Renal handling of phosphate in the first six months of life

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SUMMARY Indices of renal excretion and reabsorption of phosphate were studied in 20 neonatal infants, 20 infants aged 3 months, and 20 infants aged 6 months. All subjects were normal and were fed a modified formula enriched with vitamin D. In neonatal infants all indices of phosphate excretion were found to be significantly lower and those of phosphate reabsorption significantly higher than in older infants. Phosphate excretion gradually increased with age, while its reabsorption decreased. The positive correlation between serum phosphorus and renal threshold phosphate concentration (TmP/GFR) and the negative correlation between phosphorus excretion index and TmP/GFR found in this study shows that in young infants as in adults TmP/GFR is the principal determinant of renal phosphate homeostasis. Among the many indices of renal phosphate handling in use TmP/GFR is the best for studies of phosphorus or calcium metabolism disorders, or both, especially in the first three months of life.

The serum concentration of phosphate is much higher in neonates and infants than in older children or adults. The reason for this phenomenon remains obscure, although a relation between red cell 2,3 DPG, adenosine triphosphate, blood haemoglobin concentration, and serum phosphorus concentration has been previously reported. The mechanisms involved in maintaining a high serum phosphorus concentration in neonates and infants are numerous. The main food of this age is milk, which contains high quantities of freely absorbable phosphorus. Moreover, during the postneonatal period various hormonal and non-hormonal factors act on bones and kidneys, influencing the metabolism of phosphorus.

Excretion of phosphate in the urine represents the final result of all these interactions and therefore can be used as an index of phosphate metabolism. Reports have been made on phosphorus excretion index in Bantu infants older than 4 months, urinary phosphate excretion in normal children older than one year, and renal threshold phosphate concentration (TmP/GFR) in children older than 6 years. These studies emphasised that proper interpretation of all indices of phosphorus excretion firstly required definition of age specific normal ranges, a condition that applies also for indices of phosphate reabsorption. The neonatal period and the first six months of life have their own specific metabolic characteristics, which for phosphate metabolism is primarily the high dietary intake of phosphorus. For this reason and also because of the unavailability of normal ranges for the renal handling of phosphate in this age group in the published reports we undertook the present study. Our results define the indices of urinary phosphate excretion and reabsorption in normal neonates and infants 3 and 6 months old.

Subjects and methods

Three groups of subjects were studied. The first group consisted of 20 neonatal infants of both sexes aged 2–4 weeks. The second and third groups each consisted of 20 infants of both sexes and aged 3±0.5 and 6±0.5 months old, respectively. All infants were admitted to hospital for reasons unrelated to endocrine disorders or abnormalities of calcium and phosphorus metabolism, mainly for elective surgical procedures or clinical observation. All infants were bottle fed a modified formula enriched with vitamin D₃. Their gestational age was 38–41 weeks and their body weight, height, and head circumference were within the normal range.

During the day of study all infants had no diarrhoea, vomiting, or fever. Before collection of
urine and blood specimens neonates were fasted for three hours and older infants for six to nine hours. During this period water was offered freely. At 0700 h a plastic urine collection bag was attached, which was removed after two to three hours. During this period venous blood was obtained for investigations related to the reasons of admission and for the aims of this study.

Serum (S) and urine (U) calcium (C), phosphorus (P), and creatinine (Cr) concentrations and alkaline phosphatase activity were measured with methods described previously. Standard equations were utilised for calculation of the following indices of renal phosphate handling:

 Unary phosphate to creatinine ratio: UP/UCr.
 Fractional phosphate clearance: CP/CCR.
 Fractional phosphate excretion: UPxCCR/UCr.
 Phosphorus excretion index: CP/UCr - 0-055 SP (mg/dl) + 0.007.

Fractional tubular reabsorption of phosphate (TRP = 1 - CP/CCR) and transport maximum of phosphate in relation to glomerular filtration rate (renal threshold phosphate concentration, TmP/GFR mmol/l). 

Statistical analysis was performed by the unpaired two tailed t test using the General Statistics Pac of Hewlett-Packard 85.

Results

The mean values, standard deviations, range, and statistical data of all variables for the three groups are presented in the Table. Serum calcium concentrations and serum alkaline phosphatase activities were within the normal range, and there were no significant differences between the three groups. As expected, serum phosphorus was high and its mean concentration was almost identical in neonates and 3 month old infants. There was a slight, though not significant, decrease at the age of 6 months.

There was no difference in the UP/UCr ratio for neonates and 3 month old infants, but there was a significant increase at the age of 6 months, while there was no notable change in serum phosphorus concentrations. A significant correlation was found between serum phosphorus and UP/UCr when values of all infants were considered (r= 0.23, p<0.05). The CP/CCR ratio was increased significantly at the age of 3 months and was almost identical at 6 months.

Fractional excretion of phosphorus was similar in the three groups. Mean values of the phosphorus excretion index were also comparable in neonates and 3 month old infants, whereas the value was significantly higher at 6 months. In general, the phosphorus excretion index was lower in all groups than the normal range for adults. There were, however, three neonates, four infants aged 3 months, and 10 infants aged 6 months whose index fell within the normal adult range (Fig. 1).

Tubular reabsorption of phosphate was significantly lower after the age of 3 months, while TmP/GFR was similar in neonates and infants aged 3 months. Thereafter, renal phosphate threshold

Table

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum</th>
<th>Phosphorus excretion</th>
<th>Phosphorus reabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium (mmol/l)</td>
<td>Phosphorus (mmol/l)</td>
<td>Alkaline phosphatase (IU/l)</td>
</tr>
<tr>
<td>Neonates:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.41</td>
<td>2.14</td>
<td>109</td>
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<tr>
<td>Mean</td>
<td>0.18</td>
<td>0.45</td>
<td>38</td>
</tr>
<tr>
<td>Range</td>
<td>2.04-2.72</td>
<td>1.48-3.19</td>
<td>77-170</td>
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<tr>
<td>Infants aged 3 months:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.38</td>
<td>2.09</td>
<td>119</td>
</tr>
<tr>
<td>Mean</td>
<td>0.12</td>
<td>0.26</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td>2.02-2.49</td>
<td>1.42-2.42</td>
<td>75-180</td>
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<tr>
<td>Infants aged 6 months:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.37</td>
<td>1.96</td>
<td>115</td>
</tr>
<tr>
<td>Mean</td>
<td>0.13</td>
<td>0.27</td>
<td>22</td>
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<tr>
<td>Range</td>
<td>2.12-2.59</td>
<td>1.55-2.51</td>
<td>69-147</td>
</tr>
</tbody>
</table>

Conversion: SI to traditional units—Calcium: 1 mmol/l = 4 mg/100 ml. Phosphorus: 1 mmol/l = 3.1 mg/100 ml.

UP/UCr= urinary phosphate to creatinine ratio; CP/CCR= fractional phosphate clearance; PE/GMR= phosphorus excretion in relation to glomerular filtration rate; TRP= fractional tubular reabsorption of phosphate; TmP/GFR= transport maximum of phosphate in relation to glomerular filtration rate.

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Mean -0.2 -0.16 0.10
SD 0.1 0.07 0.08

Fig. 1 Phosphorus excretion index in the three groups of infants. Hatched area=normal adult range. Three neonates, four infants of 3 months, and 10 infants of 6 months had index values within the normal adult range.

Fig. 2 Values of transport maximum of phosphate in relation to renal threshold phosphate concentration (TmP/GFR) in the three groups of infants. Hatched area=normal adult range. All values for newborns and infants of 3 months were found to be higher than normal range for adults. Only three infants of 6 months had values of TmP/GFR within the normal adult range.

decreased significantly but remained considerably higher than in normal adults in all infants aged 3 months and in all but three of the infants aged 6 months (Fig. 2). When the data for all 60 infants studied were considered we observed a highly significant negative correlation ($r=-0.86$, $p<0.0001$) between TmP/GFR and phosphorus excretion index (Fig. 3) and a significant positive correlation ($r=0.52$, $p<0.0001$) between serum phosphorus concentration and TmP/GFR (Fig. 4).

Fig. 3 Correlation (positive) between serum phosphorus and transport maximum of phosphate in relation to renal threshold phosphate concentration (TmP/GFR), showing that the setting of serum phosphate concentration is a function of reabsorption.

Fig. 4 Correlation (negative) between phosphorus excretion index and transport maximum of phosphate in relation to renal threshold phosphate concentration (TmP/GFR), meaning that phosphorus excretion is a function of reabsorption.
Discussion

Although the clinical value and importance of phosphate clearance studies is somewhat unclear, particularly with modern techniques for measuring parathyroid hormone in the blood etc, there are conditions early in life (such as vitamin D resistant rickets, neonatal hypocalcaemia, idiopathic hypoparathyroidism, and primary hyperparathyroidism) in which they could be useful and easily performed. Reference data could therefore be of value in an age range for which they were not previously available.

In this study we examined the urinary excretion and reabsorption of phosphate in normal neonatal infants and infants aged 3 and 6 months. In all infants serum calcium and phosphorus concentrations and alkaline phosphatase activities were normal when adjusted for age, and there were no significant differences in these variables between the three groups. These findings confirm our clinical impression that all infants included in this study had no disorders related to calcium or phosphorus metabolism. Other investigators have used considerably longer overnight fasting periods before sample collection.4 5 In our study we considered such a practice inadvisable, especially as our subjects included very young infants and neonates.

We wish to emphasise, therefore, that our results cannot be compared with those previously reported for older children and adults who were fasted considerably longer before study. Nevertheless, we believe that our findings are particularly useful for comparisons with data obtained under the same fasting conditions, which we believe are both ethical and convenient for young babies.

The mean UP/UCr ratio, which is simple to measure, was found to be high, especially at the age of 6 months, ranging from 3.5 to 11.3, with the exception of a single value of 1.53. This ratio was similar in 3 month old infants and neonates, the value for neonates being significantly lower than in 6 month olds. This finding emphasises the need for an age specific range for these variables even in the first months of life. Previous studies have indicated that a positive correlation exists between UP/UCr and serum phosphorus concentration in adults2 and children.4 We have observed, however, that while serum phosphorus concentrations remained stable and high the UP/UCr ratio increased significantly with age. The same is true for the CP/CCr ratio and the phosphorus excretion index, whereas TmP/GFR significantly decreases with age.

It is obvious that all these variables behave differently in adults and children,2 4-6 which could be at least partially due to the effects of human growth hormone.4 8

Previous studies have shown that phosphorus excretion index is low in children, and Taitz and deLacy have reported a range between −0.22 and +0.04 in eight normal children older than 4 months.3 Our findings are in agreement with this range, although lower values than −0.22 were also observed (−0.32 to +0.05). It should also be emphasised that two neonatal infants, three infants aged 3 months, and eight infants aged 6 months had index values within the adult range. Low phosphorus excretion index values have been reported in children older than 1.5 years,4 although some of them fell within the adult range. High milk intake has been proposed as the reason for high phosphorus excretion index values.4 This interpretation, however, does not explain the variability with infant age of this variable observed in our study population, which was fed exclusively with milk. Although the role of dietary phosphorus seems to be minimal in its renal handling,10 it would be of interest to be shown that phosphate indices were in no way different in babies breast fed or fed unmodified cow’s milk.

The maximum tubular reabsorption of phosphate in relation to GFR (renal phosphate threshold—TmP/GFR) is considered to be the index of choice for evaluation to the renal handling of phosphate.6 In all our infants except two (both in the 6 month age group) TmP/GFR was found to be higher than that reported in adults and older children. We failed to observe differences between 1 and 3 month old infants and the range was almost the same (Table 1). On the other hand, mean values and the range of TmP/GFR were significantly lower at 6 months.

The significant correlation (r=0.52, p<0.0001) between serum phosphorus concentration and TmP/GFR (Fig. 3) in neonates and 6 month old infants shows, as in older children2 and adults,4 that the setting of plasma phosphate concentration is a function of renal phosphate reabsorption.

Furthermore, the highly significant negative correlation (r=0.86, p<0.0001) between TmP/GFR and phosphorus excretion index (Fig. 4) indicates that as phosphorus reabsorption increases excretion decreases—that is, that renal phosphate excretion is also a function of reabsorption. TmP/GFR therefore expresses the fundamental function and gives direct information about phosphate homeostasis in fasting and non-fasting states.9

In conclusion, for evaluation of infants suspected of phosphorus or calcium metabolism disorders, or both, TmP/GFR should preferably be estimated among all available indices of renal phosphate excretion. The present study provides data on the normal range in neonates and children younger than
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6 months of TmP/GFR and other variables of renal handling of phosphate.

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