Effect of Age on the Response to Parathyroid Hormone

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Serum phosphate (PO_4) levels and the tubular threshold for PO_4 corrected for glomerular filtration (TP/GF) are age-dependent, being higher in children than in adults. We evaluated the effect of age on the response to infusion of parathyroid hormone(1-34) (PTH) in healthy children (n = 8) and adults (n = 12). In addition, six patients with pseudohypoparathyroidism (PHP) and two with PTH deficiency (hypoparathyroidism [HP]) were also studied. At baseline, TP/GF in normal subjects was inversely correlated with urinary cyclic adenosine monophosphate corrected for glomerular filtration (UcAMP/GF) ($P < .0359$). After PTH administration in the controls, UcAMP/GF was inversely correlated with TP/GF ($P < .0007$) and directly correlated with maximal fractional extraction of PO_4 (FEP) ($P < .0002$). The slope of the regression of TP/GF ($P < .0076$) and FEP ($P < .0034$) with UcAMP/GF was steeper in children than in adults. Two HP patients had high PTH-stimulated UcAMP/GF levels, but stimulated TP/GF and FEP were not changed commensurate with levels that would expected from the normative data. In six patients with PHP, PTH-stimulated TP/GF was also correlated with peak UcAMP/GF ($r = .96$, $P < .002$). PHP patients could be distinguished from normal controls based on the combination of low peak FEP or high TP/GF together with low peak UcAMP/GF. Thus, in normal subjects, the phosphaturic response to PTH is correlated with the increase in urinary cAMP and is age-dependent, with a greater decrease of TP/GF in children than in adults.

PARATHYROID HORMONE (PTH) is an important regulator of serum phosphate (PO_4) levels, acting on the kidney to decrease renal tubular reabsorption of PO_4. In vitro, PTH binds to receptors on proximal renal tubular epithelia and activates adenylyl cyclase, leading to generation of intracellular cyclic adenosine monophosphate (cAMP).[1-3] The PTH-stimulated increase in cAMP is associated with inhibition of PO_4 transport into the cell.

A similar effect of PTH can be observed clinically: intravenous infusion of PTH in healthy individuals leads to an increase in nephrogenous cAMP and an increase in the urinary fractional excretion of PO_4 (FEP). This effect can be used clinically to assess the responsiveness to PTH, and forms the basis of a diagnostic test for disorders of PTH secretion and action.[7] For example, in patients with pseudohypoparathyroidism (PHP) type 1, phosphaturic and urine cAMP responses to PTH are markedly blunted compared with the responses in normal individuals.[8,9] The basis for this defective PTH responsiveness in PHP type 1a patients is a decreased expression or function of $G_{s\alpha}$, the G protein that couples the PTH receptor to adenylyl cyclase. This defect impairs the generation of cAMP and blunts the subsequent inhibition of the PO_4 transporter.[10]

Serum PO_4 levels and the renal tubular threshold for PO_4 are age-dependent.[11,12] Children have higher serum PO_4 concentrations and higher renal tubular PO_4 thresholds than adults.[11,12] Serum levels of PTH have been found to be similar between children and young adults.[13,14] Thus, the age variation in the renal tubular PO_4 threshold and serum PO_4 levels does not appear to be due to differences in circulating PTH levels between adults and children. We hypothesized that the responsiveness to PTH infusion might be influenced by age. We therefore undertook a study of the response to infusion of PTH(1-34) in healthy children and adults and evaluated the changes in urinary cAMP, renal tubular PO_4 threshold, and tubular PO_4 excretion with respect to age. For comparison to the normative data, the response of patients with defects in PTH secretion and action was also included. In normal subjects, we found that the post-PTH tubular threshold for PO_4 corrected for glomerular filtration (TP/GF) and FEP were both correlated with peak urinary cAMP corrected for glomerular filtration (UcAMP/GF), and the magnitude of the relationship was age-dependent.

SUBJECTS AND METHODS

Subjects

We recruited 12 adults (seven men and five women aged 23 to 41.7 years) and eight healthy children with normal height and weight (four boys and four girls aged 2.8 to 15 years) for participation in this study. All controls were volunteers in good health and without a history of chronic illness. All were consuming an unrestricted standard diet before testing.

In addition, six children with PHP type 1 (two boys and four girls aged 6.3 to 15.2 years) and two children with hypoparathyroidism (HP) (a girl aged 1 year and a boy aged 13.2 years) were also studied with PTH infusion. Among the PHP type 1 patients, five had the characteristic features of Albright hereditary osteodystrophy (AHO) with short stature, round facies, brachydactyly, and subcutaneous ossification, which is typical of PHP type 1a. One patient had no features of AHO and would be classified as PHP type 1b. The two patients with HP included a girl with congenital HP and a boy with HP as part of autoimmune polyglandular syndrome type 1.

The study protocol was approved by the Institutional Review Board at the University of Maryland. Informed consent was obtained from each subject and the parents in the case of minors.

PTH Infusion Test

PTH infusion was performed after an overnight fast with the exception of ad libitum intake of water. Human PTH(1-34) (Teriparatide Acetate; Rorer Pharmaceutical, Fort Washington, PA) was infused at a dosage of 5 U/kg (maximal dose, 200 U) over 15 minutes. Oral intake of water was encouraged throughout the study. Urine

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samples were obtained 60 minutes before and immediately before PTH infusion, as well as 30, 60, 120, and 180 minutes after beginning PTH administration (at time 0). Blood samples were obtained before and 120 minutes after PTH infusion.[15] All urine samples were kept frozen until assayed for cAMP, PO_4, and creatinine (Cr). Serum samples were analyzed for PO_4 and Cr.

Assays

PO_4 and Cr levels were measured by a dry-slide technique (Kodak-Ektachem). Urine cAMP levels were determined in duplicate by radioimmunoassay using reagents purchased from Incstar (Stillwater, MN). The sensitivity of the cAMP test was 0.3 nmol/L; the intraassay coefficient of variation was 5.8%, and the interassay coefficient of variation was 9%.

Methods of Analysis

UcAMP/GF levels were corrected for 100 mL glomerular filtration, expressed as namomoles per deciliter GF as previously described[16]:

$$\text{UcAMP/GF} = \left(\frac{\text{urine cAMP}}{\text{urine Cr}}\right) \times \text{serum Cr.}$$

Renal PO_4 handling was assessed by determination of the renal PO_4 threshold (TP/GF) and FEP. FEP is the C_{PO4}/C_{Cr} expressed as a percent, according to the following formula[16]:

$$\text{FEP} = \left(\frac{\text{serum Cr} \times \text{urine Po}_4}{\text{serum Po} \times \text{urine Cr}}\right) \times 100.$$

The renal phosphate threshold (TP/GF) was calculated from serum and urine parameters as described by Stark et al.[12] TP/GF values are highly correlated with TmP/GF values obtained from the Walton-Bijvoet nomogram,[17] with the advantage of being applicable to children at all ages, particularly those whose serum PO_4 levels are outside the range of the nomogram.[12] For similar reasons, the data for FEP are also presented, since it is readily calculated from urine and serum Cr and PO_4 measurements. The formula for calculating TP/GF is

$$\text{TP/GF} = \text{serum Po}_4 - \left(\frac{\text{urine Po}_4 \times \text{serum Cr}}{\text{urine Cr}}\right).$$

Basal UcAMP/GF, TP/GF and FEP values were the mean of the two preinfusion values.

Statistical Analysis

All data are reported as the mean ± 1 SD. Differences in variable means between children and adults were tested by the Student *t* test, and by ANOVA where appropriate. Statistical analysis of basal versus post-PTH variables was performed by paired *t* test. Multiple regression analysis was used to evaluate relationships between variables; the significance level reported for the independent variables in the regression analysis is taken from the type III sums of squares. Statistical computations were performed on a desktop computer using SAS software.[18]

RESULTS

Normal Subjects

Basal and stimulated levels of UcAMP/GF for the subjects are presented in Table 1, and measures of PO_4 metabolism are presented in Table 2. Baseline measurements of UcAMP/GF levels were obtained after an overnight fast and tended to be lower in children than in adults ($P < .07$; Table 1). Basal serum PO_4 and basal TP/GF were higher in the normal children compared with adults ($P < .002$). Basal FEP was not different between normal adults and children (Table 2).

PTH infusion produced a significant increase in UcAMP/GF in both normal children and adults. Peak PTH-stimulated UcAMP/GF levels ($P < .13$), the difference in basal and peak UcAMP/GF levels ($P < .15$), and the peak to basal UcAMP/GF ratio ($P < .3$) were statistically similar in the adults and children (Table 1). Basal UcAMP/GF values were not statistically correlated with post-PTH peak levels of UcAMP/GF in the controls ($r = .24$, $P < .3$).

TP/GF after PTH did not decrease as much in children as in adults ($P < .004$). The absolute change (basal TP/GF − stimulated TP/GF) was similar in children and adults. Mean PTH-stimulated FEP levels were not different between children and adults. However, the change in FEP in response to PTH (peak stimulated FEP − basal FEP) was significantly greater in children than in adults (6.8% ± 4.4% *v* 3.3% ± 2.8%, $P < .05$; Table 2).

In normal subjects, the post-PTH TP/GF was significantly correlated with the basal TP/GF ($r = .92$, $P < .0001$). Using multiple regression analysis, basal TP/GF was inversely associated with basal UcAMP/GF ($P < .0359$) when statistically adjusted for age group in the model (Fig 1A). In this model, there was no statistical interactive effect of UcAMP/GF with age group. By multiple regression, the lowest post-PTH TP/GF was inversely correlated with peak stimulated UcAMP/GF ($P < .0007$) and significantly influenced by age group ($P < .0001$), as well as the interaction of age group and UcAMP/GF ($P < .0076$; Fig 1B). Thus, the slope of the regression for normal children was steeper than for normal adults for the overall regression model ($r^2 = .76$, $P < .001$). A regression model evaluating change in UcAMP/GF (stimulated − basal) and age group on change in TP/GF

Table 1. Basal and PTH-Stimulated UcAMP/GF Levels in Control Children and Adults and in Children With PHP and HP (mean ± SD)

Parameter	Controls		PHP	HP
	Children	Adults		
No. of subjects	8	12	6	2
Basal UcAMP/GF (nmol/dL GF)	2.5 ± 0.8	3.4 ± 1.2*	1.9 ± 0.6	1.5 ± .05
Peak UcAMP/GF (nmol/dL GF)	20.4 ± 11.4	33.1 ± 24.2	3.1 ± 1.5†	161.4 ± 2.0
ΔUcAMP/GF (nmol/dL GF)	18.0 ± 11.0	29.8 ± 24.1	1.2 ± 1.9†	160.0 ± 2.0
Peak/basal UcAMP/GF	8.2 ± 3.5	11.0 ± 10.0	2.0 ± 1.7	111.5 ± 6.9

NOTE. Δ represents the arithmetic difference between basal and PTH-stimulated levels.

*$P < .07$ *v* control children.

†$P < .01$ *v* control children.

Table 2. Basal and PTH-Stimulated Markers of PO_4 Metabolism in Control Subjects and in Children With PHP and HP (mean ± SD)

Parameter	Controls		PHP	HP
	Children	Adults		
No. of subjects	8	12	6	2
Serum PO_4 (mg/dL)	4.6 ± 0.4	3.6 ± 0.3‖	6.3 ± 1.0†	8.3 ± 2.5
Basal TP/GF (mg/dL)	4.2 ± 0.6	3.3 ± 0.3§	6.1 ± 1.1§	8.2 ± 2.5
Lowest TP/GF (mg/dL)	3.9 ± 0.6	3.1 ± 0.3†	6.0 ± 1.0§	7.4 ± 2.4
ΔTP/GF (mg/dL)	−0.30 ± .28	−0.25 ± .24	−0.13 ± .11	−.83 ± .05
Basal FEP (%)	7.9 ± 6.8	8.7 ± 3.4	3.4 ± 1.5	0.4 ± 0.1
Peak FEP (%)	14.7 ± 9.3	12.0 ± 3.6	4.6 ± 1.6†	9.4 ± .62
ΔFEP (%)	6.8 ± 4.4	3.3 ± 2.8*	1.2 ± 0.6†	9.1 ± .51

NOTE. Δ represents the arithmetic difference between basal and PTH-stimulated levels.
*$P < .05$, †$P < .01$, ‡$P < .001$, §$P < .0005$, ‖$P < .0001$: *v* control children.

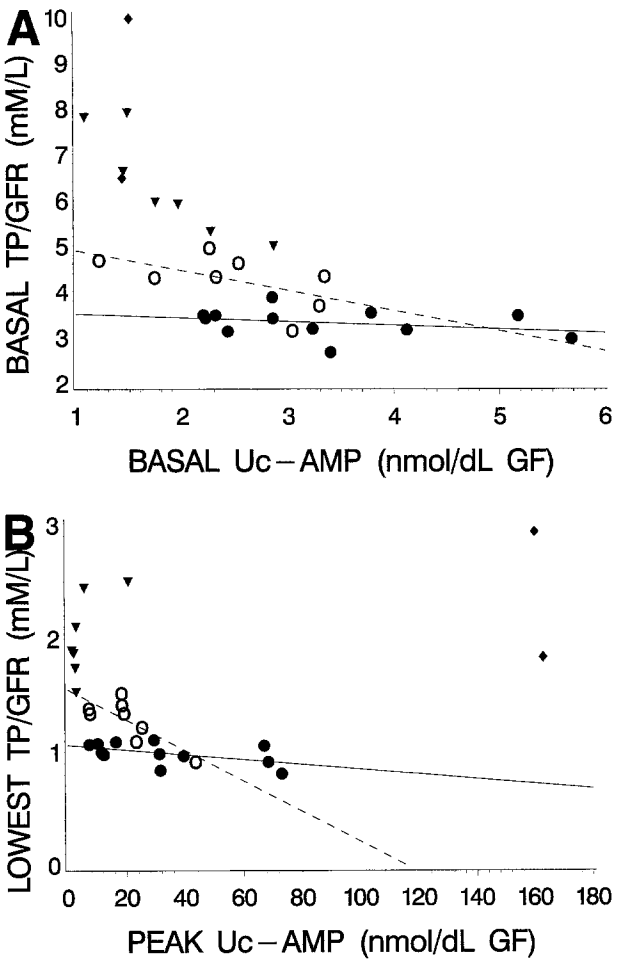

Fig 1. Relationship of TP/GF with UcAMP/GF in normal children (○ and dotted regress) and adults (● and solid regression line). Patients with PHP (▼) and HP (◆) are depicted in the graphs but were not included in calculation of the regression models. (A) Basal TP/GF *v* basal UcAMP/GF. TP/GF is correlated with UcAMP/GF ($r = -.55$, $P < .012$); there was no effect of age, and thus the slopes of the regression lines for children and adults were not statistically different. In PHP patients (▼), basal TP/GF was also strongly correlated with basal UcAMP/GF ($r = .961$, $P < .002$). (B) Post-PTH TP/GF (lowest observed value) *v* peak UcAMP/GF. In a multiple regression model, TP/GF was inversely correlated with peak UcAMP/GF ($P < .0007$); there was also an effect of age group (children > adults, $P < .0001$) and an interactive effect of age group with UcAMP/GF ($P < .0076$). Thus, the slope of the regression of TP/GF with UcAMP/GF is steeper for children than for adults.

(stimulated − basal) was not statistically significant ($R^2 = .14$, $P < .46$).

Basal FEP was correlated with the peak PTH-stimulated FEP ($r = .80$, $P < .0001$). FEP was also found to be correlated with TP/GF when statistically adjusted for age group. At baseline, FEP was not correlated with basal UcAMP/GF (Fig 2A). In response to PTH administration, peak FEP was found to be directly correlated with peak stimulated UcAMP/GF ($P < .0002$). There was also an interaction of UcAMP/GF with age group ($P < .0034$). Thus, the slope of the regression of FEP with UcAMP/GF was steeper in children than in adults (Fig 2B). The statistical model of peak stimulated FEP regressed with UcAMP/GF, age group, and the interaction of age group with UcAMP/GF was significant ($P < .0013$, $R^2 = .61$). Addition of basal serum PO_4 level as a covariate in the regression model was not found to have a statistically significant influence on FEP. The change in FEP (PTH-stimulated FEP − basal FEP) was significantly associated ($R^2 = .46$, $P < .017$ overall) with the PTH-stimulated change in the level of UcAMP/GF ($P < .026$) when adjusted for age group and the interaction of age group with UcAMP/GF (Fig 2C).

Subjects With PTH Disorders

Basal serum PO_4 ($P < .001$) and TP/GF ($P < .001$) were higher in PHP patients compared with controls. Basal UcAMP/GF was not different between control children and PHP patients. The PHP patients could be distinguished from the controls based on a blunted peak UcAMP/GF and/or blunted peak FEP response (Fig 2B). By paired *t* test, the lowest post-PTH TP/GF ($P < .018$) was significantly different from basal TP/GF, but basal FEP versus stimulated FEP ($P < .06$) and basal UcAMP versus stimulated UcAMP ($P < .2$) were not statistically different. PTH-stimulated TP/GF levels remained higher in PHP patients compared with controls ($P < .001$; Table 2). Peak FEP was blunted in PHP patients compared with controls. PTH-stimulated peak levels of UcAMP/GF ($P < .05$) and FEP ($P < .05$) were both blunted in PHP patients compared with controls. As in the control subjects, basal TP/GF was correlated with basal UcAMP/GF in the PHP patients ($r = .961$, $P < .002$; Fig 1A).

Basal FEP in HP patients was less than the levels observed in normal children and adults. Similarly, TP/GF in HP patients exceeded the control levels. It should be pointed out that at the time of testing serum calcium levels in both patients were less than the normal range. PTH-stimulated peak UcAMP/GF

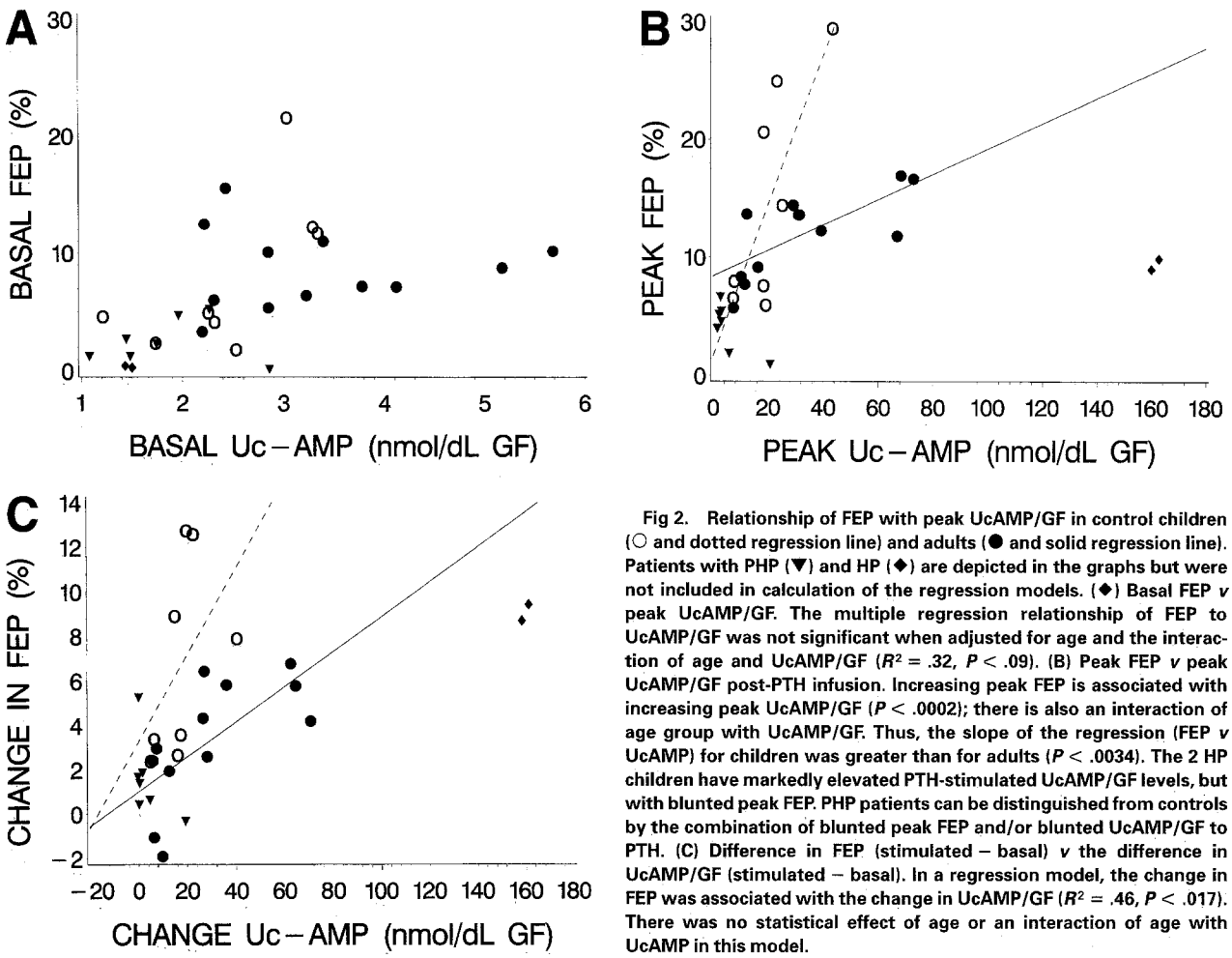

Fig 2. Relationship of FEP with peak UcAMP/GF in control children (○ and dotted regression line) and adults (● and solid regression line). Patients with PHP (▼) and HP (◆) are depicted in the graphs but were not included in calculation of the regression models. (◆) Basal FEP *v* peak UcAMP/GF. The multiple regression relationship of FEP to UcAMP/GF was not significant when adjusted for age and the interaction of age and UcAMP/GF ($R^2 = .32$, $P < .09$). (B) Peak FEP *v* peak UcAMP/GF post-PTH infusion. Increasing peak FEP is associated with increasing peak UcAMP/GF ($P < .0002$); there is also an interaction of age group with UcAMP/GF. Thus, the slope of the regression (FEP *v* UcAMP) for children was greater than for adults ($P < .0034$). The 2 HP children have markedly elevated PTH-stimulated UcAMP/GF levels, but with blunted peak FEP. PHP patients can be distinguished from controls by the combination of blunted peak FEP and/or blunted UcAMP/GF to PTH. (C) Difference in FEP (stimulated − basal) *v* the difference in UcAMP/GF (stimulated − basal). In a regression model, the change in FEP was associated with the change in UcAMP/GF ($R^2 = .46$, $P < .017$). There was no statistical effect of age or an interaction of age with UcAMP in this model.

values in HP (162.8 and 160 nmol/dL GF) were considerably higher than the upper limit of responses in controls. Despite the high UcAMP/GF levels in response to PTH, stimulated FEP levels were much lower than anticipated from the responses in both normal children and adults (Fig 2B and C). However, the change in TP/GF in response to stimulation was among the highest observed (Fig 1C). Thus, with an exaggerated UcAMP/GF response, HP patients did not achieve the expected changes in FEP, while the change in TP/GF was within the range of normal responses.

DISCUSSION

Intravenous infusion of PTH with measurement of the subsequent UcAMP/GF and phosphaturic responses has provided diagnostic criteria for discrimination between patients with HP and patients with various forms of PHP.[5-9,19] More recently, the PTH test has revealed differences in the responsiveness of patients with McCune-Albright syndrome[15] compared with normal controls. In many previous studies, either bovine PTH extract or PTH(1-38) was used as the PTH stimulus and the influence of age was not evaluated. More recently, biosynthetic PTH(1-34) has replaced the use of PTH extract for diagnostic studies in the United States, and its use is described in adult subjects.[19,20] In this study, we examined the relationship of urinary cAMP generation with PO_4 excretion in response to infused PTH(1-34) in healthy children compared with adult controls. We found that, like PO_4 and TP/GF, the phosphaturic response to PTH and its relationship to UcAMP/GF were age-dependent.

In the control group of 12 adults and eight children, there was a trend for the children to have lower basal urinary cAMP levels ($P < .07$) compared with the adults. Basal TP/GF was inversely correlated with basal UcAMP/GF in the control subjects. After PTH stimulation, TP/GF was inversely correlated with the stimulated level of UcAMP/GF. In addition, we also noted a correlation between basal TP/GF and UcAMP/GF in PHP patients, although this relationship was shifted upward compared with normals due to the higher basal PO_4 and consequent higher TP/GF in PHP patients. These findings are in accordance with previous studies by Stark et al,[12,21] who reported that basal UcAMP/GF levels were statistically lower in a larger sample of children (N = 25) compared with adults. They also found an inverse correlation between basal TP/GF and basal UcAMP/GF. Their group reported that basal PTH levels were lower in children than in adults, but they found no correlation between TP/GF and PTH levels.[21] These observations in children extend the data from adults showing an influence of aging on TmP/GF and nephrogenous cAMP, with young adults having higher TmP/GF and lower urinary cAMP than elderly adults.[22] In contrast, Kruse and Kracht,[23] using a somewhat different

methodology, found no influence of age on UcAMP/GF or PTH and no relationship between UcAMP/GF or PTH on TmP/GF.

The current finding of an inverse association of TP/GF with UcAMP/GF in both controls and PHP patients suggests a role for basal PTH and/or cAMP activity in determining serum PO_4 level. Thus, the defect in PHP patients may not completely interrupt the PTH/cAMP effect under basal conditions. PTH action on the renal tubules has been shown to be mediated through the protein kinase A pathway, with generation of intracellular cAMP leading to inhibition of the sodium-dependent PO_4 transporter with a decrease in resorption of PO_4. Extremes of this phenomenon can be seen clinically: an absence of PTH, as occurs in HP, leads to low UcAMP/GF levels with enhanced resorption of PO_4 and high TP/GF and high serum PO_4 levels.[16] Conversely, hyperparathyroidism leads to high UcAMP/GF and decreased TP/GF and serum PO_4 levels.[16]

Infusion of PTH(1-34) stimulated an increase in UcAMP/GF and an increase in FEP. We found that the peak stimulated levels of FEP were directly correlated with peak UcAMP/GF levels in children and adults. This response to PTH was age-dependent, with children showing higher FEP levels as UcAMP/GF levels increased than adults. Thus, FEP levels in children were higher with increases in UcAMP/GF than the levels found in adults. The steepness of the relationship between FEP and UcAMP/GF in children versus adults might be assumed to occur on the basis of higher plasma PO_4 levels, which would be filtered and then lost in the urine when PO_4 resorption is inhibited by PTH. However, we did not find a relationship between serum PO_4 and stimulated FEP when the basal PO_4 level was added to the regression model as a covariate. Another possibility is that cAMP generated intracellularly is not released into the urine as readily in children as in adults. Thus, children might have higher intracellular levels of cAMP that are not reflected by UcAMP/GF. At present, there is no evidence to suggest that such a difference in the relationship between intracellular cAMP generation and urinary cAMP loss exists between children and adults.

It should be pointed out that acute intravenous bolus infusion of PTH leads to very high levels of circulating PTH and probable saturation of cellular receptors. The observed post-PTH bolus effects have not been compared with effects that would occur during physiologic changes in PTH concentration. Evaluation of a dose-response curve to PTH infusion in children and adults would be necessary to evaluate whether PTH bolus effects represent effects occurring at lower concentrations of PTH.

Of interest was the PTH(1-34)-stimulated FEP in the two HP patients when considered in light of the normative data that permit comparison of stimulated FEP to UcAMP/GF data. The two HP patients had supranormal elevations in UcAMP/GF well above the mean peak UcAMP/GF observed in normal children. Despite an exaggeratedly high UcAMP/GF response to PTH, the FEP response was modest and similar to that of the control subjects who had low UcAMP/GF responses. Both HP subjects had PTH-stimulated changes in FEP higher than the mean levels observed in the control groups but not exceeding the responses of normal subjects. We found that the change in TP/GF and FEP of HP patients was at the upper limit observed for controls, although the controls achieved this difference with a much smaller change in UcAMP/GF. Using PTH(1-34), Mallette et al[24] reported that adult HP patients generally had a larger change in urinary cAMP with a smaller change in TmP/GF than normal adult controls. Other investigators using other types of PTH preparations have reported an enhanced or normal UcAMP/GF in HP patients with a FEP response either similar to or slightly higher than that of control subjects.[5,7] The current observation of a discrepancy between the stimulated UcAMP/GF and FEP response to PTH suggests a possible alteration of the response to second-messenger signal in HP. A chronic absence of PTH may upregulate PTH receptors or enhance the G protein–mediated generation of intracellular cAMP, which leads to enhanced UcAMP/GF after PTH infusion. However, a chronic lack of PTH stimulation or intracellular cAMP may prevent maximal inhibition of the PO_4 transporter after the large acute increase in cAMP generated by PTH infusion.[7] An alternative explanation comes from clinical[25-28] and in vitro evidence[29] that the phosphaturic response to PTH is dependent on serum calcium levels. At the time of the PTH infusion, one HP patient had a subnormal serum calcium level and the other had a low-normal level. It has also been hypothesized that elevated levels of PO_4 may have the ability to alter the tubular reabsorption of PO_4 independently of PTH and calcium levels.[30]

In conclusion, there is an age-dependent correlation between FEP and urinary cAMP in response to PTH infusion. Children have a steeper change in TP/GF and FEP than adults. Consideration of this age-dependent relationship between UcAMP/GF and FEP may permit a more detailed assessment of the responsiveness to PTH in individuals with disorders of calcium and phosphorus and abnormalities of mineral-regulating hormones.

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