity above 900 IU/l and plasma PO₄ below 1.8 mmol/l yields a sensitivity of 100% and a specificity of 70% for detection of low bone mineral density in preterm infants.

Infants in this study with higher plasma Ca had a higher UCa/Cr ratio as expected, but we found no correlation between UCa/Cr and gestational age at birth, AGA/SGA, or gender. Hillman et al. [24] reported a similar lack of correlation between UCa and gestational age or birth weight, and a number of studies found no correlation between UCa and gender in children [1, 2, 3, 4, 5, 23], but there are no available comparative data in preterm infants. We did not analyse our data according to race, as our population was predominantly Caucasian. It has been shown however that UCa/Cr is lower in African-American [38] and Asian children [39] than Caucasian children due to differences in diet. However, any racial differences in UCa/Cr in preterm infants are unlikely as all infants receive similar nutrition according to their clinical state/need.

We found the UPO₄/Cr ratio remained stable from the 3rd week to the 18th week of PNA. These findings are similar to those of Mihatsch et al. [40] who reported that in infants sufficiently substituted with PO₄, although the plasma PO₄ decreased with increasing PNA, the urinary PO₄ excretion remained stable due to a progressive decrease in renal phosphate threshold. Karlen et al. [7] found that UPO₄ was high during the 1st postnatal week, decreased during the 2nd, remained low up to the 5th, increased from the 6th, and remained stable until at least 3 months of PNA. However, it is difficult to compare these data with our own as the study group of Karlen et al. [7] was not supplemented with PO₄, was more mature, and the data were given as a mean value and not as a percentile. In addition, a number of reports have documented low UPO₄ in PO₄-deficient infants [9, 34].

In the present study, the infants on TPN and of low gestational age (24–29 weeks) had lower UPO_4/Cr . This may be the result of a lower PO_4 intake and/or an increased mineral demand for growth [41]. We found no gender differences in UPO_4/Cr and no differences between infants who were AGA compared with those SGA. UPO_4/Cr did not vary with different milk intake, and we feel this resulted from our PO_4 supplementation policy.

Infants who received frusemide [16, 17] and theophylline [18, 19] had significantly higher UCa/Cr as previously reported. Infants on dexamethasone also had higher UCa/Cr , but this did not achieve statistical significance, in contrast to the data of Kamitsuka et al. [20], perhaps because of the relatively small numbers in this study. Frusemide, theophylline, and dexamethasone had no effect on the UPO_4/Cr ratio, but there are no comparative published data available.

In conclusion, we report reference ranges for UCa/Cr and UPO_4/Cr ratio in a population of preterm infants between 24 and 34 weeks' gestation. The UCa/Cr ratio is inversely related to PNA, whereas the UPO_4/Cr ratio remained stable between the 3rd to 18th weeks of PNA. Gender and SGA had no effect on either ratio. Infants on TPN had higher UCa/Cr and lower UPO_4/Cr ratios. Frusemide and theophylline increased UCa/Cr but not the UPO_4/Cr ratio.

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