Renal threshold phosphate concentration (TmPO₄/GFR)

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SUMMARY The ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO₄/GFR) was determined in 546 schoolchildren, aged between 6 and 17.9 years, using the nomogram of Walton and Bijvoet. TmPO₄/GFR correlated with chronological age in girls and boys and in each remained significantly higher than in adults. TmPO₄/GFR in the children correlated neither with fasting serum immunoreactive calcitonin and parathyroid hormone levels nor with the urinary cyclic AMP excretion. The study showed a parallel decrease in TmPO₄/GFR, excretion of total hydroxyproline and serum alkaline phosphatase activities after puberty, with a significant relationship of both these indices of bone turnover to TmPO₄/GFR values. This indicates that the high renal phosphate threshold of children may be an important factor for bone mineralisation by providing high extracellular inorganic phosphate concentrations during normal growth.

It is known that fasting serum PO₄ concentrations are high in children, and fall to adult values after puberty. Serum PO₄ levels are determined mainly by renal tubular PO₄ reabsorption, which shows a transport maximum (TmPO₄) above which all filtered PO₄ is excreted. TmPO₄ has been found to be proportional to the glomerular filtration rate and the measurement of the ratio TmPO₄/GFR is preferred to other indices of the renal handling of PO₄. According to Walton and Bijvoet an approximation of TmPO₄/GFR can be obtained without phosphate infusions.

Studies on a few children have shown that TmPO₄/GFR is increased in them. Thus interpretation of TmPO₄/GFR in childhood requires a separate age specific normal range, which has not been established in a large study until now. In this study we have determined mean and range of TmPO₄/GFR at different ages in healthy schoolchildren using the nomogram of Walton and Bijvoet.

Subjects and methods

The study was performed at an elementary school in Kiel and comprised 564 healthy children (291 girls and 273 boys) aged between 6 and 17.9 years. Written informed consent was given by the parents.

After an overnight fast of at least 10 hours the bladder was emptied at 0700 hours and the urine flushed away. At about 0900 hours urine samples were collected by voluntary voiding.

At the same time venous blood samples were obtained with minimum stasis, and serum was separated within an hour. PO₄ and Cr concentrations were measured in serum and urine samples of all the children on the day of collection.

Serum and urine samples from 120 of these children, 60 girls and 60 boys, were stored at −20°C until analysed in duplicate for AP, iPTH, and CT in serum and for cAMP and total OH-P in urine. These children were divided into 2-yearly age groups.

Abbreviations:

PO₄: inorganic phosphate
TmPO₄: transport maximum of inorganic phosphate
GFR: glomerular filtration rate
Cr: creatinine
AP: alkaline phosphatase
iPTH: immunoreactive parathyroid hormone
CT: calcitonin
cAMP: cyclic adenosine-3',5'-monophosphate
OH-P: hydroxyproline
from 6 to 17.9 years, 10 girls and 10 boys being included in each group. PO₄ was determined by the method of Fiske and Subbarow using the test kit from Harleco (Merz and Dade, Munich, FRG), Cr with the Beckman autoanalyser, AP photometrically. iPTH was measured by radioimmunoassay according to the method of Hehrmann et al. using a pre-"pominate carboxy-regional antibody (Sa78), which can discriminate between hyperparathyroid patients and normal ones (normal range: <0.850 pmol/l), the intra- and interassay variance being 12.4 and 18.2% respectively. Serum CT was assayed by radioimmunoassay using the test kit of Byk-Mallingrodt (Dietzenbach, FRG). The method is sensitive to about 40 pg/ml, the intra- and interassay variance being below 10% (normal range: 40-500 pg/ml). Urinary cAMP was measured by competitive protein binding. The intra- and interassay variance was 3.6 and 8.7% respectively. Urinary OH-P was assayed using the Hypronosticon kit (Organon Teknika, Munich, FRG), the within-assay coefficient of variation being 2.9% and the interassay variance being 13.2%.

The GFR was estimated as being equal to Cr clearance.

The urinary excretion of PO₄ was expressed as:
1. the fractional PO₄ excretion (CPO₄/Cr) according to Cr clearance (C), calculated as urine PO₄ concentration × serum Cr concentration/urine Cr concentration × serum PO₄ concentration, the units of measurement for the concentrations being mg/100 ml or mmol/l.
2. the urinary PO₄/Cr ratio in μg/mg, and
3. urinary PO₄ as a function of GFR. This was calculated by multiplying the urinary PO₄/Cr ratio in μg/mg with the corresponding serum Cr in mg/100 ml, to give a value in μg/100 ml GF.

The fractional tubular reabsorption of PO₄ (TRP) was calculated as the complement of CPO₄/Cr:

$$100 \times (1 - \frac{C_{PO_4}}{C_{Cr}})$$

The tubular maximum rate of PO₄ reabsorption in relation to GFR (TmPO₄/GFR) was calculated from a nomogram of Walton and Bijvoet using the slide-rule method they recommended. The method is based on data of Bijvoet and Morgan which showed a constant relationship between TRP and the ratio of TmPO₄/GFR and plasma PO₄.

The urinary cAMP excretion was expressed in relation to GFR (nmol/100 ml GF) by multiplying the values obtained relative to urinary Cr with the corresponding serum Cr. Urinary OH-P was expressed as OH-P/Cr (mg/mg).

TmPO₄/GFR, cAMP/GFR, AP, and OH-P/Cr were also determined in 24 healthy adults, 12 women and 12 men, aged between 20 and 40 years (physicians or laboratory staff).

Table 1: Renal threshold phosphate concentration (TmPO₄/GFR), serum phosphate, and other indices of renal handling of phosphate at different ages

<table>
<thead>
<tr>
<th>Index</th>
<th>Age (years)</th>
<th>Girls</th>
<th>Boys</th>
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<tr>
<td>TmPO₄/GFR (mg/100 ml GF)</td>
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<td>TRP (%)</td>
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Renal threshold phosphate concentration (TmPO₄/GFR)

Table 1—continued

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CPO₄/CCr × 100</th>
<th>UPO₄/GFR (µg/100 ml GFr)</th>
<th>UPO₄/Cr (µg/mg)</th>
<th>SPO₄ (mg/100 ml)</th>
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<tr>
<td></td>
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<td><strong>Girls</strong></td>
<td><strong>Boys</strong></td>
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<td>12</td>
<td>10-5</td>
<td>11-1</td>
<td>4-30</td>
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</tbody>
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- **UPO₄/GFR (µg/100 ml GFr)**
  - 6-6.9: 437-447 (240-871)
  - 7-7.9: 240-257
  - 8-8.9: 316-316
  - 9-9.9: 316-316
  - 10-10.9: 316-316
  - 11-11.9: 282-282
  - 12-12.9: 267-275
  - 14-14.9: 224-224
  - 15-15.9: 398-398
  - 16-16.9: 407-380
  - 17-17.9: 124-375

- **UPO₄/Cr (µg/mg)**
  - 6-6.9: 832
  - 7-7.9: 437-468
  - 8-8.9: 562-562
  - 9-9.9: 525-525
  - 10-10.9: 513-513
  - 11-11.9: 468-447
  - 12-12.9: 389-389
  - 13-13.9: 389-389
  - 14-14.9: 398-355
  - 16-16.9: 437-468
  - 17-17.9: 513-490
  - 20-40: 437-398

- **SPO₄ (mg/100 ml)**
  - 6-6.9: 5.49
  - 7-7.9: 5.25
  - 8-8.9: 5.25
  - 9-9.9: 5.25
  - 10-10.9: 5.25
  - 11-11.9: 5.02
  - 12-12.9: 4.81
  - 13-13.9: 4.81
  - 14-14.9: 4.42
  - 15-15.9: 4.03
  - 16-16.9: 3.90
  - 17-17.9: 3.81
  - 20-40: 3.50

**Results**

Mean and median values, regression equations, and correlation coefficients were calculated by standard methods using a Dec 11/60 computer.

**Statistical analysis**

Table 1 gives the means and SDs as well as the median and ranges for each sex and age group for TmPO₄/GFR, TRP, PO₄/Cr-clearances, and urinary...
PO₄ excretion in relation to GFR and Cr, and the serum PO₄ concentrations.

TRP remained high until age 15 years in girls and until 14 years in boys; thereafter it decreased steadily to adult levels. The fractional PO₄ excretion (CPO₄/Ccr) as well as PO₄/GFR increased at an inverse ratio to TRP.

The PO₄/Cr ratio fluctuated until age 11 years, declined to low values after age 12 years, and increased again after age 15-16 years in both sexes without reaching the ratios found in children aged 6-11 years.

TmPO₄/GFR and serum PO₄ declined with age in girls and boys. Fig. 1 shows the distribution of the individual values of TmPO₄/GFR in girls (n=291) and boys (n=273) according to their ages.

**Girls**
The PO₄ reabsorption decreased slightly from 6-0 to 13-9 years and decreased further thereafter but had not reached normal adult levels at age 17 years (Table 1). The relationship between TmPO₄/GFR levels and age (6-0-17-9 years) had a negative correlation coefficient of r = -0.64 (P<0.001).

**Boys**
TmPO₄/GFR remained fairly constant until age 10-9 years. At between ages 11 and 11-9 years there was first a decrease and then a steady rise until age 13-9 years. Thereafter the values again declined until age 17-9 years, remaining still significantly higher (P<0.01) than the adult levels (Table 1). As in the girls a negative correlation was found between age (6-17-9 years) and TmPO₄/GFR (r = -0.46, P<0.001).

Serum AP rose until age 11-9 years in girls and until 13-9 years in boys and declined after age 13-9 and 15-9 years in girls and boys, respectively (Fig. 2). Urinary OH-P/Cr remained fairly constant.

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![Fig. 1](Fig. 1 Individual values of TmPO₄/GFR in relation to age in 291 girls and 273 boys. The normal range for adults, determined by Walton and Bijvoet, is also shown.)
Renal threshold phosphate concentration (TmPO₄/GFR)

Females

Alkaline phosphatase

OH-P/creatinine

TmPO₄/glomerular filtration rate

Males

Alkaline phosphatase

OH-P/creatinine

TmPO₄/glomerular filtration rate

Fig. 2  Fasting serum alkaline phosphatase activities, urinary total hydroxyproline excretion (OH-P/Cr), and TmPO₄/GFR in girls and boys in relation to age. In the children mean ± SD levels of alkaline phosphatase and OH-P/Cr were determined every 2 years (n=10), whereas mean ± SD values of TmPO₄/GFR were calculated yearly (n=9-36, Table 2). For comparison the mean ± SD levels of 12 women and 12 men aged 20-40 years are also shown.

Table 2  Relationship between TmPO₄/GFR and iPTH, CT, AP, cAMP/GFR, and OH-P/Cr in 120 schoolchildren, aged 6-17·9 years

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
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<tbody>
<tr>
<td>iPTH</td>
<td>0·15</td>
<td>NS</td>
</tr>
<tr>
<td>CT</td>
<td>0·12</td>
<td>NS</td>
</tr>
<tr>
<td>AP</td>
<td>0·27</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>OH-P/Cr</td>
<td>0·46</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>cAMP/GFR</td>
<td>-0·17</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant (P>0·05).

Discussion

Many factors are known to influence the renal handling of PO₄ by increasing (for example growth hormone and vitamin D metabolites) or decreasing (for example PTH, CT, and oestrogens) TmPO₄/GFR.
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Fig. 3 Relationship between TmPO₄/GFR and fasting urinary total hydroxyproline excretion (OH-P/Cr) in 60 girls and 60 boys aged 6 to 17-9 years.

Fig. 4 Relationship between TmPO₄/GFR and serum alkaline phosphatase activities (AP) in 60 girls and 60 boys aged 6 to 17-9 years.

This study shows that TmPO₄/GFR values are significantly higher in girls and boys aged between 6 and 17.9 years than in adults. Furthermore an age dependency and sex-difference was found in these children.

Despite the fact that the renal PO₄ threshold was not measured directly the levels were similar to those found by phosphate infusions exhibiting TmPO₄/GFR values of 4.97±0.61 mg/100 ml (mean±SD) in 15 children aged between 5 and 14 years. In our study the age-related variation of TmPO₄/GFR in schoolchildren did not correlate with serum CT, iPTH, or urinary cAMP/GFR levels, so no major influence of CT and PTH secretion or PTH-induced renal cAMP formation was shown on the increased renal tubular reabsorptive activity during childhood. On the other hand, we found there was a relationship between TmPO₄/GFR and urinary OH-P excretion—reflecting bone resorption—and serum AP activity—reflecting bone turnover, particularly bone formation. This indicates that the high renal PO₄ threshold may be an important factor for normal growth and it may provide high extracellular PO₄ for mineralisation of growing cartilage and bone. Accordingly TmPO₄/GFR, AP, and OH-P/Cr decreased in parallel in girls and boys (Fig. 2) during the age of rapidly declining height velocity.

Growth hormone secretion, sexual maturation, and intrinsic differences in the renal tubules may influence the changing renal PO₄ threshold before, during, and after puberty. Such age-related differences in the renal handling of PO₄ should be taken into account when TmPO₄/GFR is estimated in childhood.

We thank Professor P Heintzen, Department of Paediatric Cardiology and Bioengineering, University of Kiel, for permission to use the Dec 11/60 computer unit, and Dr D Onnasch and Dr K Moldenhauer for help with the statistical analysis.

This study was supported by Deutsche Forschungsgemeinschaft Kr 702/1.

References


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