

Bone mineral homeostasis, bone growth, and mineralisation during years of pubertal growth: a unifying concept

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SUMMARY Serum calcium, magnesium, proteins, phosphate, and immunoparathyroid hormone were measured in 338 normal children and adolescents aged between 7 and 20 years and in 123 normal adults aged between 21 and 50 years. Protein corrected serum calcium and magnesium remained stable throughout the study. Despite hyperphosphataemia protein corrected calcium exceeded the concentrations of normal adults. Serum phosphate and the $\text{Ca} \times \text{P}$ product greatly exceeded adult values and fell rather slowly towards adult levels after the pubertal growth spurt. Serum immunoparathyroid hormone tended to exceed normal adult values and was judged high for the level of serum calcium. Similarities between mineral metabolism in childhood and adolescence and in acromegaly were striking. On this basis and in the light of studies demonstrating stimulatory actions of gonadal hormones on growth hormone and of growth hormone on the secretion of parathyroid hormone and 1,25-dihydroxyvitamin D_3 , a unifying concept is developed. This concept places growth hormone in the unique position of being the main driver and co-ordinator during childhood and adolescence of bone growth and mineralisation on the one hand, and of blood mineral homeostasis on the other. Gonadal hormones probably express some of their actions through stimulation of growth hormone secretion and others by different mechanisms. According to this concept growth hormone is maintaining the $\text{Ca} \times \text{P}$ product at a suitable high level as long as growth hormone and gonadal hormones deliver bone matrix for mineralisation at a high rate.

Bone development is governed by growth hormone, thyroid hormone, insulin, and nutrition, mainly through the actions of the somatomedins.¹ Recently we described three distinctly different phases of bone growth and mineralisation in normal children and adolescents.² After a prepubertal phase of moderate growth velocity and little mineralisation the pubertal growth spurt, which coincided with a steep increase in serum testosterone in boys, indicated a short phase of grossly accelerated skeletal growth and mineralisation in both genders. During the following third phase linear growth took place at a low rate while intensive mineralisation continued.² Thus, most of the minerals finally deposited in the skeleton traverse the blood stream during the last two phases of bone development. How this challenge to blood mineral homeostasis is met is not known in detail, but recent studies implicating growth hormone as a stimulator of parathyroid hormone secretion³ and 1,25-dihydroxyvitamin D

production^{4–6} deserve attention. Previous studies in children and adolescents indicate favourable conditions for bone mineralisation—namely hyperphosphatasia^{7,8} and hyperphosphataemia.^{7,9} Serum concentrations of immunoreactive parathyroid hormone (iPTH) are either high,¹⁰ high to normal,¹¹ or normal,¹² while reports on serum calcium are more divergent. Compared with normal adult standards high,^{10,12} normal,^{7,10} and low¹³ serum calcium concentrations have been reported.

Here we contribute information on the normal variation of serum calcium, magnesium, phosphate, and iPTH in groups of normal children, adolescents, and adults in order to substantiate the basis from which a unifying concept of bone growth and mineralisation and blood mineral homeostasis can be formulated.

Participants

Normal children and adolescents. A total of 338

normal children and adolescents aged between 7 and 20 years took part in the study. They were randomly selected from two schools in a suburban area. Pupils below age 18 years obtained written consent from their parents. All were in good health without symptoms of gastrointestinal or renal diseases. None took contraceptive pills or any other type of drug.

Normal adults. Sixty normal women and 63 normal men aged between 21 and 50 years were randomly selected from the blood donor corps at Glostrup Hospital, serving the same suburban area.

Methods

Serum calcium and magnesium were determined by atomic absorption spectrophotometry (Perkin Elmer 403), and serum proteins by refractometry. Serum

calcium and magnesium were corrected to a constant level of serum proteins. Serum phosphate was measured colorimetrically and iPTH by a mainly C-terminal specific double-antibody radioimmunoassay.¹⁴ The coefficients of variation calculated from duplicate measurements were 1.1% for serum calcium, 1.2% for serum magnesium, 0.4% for serum proteins, 1.0% for serum phosphate, 3.0% for serum alkaline phosphatases, and 4.3% in the case of iPTH. The analyses were performed either in all subjects or in randomly selected subpopulations thereof.*

For statistical evaluation of group average Student's *t* test was used.

Results

Protein corrected serum calcium (Tables 1 and 2,

* Tables giving the raw data are available on request.

Table 1 Average values of chemical variables in normal boys grouped according to the three phases of bone development. Average values of normal men are shown for comparison. Values are given as mean \pm 1 SE of mean

Chemical variables	Before growth spurt (7-12 years)	At growth spurt (13-14 years)	After growth spurt (15-20 years)	Men (21-50 years)	Significance of difference (P)		
					1:3	1:4	3:4
Serum calcium (uncorrected) (mg/100 ml)	10.02 \pm 0.04	10.14 \pm 0.04	10.22 \pm 0.04	9.95 \pm 0.04	<0.001	NS	<0.001
Serum proteins (g/100 ml)	7.16 \pm 0.05	7.39 \pm 0.09	7.55 \pm 0.05	7.67 \pm 0.05	<0.001	<0.001	NS
Serum calcium (protein corrected) (mg/100 ml)	10.21 \pm 0.03	10.20 \pm 0.06	10.20 \pm 0.03	9.89 \pm 0.04	NS	<0.001	<0.001
Serum magnesium (protein corrected) (mg/100 ml)	2.01 \pm 0.02	1.99 \pm 0.02	1.98 \pm 0.01	2.03 \pm 0.02	NS	NS	NS
Serum phosphate (mg/100 ml)	4.55 \pm 0.07	4.80 \pm 0.10	4.04 \pm 0.07	3.23 \pm 0.06	<0.001	<0.001	<0.001
Serum-Ca \times P product	47.30 \pm 0.94	49.22 \pm 1.05	41.19 \pm 0.64	32.15 \pm 0.62	<0.001	<0.001	<0.001
Serum-iPTH (μ g/l)	0.35 \pm 0.02	0.34 \pm 0.01	0.35 \pm 0.01	0.33 \pm 0.02	NS	NS	NS

NS > 0.05.

Conversion: traditional to SI units—calcium: 1 mg/100 ml \approx 0.250 mmol/l; magnesium: 1 mg/100 ml \approx 0.411 mmol/l; phosphate: 1 mg/100 ml \approx 0.323 mmol/l.

Table 2 Average values of chemical variables in normal girls grouped according to the three phases of bone development. Average values of normal women are shown for comparison. Values are given as mean \pm 1 SE of mean

Chemical variables	Before growth spurt (7-10 years)	At growth spurt (11-12 years)	After growth spurt (13-20 years)	Women (21-50 years)	Significance of difference (P)		
					1:3	1:4	3:4
Serum calcium (uncorrected) (mg/100 ml)	10.03 \pm 0.05	10.06 \pm 0.05	10.09 \pm 0.04	9.75 \pm 0.04	NS	<0.001	<0.001
Serum proteins (g/100 ml)	7.37 \pm 0.07	7.40 \pm 0.07	7.46 \pm 0.04	7.40 \pm 0.05	NS	NS	NS
Serum calcium (protein corrected) (mg/100 ml)	10.10 \pm 0.04	10.12 \pm 0.06	10.11 \pm 0.03	9.82 \pm 0.04	NS	<0.001	<0.001
Serum magnesium (protein corrected) (mg/100 ml)	1.98 \pm 0.02	1.99 \pm 0.03	2.00 \pm 0.01	2.00 \pm 0.02	NS	NS	NS
Serum phosphate (mg/100 ml)	4.51 \pm 0.08	4.41 \pm 0.10	4.02 \pm 0.06	3.71 \pm 0.07	<0.001	<0.001	<0.01
Serum-Ca \times P product	46.71 \pm 0.65	44.71 \pm 1.01	40.71 \pm 0.58	36.20 \pm 0.81	<0.001	<0.001	<0.001
Serum-iPTH (μ g/l)	0.39 \pm 0.02	0.40 \pm 0.03	0.34 \pm 0.01	0.32 \pm 0.01	<0.05	<0.01	NS

NS > 0.05.

Fig. 1) remains stable throughout childhood and adolescence, but at a level clearly exceeding that of normal adults ($P < 0.001$). When compared with serum uncorrected calcium (Tables 1 and 2) it is noteworthy that protein correction reduces the intra- and intergroup variability. Protein corrected serum magnesium is constant and similar to that observed in adults.

Serum phosphate exceeds adult levels at all ages and in both genders (Fig. 2). It reaches maximum values at 10 years in girls and at 12–14 years in boys, and decreases thereafter gradually towards normal adult values. These are reached at age 18 to 20 years in girls and probably later than 20 years in boys.

The $Ca \times P$ product greatly exceeds that of adults (Tables 1 and 2) and follows the same pattern as the serum phosphate. For methodological reasons—in part at least—serum iPTH values scatter rather widely. No distinct pattern was observed (Fig. 3). Serum iPTH tended to exceed normal adult values.

Discussion

Together with recent reports^{7 10–12} our observations established firmly that an ‘acromegaloid’ pattern of

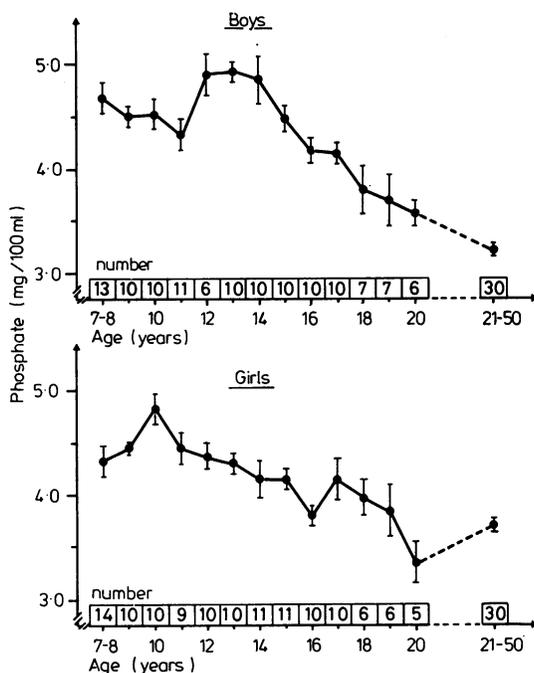


Fig. 2 Serum phosphate (mean \pm SEM) as a function of age. See legend to Fig. 1.

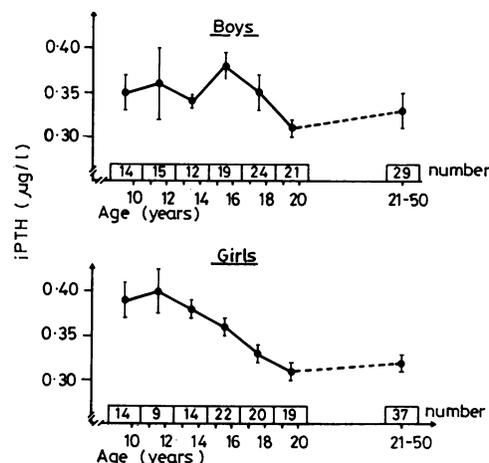


Fig. 3 Serum immunoreactive parathyroid hormone (iPTH) (mean \pm SEM) as a function of age in 105 normal boys (above) and 98 normal girls (below) aged 7 to 20 years. Average values of 29 normal men (above) and 37 normal women (below) aged 21 to 50 years are shown for comparison.

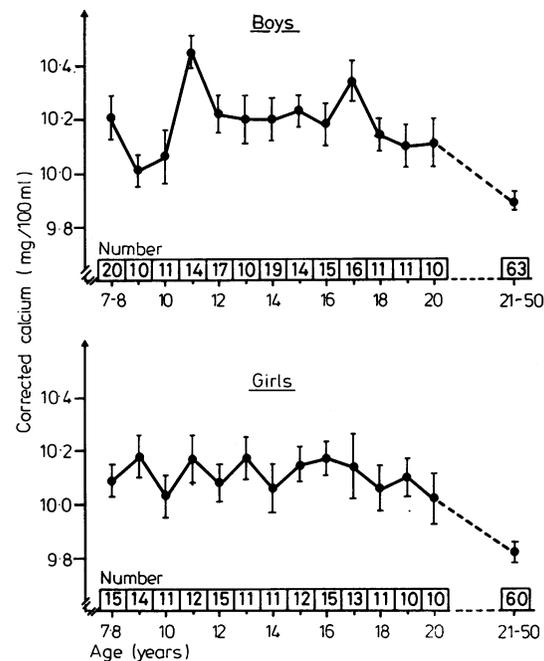


Fig. 1 Serum protein corrected calcium (mean \pm SEM) as a function of age in 178 normal boys (above) and 160 normal girls (below) aged 7 to 20 years. Average values of 63 men (above) and 60 women (below) aged 21 to 50 years are shown for comparison.

mineral homeostasis¹⁵ is found in normal children and adolescents. Our observations show striking similarities to those of others. Such similarities include (1) the hormonal control of mineral homeostasis, (2) mineral transport, (3) blood mineral levels, and (4) the development of mineralised bone mass.

Hormonal control. The points of similarity include raised levels of serum growth hormone¹⁶⁻¹⁸ and somatomedins,^{18,19} and high concentrations of serum 1,25-dihydroxyvitamin D.^{5,6,20} Serum iPTH is normal to slightly raised^{5,10-12,15} (Tables 1 and 2), but inappropriately high as judged from the level of serum calcium. The serum concentrations of growth hormone and somatomedins in children and adolescents are much lower than most of the values seen in acromegaly but differences in target organ sensitivities may account for the similarity of response.

Transport of minerals. An increased transport of minerals into the blood stream is also common to childhood, adolescence, and acromegaly. Both the intestinal absorption of calcium²¹ and the tubular reabsorption of phosphate^{9,15} are clearly raised. High levels of serum 1,25-dihydroxyvitamin D supposedly explain hyperabsorption of calcium and of phosphate²² from the gut. Its action on the renal transport of phosphate however, is disputable.

Hyperphosphataemia. Not surprisingly hyperphosphataemia is a prominent feature of childhood and adolescence^{7,12} (Tables 1 and 2) as of acromegaly.¹⁵ As hyperphosphataemia is bound to cause hypocalcaemia on its own, and only stimulates the secretion of parathyroid hormone through this mechanism,²³ it is worth noticing that hypercalcaemia, relative or absolute, is characteristic of both conditions^{7,10,12,15,21} (Tables 1 and 2). Accordingly, the serum Ca × P product is increased (Tables 1 and 2), thus creating favourable conditions for the mineralisation of bone matrix.

Hyperphosphatasia. Finally, childhood, adolescence, and acromegaly also have hyperphosphatasia^{7,8,12,24} and an increasing mineralised bone mass^{2,24,25} in common.

Although growth hormone replacement therapy has failed to augment serum 1,25-dihydroxyvitamin D and iPTH in two small series of growth hormone-deficient children^{26,27} the bulk of evidence favours a hypothesis considering growth hormone as the primary driver and co-ordinator of mineral homeostasis and bone growth and mineralisation during childhood and adolescence. The main actions of growth hormone are outlined in Fig. 4.

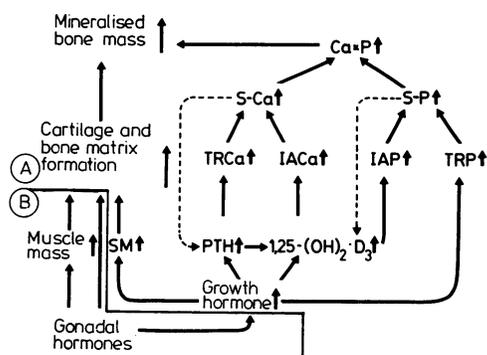


Fig. 4 A unifying concept of the main actions taking part in blood mineral homeostasis and bone formation and mineralisation (A) during childhood, and (B) during puberty and adolescence.

SM=somatomedins, PTH=parathyroid hormone, 1,25(OH)₂D₃=1,25-dihydroxyvitamin D₃, TRCa and TRP=tubular reabsorption of calcium and phosphate, IACa and IAP=intestinal absorption of calcium and phosphate, and Ca × P=the calcium and phosphate ion activity product in plasma. Lines indicate stimulation and the dashes inhibition.

By its several actions growth hormone is uniquely suited for adjusting mineral input, the Ca × P ion activity product, and bone matrix formation.

Rising levels of gonadal hormones, accelerated mineralisation of bone, and the growth spurt are intimately connected.² Simultaneously, rising serum levels of growth hormone,¹⁷ somatomedins,^{18,19} 1,25-dihydroxyvitamin D,²⁰ and alkaline phosphatases^{7,8} are reported. The serum Ca × P product stays constant but high despite increased bone mineralisation. Later, mineralisation continues for some years,^{2,28} while the longitudinal growth slows down and all other variables start falling towards normal adult values.^{7,8,12,17,19,20}

Gonadal hormones may exert their actions in several ways. Firstly, they have been found to promote the secretion of growth hormone.²⁸ Secondly, testosterone may add directly to periosteal apposition²⁸ through its anabolic action on bone-forming cells, or more indirectly by promoting the development of skeletal muscle mass. Much evidence suggests a role for muscle power in bone mass development.^{28,30} Finally, endosteal bone apposition predominates during female adolescence, suggesting an antiresorptive action of oestrogens. They probably act directly on bone as well as through their stimulation of calcitonin secretion.^{31,32}

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Received 17 August 1981