Effect of puberty on rates of bone growth and mineralisation

With observations in male delayed puberty

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SUMMARY The bone mineral content (BMC) and body height were measured in 301 normal children and adolescents aged 7–20 years, and in 8 boys with constitutional delayed puberty aged 14–17 years. Serum testosterone was measured in the last group as well as in a subpopulation of the normal children and adolescents. The growth spurt, which coincided with a steep increase of serum testosterone in boys, indicated a great change in skeletal growth and mineralisation in both sexes. After the growth spurt, linear growth slowed down considerably while bone mineralisation rose steeply. When low levels of serum testosterone were maintained, as in delayed puberty, these combined changes of skeletal growth and mineralisation did not occur. It is suggested that gonadal hormones are the true initiators of the short-lived growth spurt as well as of prolonged acceleration of bone mineralisation.

Measurement of bone mineral content (BMC) by photon absorptiometry is a precise, reliable, and easy method for assessing skeletal status (Christiansen *et al.*, 1975a). BMC varies with age and sex and the biological variation is greatest during puberty (Christiansen *et al.*, 1975b). In this period of outstanding growth the chronological age may be a poor indicator of physical development, as there is a wide range of growth and sexual maturation in individuals of the same age (Marshall and Tanner, 1970). In boys, serum levels of testosterone correlate well with the pubertal stage (Knorr *et al.*, 1974), and this is a better measure of physical development than chronological age during adolescence. Determinations of serum testosterone and of various indicators of bone status have been used to assess the physical development in the adolescent, but comparisons

between BMC and serum testosterone have not been reported.

In order to evaluate skeletal growth and mineralisation in relation to age and development we examined BMC, serum testosterone, and body height in normal boys during childhood and adolescence, and in boys with constitutional delayed puberty.

Patients and methods

Normal children and adolescents. A total of 301 normal children and adolescents aged between 7 and 20 years participated in the study. They were randomly selected from pupils at two schools in a suburban area. Pupils below 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. Data on sex, age, and height are given in Figs 1 and 2.

Boys with delayed puberty. Eight boys, referred to the clinic for delayed growth or delayed pubertal development, or both, were chosen. The diagnosis was constitutional or familial delayed puberty

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(Wilkins, 1965) without signs of other endocrine disease. Based on data on pubertal changes in normal boys (Marshall and Tanner, 1970) the retardation in pubertal development was at least 2 SDs in 6 boys and between 1 and 2 SDs in 2 boys. Testicular size was within the pubertal range in all boys.

Methods

BMC was determined by direct photon absorptiometry (Christiansen *et al.*, 1975a). The forearm was fixed in a plexiglass container filled with distilled water. A source of radiation (25 mCi¹²⁵I) and a detector were placed on each side of the forearm to be examined. As these moved across the arm the transmission of photons through the bones decreased depending on the bone mineral content. Because the absorption in plexiglass, distilled water, and soft tissue is almost identical, the measurement was independent of the amount of soft tissue. The scanner started distally on the forearm, moving 4 mm proximally between each scan. The first scan was defined as that demonstrating a distance between radius and ulna of at least 2 mm. The bone mineral content was expressed in arbitrary units as a mean of 6 scans on each forearm. The coefficient of variation in normal subjects is about 2%.

From the 156 normal boys, a subgroup of 103 was randomly selected for determination of serum levels of testosterone. Serum testosterone was measured by radioimmunoassay including a modification of thin-layer chromatography (Pirke, 1973).

Results

Normal children and adolescents. Figs 1 and 2 give the heights and BMC values in boys and girls divided into one-year age groups. Before the growth spurt—between ages 11 and 12 years in girls, and 2 years later in boys—the mean height and BMC increments each year were similar in boys and girls. The respective height increments were 4.5 and 4.7 cm per year, while BMC increased very slowly, 0.14 and 0.09 units per year. After the growth spurt linear growth proceeded slowly at average rates of 1.5 and 0.5 cm per year respectively, while there was a large increase in BMC in both sexes. During this phase of development the BMC increments averaged 2.23 units per year in boys and 1.13 units per year in girls (Figs 1 and 2).

Fig. 3 shows the association between serum testosterone and age in the boys. A sharp increase was found at ages 13 and 14 years, simultaneous with the growth spurt (Fig. 1).

Boys with delayed puberty. For their chronological age of 15.9 ± 0.9 years these boys were small, 155.0 ± 4.8 cm, and had very low BMC values averaging 27.2 ± 4.0 units, corresponding to 66%

Fig. 1 Bone mineral content (O) and height (●) as a function of age in 156 normal boys aged 7–20 years and in 8 boys with delayed puberty (□ and ■). Values given as mean $\pm$ SE of mean.

Fig. 2 Bone mineral content (O) and height (●) as a function of age in 145 girls aged 7–20 years. Values given as mean $\pm$ 1 SE of mean.

Fig 3. Serum testosterone levels (●) as a function of age in 103 normal boys aged 7–20 years and in 8 boys with delayed puberty (□). Values given as mean $\pm$ 1 SE of mean.

Conversion: SI to traditional units—testosterone 1 nmol/l $\approx$ 0.288 ng/ml.

of age-matched normal boys. Their average level of serum testosterone was also low, 2.8 ± 4.1 nmol/l (0.80 ± 1.18 ng/ml) (Fig. 3). All these values are given as mean $\pm$ 1 SD.

Discussion

The onset of the adolescent growth spurt is an important event in skeletal development. In addition to the rather short-lived spurt of growth, it indicates the start of a much more prolonged acceleration of bone mineralisation in both sexes. The timing within the same year of a steep increase of the serum testosterone levels in boys (Fig. 3) with the growth and mineralisation spurt suggests an important role for testosterone in the initiation of both processes and probably in the maintenance over several years of the accelerated bone mineralisation. This view is supported by our observations in boys with delayed puberty: the maintenance of low levels of serum

testosterone postpones the onset of the growth and mineralisation spurt. As the peak height increment and the increase in BMC in girls occur at ages 11 to 12 years, when rising levels of plasma oestrone and oestradiol are being observed (Gupta, 1975), it also seems reasonable to assume that rising levels of these hormones serve as the initiator of both spurts in girls. Gonadal hormones may exert their effects on mineralisation through a complex of mechanisms. Firstly, these hormones may have a direct inhibiting effect on bone resorption, although data from tissue culture studies are conflicting (Atkins *et al.*, 1972; Caputo *et al.*, 1976). Secondly, gonadal hormones are potent stimulators of the production of the biologically active vitamin D₃ metabolite, 1,25 (OH)₂ D₃, in birds (Tanaka *et al.*, 1976), and have also been found to increase plasma calcitonin levels in normal man (Hillyard *et al.*, 1978). Thirdly, androgens may also enhance the skeletal sensitivity to calcitonin, as shown in the rat (Ogata *et al.*, 1970).

The results in the boys with delayed puberty show the importance of using proper reference materials especially in adolescents. If the BMC values are compared with those of age-matched controls, as is done conventionally for the purpose of calcium metabolic investigation, a diagnosis of severe osteopenia would be made. Therefore we suggest that BMC measurements in pubertal boys should be evaluated from testosterone levels or physical development, rather than from chronological age.

Figs 1 and 2 show that the greatest dissociation between skeletal growth and mineralisation takes place during the last years ahead of the growth and mineralisation spurt. This phenomenon may in fact explain the peak incidence of forearm fractures observed in children of 10–14 years of age (Alfaram and Bauer, 1962).

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- Received 6 February 1979

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