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Renal threshold phosphate concentration ($TmPO_4/GFR$)

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SUMMARY The ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate ($TmPO_4/GFR$) was determined in 546 schoolchildren, aged between 6 and 17·9 years, using the nomogram of Walton and Bijvoet.[1] $TmPO_4/GFR$ correlated with chronological age in girls and boys and in each remained significantly higher than in adults. $TmPO_4/GFR$ 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 $TmPO_4/GFR$, excretion of total hydroxyproline and serum alkaline phosphatase activities after puberty, with a significant relationship of both these indices of bone turnover to $TmPO_4/GFR$ 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 PO_4 concentrations are high in children, and fall to adult values after puberty.[2-4] Serum PO_4 levels are determined mainly by renal tubular PO_4 reabsorption, which shows a transport maximum ($TmPO_4$) above which all filtered PO_4 is excreted.[5] $TmPO_4$ has been found to be proportional to the glomerular filtration rate and the measurement of the ratio $TmPO_4/GFR$ is preferred to other indices of the renal handling of PO_4.[5] According to Walton and Bijvoet[1] an approximation of $TmPO_4/GFR$ can be obtained without phosphate infusions.

Studies on a few children have shown that $TmPO_4/GFR$ is increased in them.[6-7] Thus interpretation of $TmPO_4/GFR$ 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 $TmPO_4/GFR$ at different ages in healthy schoolchildren using the nomogram of Walton and Bijvoet.[1]

Subjects and methods

The tudy 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. PO_4 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:

PO_4:	inorganic phosphate
$TmPO_4$:	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. PO_4 was determined by the method of Fiske and Subbarow[8] using the test kit from Harleco (Merz and Dade, Munich, FRG), Cr with the Beckman autoanalyser, AP photometrically.[9] iPTH was measured by radioimmunoassay according to the method of Hehrmann *et al.*[10] using a predominantly carboxy-regional antibody (S_{478}), which can discriminate between hyperparathyroid patients and normal ones (normal range: <0·8–5·0 pmol/l), the intra- and interassay variance being 12·4 and 18·2% respectively. Serum CT was assayed by radio-immunoassay[11] 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.[12] 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 PO_4 was expressed as:

(1) the fractional PO_4 excretion (C_{PO_4}/C_{Cr}) according to Cr clearance (C) rate, calculated as urine PO_4 concentration × serum Cr concentration/urine Cr concentration × serum PO_4 concentration, the units of measurement for the concentrations being mg/100 ml or mmol/l.

(2) the urinary PO_4/Cr ratio in μg/mg, and

(3) urinary PO_4 as a function of GFR. This was calculated by multiplying the urinary PO_4/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 PO_4 (TRP) was calculated as the complement of C_{PO_4}/C_{Cr}

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

The tubular maximum rate of PO_4 reabsorption in relation to GFR ($TmPO_4$/GFR) was calculated from a nomogram of Walton and Bijvoet[1] using the slide-rule method they recommended.[13] The method is based on data of Bijvoet and Morgan[14] which showed a constant relationship between TRP and the ratio of $TmPO_4$/GFR and plasma PO_4.

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).

$TmPO_4$/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 ($TmPO_4$/GFR), serum phosphate, and other indices of renal handling of phosphate at different ages*

Index	*Age (years)*	*Girls*					*Boys*				
		n	*Median*	*Mean*	*SD*	*Range*	*n*	*Median*	*Mean*	*SD*	*Range*
$TmPO_4$/GFR (mg/100 ml GF)	6– 6·9	9	6·00	5·71	0·85	4·50–6·90	15	6·40	6·25	0·89	4·80–8·00
	7– 7·9	27	6·50	6·40	0·83	4·70–8·00	33	5·80	5·85	0·74	4·50–7·00
	8– 8·9	29	6·00	6·02	0·81	4·30–7·70	25	5·80	5·97	0·66	4·90–7·10
	9– 9·9	29	6·10	6·07	0·83	4·70–7·40	20	6·15	5·96	0·94	4·20–7·80
	10–10·9	19	5·70	5·84	0·94	4·40–7·70	27	6·10	5·89	0·96	4·07–7·50
	11–11·9	27	5·70	5·71	1·08	3·94–8·20	31	5·25	5·21	0·72	3·88–6·60
	12–12·9	28	5·67	5·50	0·88	3·42–7·30	36	5·51	5·47	0·80	3·70–6·92
	13–13·9	31	5·58	5·50	0·88	3·30–7·25	29	5·85	5·89	0·78	4·27–7·47
	14–14·9	26	4·60	4·61	0·69	3·41–6·25	19	5·40	5·39	0·94	2·58–7·05
	15–15·9	22	4·45	4·59	0·83	3·25–6·41	10	4·70	4·69	0·72	3·60–5·90
	16–16·9	33	3·45	4·07	0·66	2·48–5·10	15	4·23	4·37	0·66	3·47–5·88
	17–17·9	11	4·17	3·99	0·51	3·18–4·57	13	4·13	4·27	0·66	3·33–5·90
	20–40	12	3·87	3·55	0·66	2·58–4·85	12	3·54	3·21	0·78	2·05–4·28
TRP (%)	6– 6·9	9	92·4	91·2	3·86	83·9–95·8	15	94·5	94·1	2·68	86·8–98·1
	7– 7·9	27	95·5	94·7	2·68	89·0–98·1	33	93·8	93·4	1·86	88·3–98·1
	8– 8·9	29	93·4	93·5	2·26	85·7–97·5	25	93·6	93·8	2·01	90·7–98·4
	9– 9·9	29	94·2	93·6	2·69	83·5–97·2	20	94·0	94·1	2·64	88·5–98·1
	10–10·9	19	94·7	93·4	2·66	88·7–97·9	27	94·4	93·4	3·78	82·1–99·3
	11–11·9	27	92·9	92·8	4·46	79·9–97·9	31	93·4	92·4	2·96	85·9–96·7
	12–12·9	28	93·7	93·2	4·67	76·2–97·7	36	94·9	93·1	4·89	79·6–98·6
	13–13·9	31	94·6	93·1	4·46	81·1–98·5	29	95·4	94·7	2·41	88·1–98·7
	14–14·9	26	92·9	93·0	3·01	86·8–98·3	19	94·0	92·6	4·29	80·2–98·4
	15–15·9	22	93·2	92·1	3·17	85·7–97·5	10	90·6	91·4	2·94	88·2–95·7
	16–16·9	33	91·0	89·8	3·60	82·3–95·8	15	90·5	90·0	3·75	83·8–96·4
	17–17·9	11	90·5	89·9	3·50	82·7–95·3	13	89·3	90·5	3·10	85·8–94·8
	20–40	12	89·5	89·9	4·30	80·7–96·1	12	89·3	87·8	5·00	81·3–95·5

Table 1—*continued*

Index	*Age (years)*	*Girls*					*Boys*				
		n	*Median*	*Mean*	*SD*	*Range*	*n*	*Median*	*Mean*	*SD*	*Range*
$C_{PO_4}/CCr \times 100$	6– 6·9	9	7·6	8·8	3·86	4·2–16·1	15	6·5	5·9	2·68	1·9–13·2
	7– 7·9	27	4·5	5·3	2·68	1·9–11·0	33	6·2	6·6	1·86	1·9–11·7
	8– 8·9	29	6·6	6·5	2·26	2·5–14·3	25	6·4	6·2	2·01	1·6– 9·3
	9– 9·9	29	5·8	6·4	2·69	2·8–16·5	20	6·0	5·9	2·64	1·9–11·5
	10–10·9	19	5·3	6·6	2·66	2·1–11·3	27	5·6	6·6	3·78	0·07–17·9
	11–11·9	27	7·1	7·2	4·46	2·1–20·1	31	6·6	7·6	2·96	3·3–14·1
	12–12·9	28	6·3	6·8	4·67	2·3–23·8	36	5·1	6·9	4·89	1·4–20·4
	13–13·9	31	5·4	6·9	4·46	1·5–18·9	29	4·6	5·3	2·41	1·5–18·9
	14–14·9	26	7·1	7·0	3·01	1·7–13·2	19	6·0	7·4	4·29	1·6–19·8
	15–15·9	22	6·8	7·9	3·17	2·5–14·3	10	9·4	8·6	2·94	4·3–11·8
	16–16·9	33	9·0	10·2	3·60	4·2–17·7	15	9·5	10·0	3·75	3·6–16·2
	17–17·9	11	9·5	10·1	3·50	4·7–17·3	13	10·7	9·5	3·10	5·2–14·2
	20–40	12	10·5	11·1	4·30	3·9–19·3	12	10·7	12·2	5·00	4·5–18·7
UPO_4/GFR (µg/100 ml GF)	6– 6·9	9	437	447		240– 871	15	295	288		110– 710
	7– 7·9	27	240	257		95–776	33	347	339		214– 617
	8– 8·9	29	331	324		145– 708	25	339	302		81– 617
	9– 9·9	29	316	316		141– 912	20	288	275		107– 603
	10–10·9	19	309	309		117– 550	27	331	316		98– 871
	11–11·9	27	316	309		112–1096	31	309	324		102– 708
	12–12·9	28	282	269		135–1072	36	245	282		65–1096
	13–13·9	31	263	275		62– 832	29	257	234		65– 724
	14–14·9	26	295	251		66– 513	19	324	324		65–1000
	15–15·9	22	324	309		91– 562	10	437	355		209– 575
	16–16·9	33	398	389		174– 851	15	372	389		155– 759
	17–17·9	11	407	380		178– 661	13	513	363		186– 550
	20–40	12	347	275		129– 646	12	457	398		158– 708
UPO_4/Cr (µg/mg)	6– 6·9	9	832	832		479–1820	15	575	562		219–1288
	7– 7·9	27	437	468		126–1698	33	617	603		363–1072
	8– 8·9	29	562	562		257–1175	25	603	562		162–1000
	9– 9·9	29	525	525		234–1820	20	447	468		174– 871
	10–10·9	19	525	513		182– 871	27	575	490		170–1230
	11–11·9	27	468	447		148–1446	31	468	479		162– 977
	12–12·9	28	389	389		105–1698	36	398	398		112–1738
	13–13·9	31	389	380		87–1148	29	398	324		85–1072
	14–14·9	26	398	355		89–1380	19	363	407		93–1148
	15–15·9	22	417	380		120– 646	10	398	398		234– 661
	16–16·9	33	437	468		234– 955	15	363	417		134– 851
	17–17·9	11	513	490		234– 813	13	457	407		209– 603
	20–40	12	437	398		151– 776	12	417	398		145– 759
SPO_4 (mg/100 ml)	6– 6·9	9	5·49	5·46	0·30	4·87–5·80	15	5·30	5·41	0·47	4·59–6·17
	7– 7·9	27	5·21	5·37	0·58	4·15–6·45	33	5·21	5·25	0·49	4·37–6·17
	8– 8·9	29	5·24	5·37	0·53	4·31–6·51	25	5·30	5·26	0·43	4·28–5·98
	9– 9·9	29	5·21	5·36	0·58	4·37–6·60	20	5·15	5·12	0·49	4·46–5·92
	10–10·9	19	5·12	5·15	0·47	4·28–6·11	27	5·12	5·27	0·57	4·03–6·57
	11–11·9	27	5·02	5·05	0·49	4·37–6·63	31	4·84	4·81	0·55	3·41–6·17
	12–12·9	28	4·81	4·81	0·49	4·03–6·29	36	4·76	4·82	0·45	4·06–5·86
	13–13·9	31	4·77	4·83	0·53	3·60–6·05	29	5·02	4·94	0·53	3·88–6·32
	14–14·9	26	4·21	4·20	0·43	3·38–5·12	19	5·02	4·95	0·50	3·97–5·80
	15–15·9	22	4·03	4·27	0·59	3·57–5·86	10	4·30	4·49	0·54	3·94–5·61
	16–16·9	33	4·09	4·07	0·52	2·98–4·96	15	4·50	4·25	0·59	3·01–5·12
	17–17·9	11	3·81	3·99	0·42	3·47–4·93	13	4·15	4·20	0·50	3·53–5·33
	20–40	12	3·50	3·61	0·51	2·85–4·40	12	3·53	3·30	0·69	2·33–4·19

GFR = glomerular filtration rate; GF = glomerular filtration; TRP = fractional tubular reabsorption of phosphate; PO_4 = inorganic phosphate; C_{PO4} = clearance of phosphate; C_{Cr} = clearance of creatinine; UPO_4 = urinary excretion of phosphate; UPO_4/Cr = urinary excretion of phosphate in relation to creatinine; SPO_4 = serum phosphate.

*The values of UPO_4/GFR and UPO_4/Cr approximately follow log-normal distributions.

Conversion: traditional to SI units: $TmPO_4/GFR$ and SPO_4: 3·1 mg/100 ml ≈ 1 mmol/l; UPO_4/GFR: 1 µg/100 ml ≈ 0·32 µmol/l GF; UPO_4/Cr: 1 µg/mg ≈ 3·65 µmol/mmol.

Statistical analysis

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

Results

Table 1 gives the mean and SDs as well as the median and ranges for each sex and age group for $TmPO_4/GFR$, TRP, PO_4/Cr-clearances, and urinary

PO_4 excretion in relation to GFR and Cr, and the serum PO_4 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 PO_4 excretion (C_{PO_4}/C_{Cr}) as well as PO_4/GFR increased at an inverse ratio to TRP.

The PO_4/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.

$TmPO_4$/GFR and serum PO_4 declined with age in girls and boys. Fig. 1 shows the distribution of the individual values of $TmPO_4$/GFR in girls (n=291) and boys (n=273) according to their ages.

Girls

The PO_4 reabsorption decreased slightly from 6·0 to 13·9 years and decreased further therafter but had not reached normal adult levels at age 17 years (Table 1). The relationship between $TmPO_4$/GFR levels and age (6·0–17·9 years) had a negative correlation coefficient of $r = -0{\cdot}64$ ($P < 0{\cdot}001$).

Boys

$TmPO_4$/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 ($P < 0{\cdot}01$) than the adult levels (Table 1). As in the girls a negative correlation was found between age (6–17·9 years) and $TmPO_4$/GFR ($r = -0{\cdot}46$, $P < 0{\cdot}001$).

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

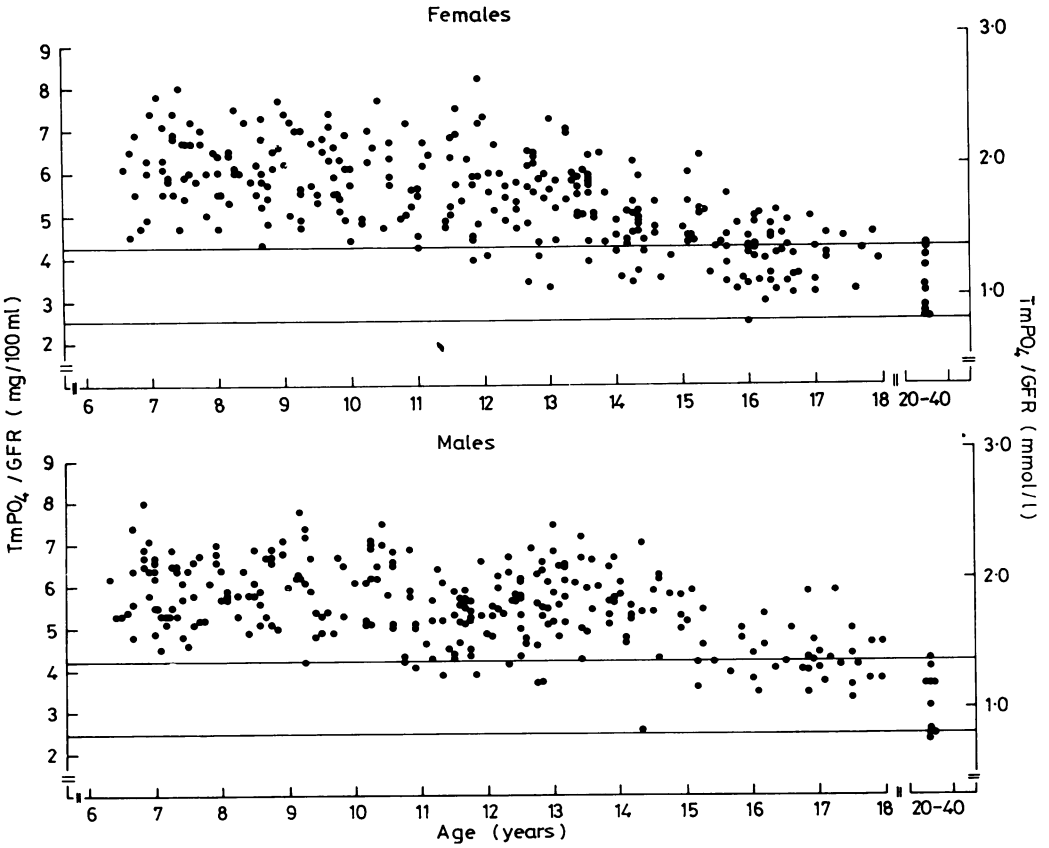

Fig. 1 *Individual values of $TmPO_4$/GFR in relation to age in 291 girls and 273 boys. The normal range for adults, determined by Walton and Bijvoet,[1] is also shown.*

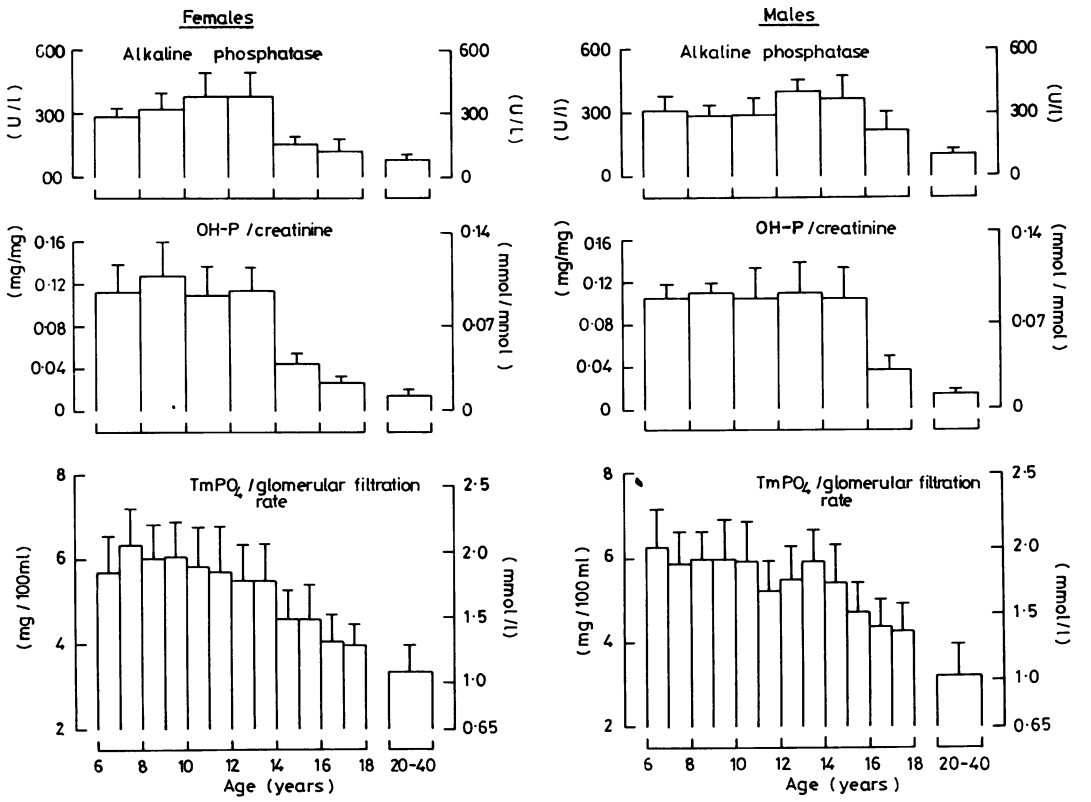

Fig. 2 *Fasting serum alkaline phosphatase activities, urinary total hydroxyproline excretion (OH-P/Cr), and $TmPO_4/GFR$ in girls and boys in relation to age. In the children mean ± SD levels of alkaline phosphatase and OH-P/Cr were determined every 2 years (n=10), whereas mean ± SD values of $TmPO_4/GFR$ 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.*

until age 13·9 years in girls and until 15·9 years in boys, followed by an exaggerated decrease thereafter in both sexes (Fig. 2).

The levels of iPTH and CT in serum and cAMP/GFR showed no significant difference between girls and boys and no age dependency. The median and ranges of iPTH (n=120) and CT (n=120) were 2·1 pmol/l (<0·8–5·4 pmol/l) and 80 pg/ml (<40–420 pg/ml), respectively. The mean ±SD value of cAMP/GFR was 3·07±0·80 nmol/100 ml GF (n=120). As shown (Table 2) no correlation was found between $TmPO_4/GFR$ and iPTH, CT, and cAMP/GFR respectively (P>0·05), whereas a significant relationship was seen between $TmPO_4/GFR$ and OH-P/Cr and between $TmPO_4/GFR$ and serum AP (Figs 3 and 4).

Serum AP correlated well with OH-P/Cr (r=0·63, n=120, P<0·001).

Table 2 *Relationship between $TmPO_4/GFR$ and iPTH, CT, AP, cAMP/GFR, and OH-P/Cr in 120 school-children, aged 6–17·9 years*

	r	*P*
iPTH	0·15	NS
CT	0·12	NS
AP	0·27	<0·001
OH-P/Cr	0·46	<0·001
cAMP/GFR	−0·17	NS

NS = not significant (P>0·05).

Discussion

Many factors are known to influence the renal handling of PO_4 by increasing (for example growth hormone and vitamin D metabolites)[5 15] or decreasing (for example PTH, CT, and oestrogens)[5 15] $TmPO_4/GFR$.

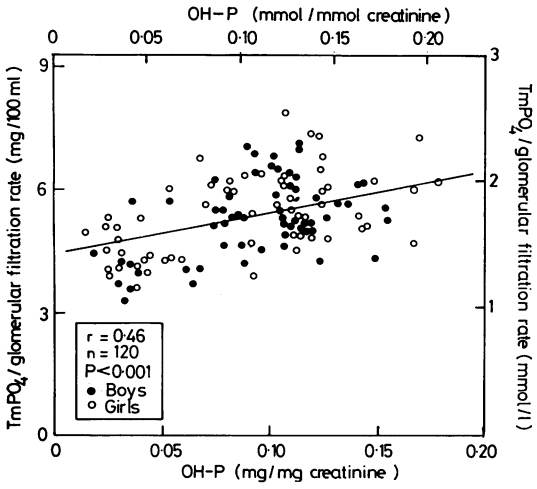

Fig. 3 *Relationship between $TmPO_4$/GFR and fasting urinary total hydroxyproline excretion (OH-P/Cr) in 60 girls and 60 boys aged 6 to 17·9 years.*

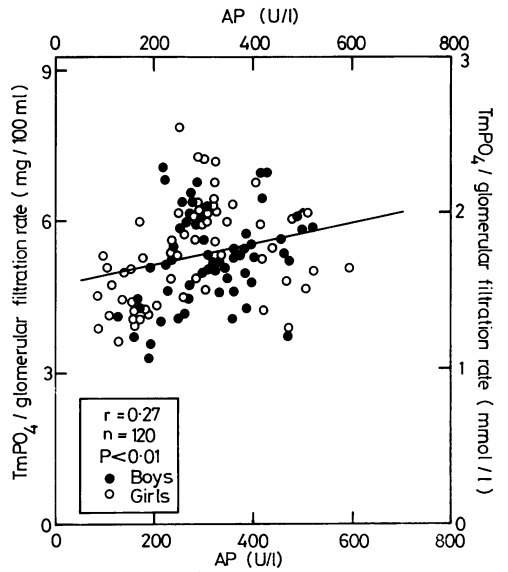

Fig. 4 *Relationship between $TmPO_4$/GFR and serum alkaline phosphatase activities (AP) in 60 girls and 60 boys aged 6 to 17·9 years.*

This study shows that $TmPO_4$/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 PO_4 threshold was not measured directly the levels were similar to those found by phosphate infusions exhibiting $TmPO_4$/GFR values of 4·97±0·61 mg/100 ml (mean±SD) in 15 children aged between 5 and 14 years.[7] In our study the age-related variation of $TmPO_4$/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 $TmPO_4$/GFR and urinary OH-P excretion—reflecting bone resorption—and serum AP activity—reflecting bone turnover, particularly bone formation.[16] This indicates that the high renal PO_4 threshold may be an important factor for normal growth and it may provide high extracellular PO_4 for mineralisation of growing cartilage and bone. Accordingly $TmPO_4$/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,[7] 1,25-dihydroxyvitamin D3,[17] sexual maturation, and intrinsic differences in the renal tubules[18] may influence the changing renal PO_4 threshold before, during, and after puberty. Such age-related differences in the renal handling of PO_4 should be taken into account when $TmPO_4$/GFR is estimated in childhood.

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