Age-dependent variations in serum 1,25-dihydroxyvitamin D in childhood

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Abstract. Circulating 1,25-dihydroxyvitamin D (1,25-(OH)2D) was measured in 87 children aged 3 months to 15 years, and in 11 adolescents 16—19 years of age. A positive correlation to growth velocity was observed, indicating that the biologically active vitamin D metabolite is an important physiological factor in the regulation of growth and development of the skeleton.

The renal production of the hormonal form of vitamin D — 1,25-dihydroxyvitamin D (1,25-(OH)2D) — is modulated by a feedback mechanism which involves calcium, phosphorus, parathyroid hormone (Boyle et al. 1971; Tanaka & DeLuca 1973; Garabedian et al. 1972), growth hormone (Spencer & Tobissen 1977; Spanos et al. 1978), factors which all show age dependent changes throughout childhood.

It is well established that 1,25-(OH)2D increases the intestinal calcium absorption (Omdahl & DeLuca 1973). Since growth is accompanied by augmented calcium requirement for bone formation, which can only be overcome by an increased calcium absorption, it is obviously of interest to study the serum concentrations of 1,25-(OH)2D in different age groups. Studies comprising minor numbers of children have indicated that serum 1,25-(OH)2D is increased in childhood (Pike et al. 1977; Chesney et al. 1978a,b,c; Scriver et al. 1978), but normal mean and range at different age levels have not been established. In the present study we have measured 1,25-(OH)2D in children of various age groups.

Patients and Methods

The study comprises 50 girls and 48 boys aged from 3 months to 19 years. They were either from the outpatient clinic or admitted to hospital with minor viral diseases. They were not immobilized in bed, and none were suffering from renal or bone disease. Informed consent was given by the parents. Blood samples were obtained in the non-fasting state in the morning. The samples from the subjects aged 16 to 18 years were either non-hospitalized gynaecological patients or healthy blood donors. Serum 1,25-(OH)2D was measured by a competitive protein-binding assay using intestinal cytosol from rachitic chicks and tritiated 1,25-(OH)2D with a specific activity of 110 Ci/mmol (Lund et al. 1979). A serum sample of 0.5—5 ml was extracted by diethyl ether, followed by chromatography on a Sephadex LH-20 column and subsequently by high pressure liquid chromatography. The inter- and intra-assay variations were both 11% and the lower detection limit was 4 pg/ml. Serum 25-hydroxyvitamin D (25-OHD) was determined by a competitive protein-binding assay using rachitic rat kidney cytosol. The inter- and intra-assay variations were

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13.5 and 9.5%, respectively. The lower detection limit was 0.80 ng/ml (Lund & Sørensen 1979). Due to limited amounts of blood, the 25-OHD analysis was only performed in 78 children.

The bone age was evaluated from a X-ray of the left hand and wrist (Greulich & Pyle 1959). Statistical analysis was made using Wilcoxon’s rank sum test for unpaired data and correlation coefficients by Spearman’s rank correlation, and multiple regression analysis.

Results

Fig. 1 shows the distribution of the 1,25-(OH)₂D values according to the bone age from 3 months to 15 years. Values for adolescents and adults are shown on the same figure.

An extremely high mean serum 1,25-(OH)₂D value of 164.7 ± 61.8 pg/ml (sd) was measured in those aged 3 months to 1 year. This was followed
by a fall to a significantly lower \((P < 0.01)\), but still very high, mean level of \(113.5 \pm 49.1\) pg/ml (SD) in those aged 1–2 years. These values were significantly \((P < 0.01)\) higher than those found in any other age group. A negative correlation was found between bone age and serum 1,25-(OH)\(_2\)D up to the age of 8–10 years \((R = 0.56, P < 0.001)\). This was followed by a positive correlation from the age of 8–10 years up to the age of 15 \((R = 0.65, P < 0.05)\). The best fit of the total number of 1,25-(OH)\(_2\)D values calculated by multiple analysis was \(y = 99.3x^{-0.35}\), \((R = 0.68)\).

When chronological age was used instead of bone age, less significance was registered \((R = 0.45, P < 0.01)\). The values of each age group were higher than those measured in adults, and no differences in serum 1,25-(OH)\(_2\)D were found between boys and girls. Table 1 shows the mean serum 1,25-(OH)\(_2\)D values and the predicted mean height velocities in boys and girls (calculated from Tanner et al. 1966). A positive correlation was found with \(R = 0.381\), \(P < 0.01\). Serum 25-OHD did not change with age and did not differ from values found in normal adults (Fig. 2). No correlation was found between serum 25-OHD and 1,25-(OH)\(_2\)D.

**Discussion**

A number of studies have demonstrated that 1,25-(OH)\(_2\)D is elevated in childhood (Pike et al. 1977; Chesney et al. 1978a,b,c; Scriver et al. 1978), but age dependent changes in the hormonal vitamin D form have not been reported. The present results demonstrate the importance of having appropriate control groups when studying disturbances of the vitamin D metabolism in children. Furthermore, subdivision according to bone age is superior to that according to chronological age.

The close relationship between serum 1,25-(OH)\(_2\)D and the height velocity scheme indicated that the hormone is an important determinant for normal growth and development. As shown by Adams et al. (1975), the growth rate of the skeleton appears to be of importance in determining the active calcium transport. Since 1,25-(OH)\(_2\)D is actively involved in both skeleton mineralisation and intestinal calcium absorption the age dependent variations are not unexpected. Similar variations have been described for serum levels of parathyroid hormone (Arnaud et al. 1973) although agreement does not exist (Root et al. 1974). Urinary growth hormone has been shown to increase linearly with age without a bimodal pattern (Hansen 1975), but serum measurements have given conflicting results (Greenwood et al. 1964; Kaplan et al. 1968). Both parathyroid hormone (Tanaka & DeLuca 1973) and growth hormone (Spencer & Tobiasen 1977; Spanos et al. 1978) have been shown to be potent stimulators of the conversion of 25-OHD to 1,25-(OH)\(_2\)D. Sex hormones also enhance this conversion (Baksi & Kenny 1978) which might contribute to the elevated 1,25-(OH)\(_2\)D levels during the growth spurt of adolescence. The hormonal interrelationship is thus very complex, and much research remains to be done to evaluate the relative importance of each factor.

We conclude that very high serum 1,25-(OH)\(_2\)D concentrations are found in childhood. The serum level fluctuates in parallel with the height velocity.
The results stress the importance of having normal values of 1,25-(OH)₂D at different age levels when studying this metabolite in pathological situations in children.

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