Correlations between bone mineral density, insulin-like growth factor I and auxological variables

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Recent studies have shown growth-related changes in spinal bone mineral density (BMD) in children; however, there is less information available on the relationship between BMD and insulin-like growth factor I (IGF-I). The aim of this study was to relate the BMD of the spine and radius with serum IGF-I levels and auxological variables in normally growing children. We used dual X-ray absorptiometry to measure the BMD in the lumbar spine (L1–L4) and distal radius of 121 children (69 boys, 52 girls) aged 3–18 years whose growth velocity was normal. Lumbar and radial BMD increased with age (p < 0.001) and puberty (p < 0.001) and was highly correlated to age, weight, height, body surface and bone age (r = 0.70–0.89 and p < 0.001 for all variables). Partial correlation, with age held constant, was weaker but still significant for most auxological variables. Serum IGF-I concentrations increased slowly during childhood and markedly during early stages of puberty, and correlated with lumbar and radial BMD (r = 0.55 and 0.45, respectively; p < 0.001) and with the auxological variables (p < 0.001). When age was held constant, IGF-I levels still correlated significantly with the auxological variables and with BMD, except in the case of radial BMD in boys. By multiple regression analysis IGF-I, unlike auxological variables, did not reach significance in the ability to predict BMD. Therefore, in healthy children, serum IGF-I levels show a weaker relationship to BMD than do auxological variables.

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Bone mineralization may be affected in slow-growing children, especially those with growth hormone (GH) deficiency (1). Most of the information available on skeletal growth has been attained by measuring the bone mineral density (BMD) of the appendicular skeleton by single photon absorptiometry (SPA) or, in recent years, by measuring the axial BMD by dual X-ray absorptiometry (DXA). It has been shown that the acquisition of bone mineral is gradual in early childhood (2–6), accelerates during puberty (7–13) and is related to auxological variables (8). However, little is known about the relationship between BMD and insulin-like growth factor I (IGF-I). Insulin-like growth factor I, a GH-dependent peptide believed to mediate many of the biological actions of GH, including growth (14, 15), is used as a biochemical variable for the evaluation of normal growth and growth disorders (16–18).

The aim of this study was to relate BMD to serum IGF-I concentrations and auxological variables in normally growing children to evaluate whether circulating IGF-I influences not only linear growth but also BMD. We have used DXA to measure BMD. This technique allows rapid and highly reproducible assessment of bone mineral content with minimal radiation exposure (19–21), making it an ideal method with which to study healthy children.

Materials and methods

Subject selection

We studied 121 healthy children and adolescents (52 girls and 69 boys) aged 3–18 years (Table 1) recruited from our outpatient clinic (Endocrine Unit, Hospital 12 de Octubre). Most of these children had consulted for presumed endocrinopathies, while others were their relatives. All participants were found to be normal and with normal growth velocities. They were not using any drugs that are known to affect bone metabolism and did not have any symptoms of any disease known to impair growth or BMD. Informed consent was obtained from the parents, as prescribed by the local human ethics committee.

Clinical examination

A medical history was obtained from all subjects, and all underwent a physical examination. Physical activity
was estimated from the number of hours per week of recreational physical exercise (range 3–7 h). Their dietary calcium was estimated from a questionnaire, standardized for children’s use, on the average intake of dairy products and other calcium-rich foods (22) (range 850–1400 mg Ca per day). Height was measured barefoot on a wall-mounted stadiometer (Holtain Limited, Crymch, Dyfd, UK) to the nearest 0.1 cm. Their weight was measured while they were in only their underwear on a balance scale (Seca Model 220, Germany) to the closest 0.1 kg. The Tanner pubertal stages (23) were determined according to breast development in females and genital development in males. The children were divided into four groups: prepubertal (Tanner stage 1, N = 83); beginning of puberty (Tanner stage 2, N = 16); advanced puberty (Tanner stage 3, N = 10); and last stages of puberty (Tanner stages 4 and 5, N = 12). The bone age was assessed from a standard X-ray of the non-dominant hand and wrist, evaluated by two observers using Greulich & Pyle tables (24), and the mean value was determined.

**Serum measurements**

Fasting blood samples were taken between 08.00 and 10.00 h and aliquots of serum stored at −20°C for later determination of IGF-I levels. Serum IGF-I was determined by RIA (Nichols Institute, San Juan Capistrano, CA). The assays were performed after acid–ethanol extraction. The detection limit and intra- and interassay variations were 1.7 nmol/l, 5% and 8.4%, respectively.

Serum calcium, phosphate and total protein levels were measured by using colorimetric assays. Total alkaline phosphatase activity was determined enzymatically.

**Bone mass measurements**

Bone mineral density was measured by DXA, which was performed with a QDR 1000/W densitometer (Hologic, Inc., Waltham, MA; software 6.10). In this DXA unit, collimated X-rays are pulsed at 70 and 140 kV through a calibration disk, then through the region of study and finally measured by a detector located above the subject. The BMD is calculated on the basis of the subject’s attenuation of the beam in comparison with that of the reference standard.

The entrance radiation dose to the child is 1–5 mrem, which is less than one-tenth of the exposure from a standard chest X-ray (25, 26). Quality control was performed every day during the study by phantom BMD measurement. The coefficient of variation was 0.32% for the phantom images and 1.3% in vivo.

The anterior/posterior lumbar spine was scanned with the subject in the supine position and physiological lumbar lordosis was flattened by elevation of the knees. Results for lumbar spine density are expressed as the average of L1–L4 values. For the non-dominant forearm scan, the patient was seated on a chair next to the scanner. Distal radial measurements were divided by the computer software into the following three sites: diaphyseal (proximal part of the distal one-third of the radius), mid-distal and ulradial. Results for distal radius was expressed as the average of the three regions. All images were processed by the same investigator. The scanning time for the global region of interest was similar for lumbar spine and distal radius and ranged between 5 and 10 min, depending on the age of the child. Results are expressed as BMD in grams per square centimeter.

**Statistical analysis**

Descriptive statistics and the Kolmogorov–Smirnov test to check the Gaussian distribution were performed. Analysis of variance (ANOVA) was used to compare BMD at the different ages. To analyze the relationship between BMD and the other variables, simple correlation, multiple regression analysis (stepwise method, PIN < 0.05; tolerance < 0.01) and partial correlation, holding the age constant, were performed. A level of p < 0.05 was considered statistically significant. Values are expressed as the mean ± SEM.

**Results**

In both the lumbar spine and distal radius, BMD increased significantly with age in children of both sexes (ANOVA, p < 0.001). Boys and girls did not show significant differences in BMD, except at the age of 10–11 years when boys had a higher distal radius BMD than girls (0.408 ± 0.007 vs 0.379 ± 0.007 g/cm²; p < 0.01) and at the age of 12–13 years when girls had a higher lumbar BMD than boys (0.778 ± 0.031 vs 0.679 ± 0.016 g/cm²; p < 0.01).

In children between 10 and 18 years of age, BMD increased significantly with advancing stages of puberty (p < 0.001). The increase from prepuberty to later
developmental stages was 40% for lumbar BMD and 20% for radial BMD.

There was a good correlation between lumbar and radial BMD \( (r = 0.82; p < 0.001) \), and each was correlated highly with age, weight, height, body surface and bone age (Table 2). Partial correlation between BMD and auxological variables after controlling for age was significant for most of the variables (Table 2).

Mean serum IGF-I levels increased slowly with age in both sexes, showing a steeper increase at the time of normal puberty and then decreasing. A pubertal peak was observed about 2 years earlier in girls than in boys (Fig. 1). In children aged 10–18 years there was a progressive increase in mean serum IGF-I levels between Tanner stages 1 and 3. Individual values showed a large overlap in all pubertal stages (Fig. 2).

There was a significant correlation between serum IGF-I levels and both lumbar and radial BMD \( (r = 0.55 \) and 0.45, respectively; \( p < 0.001 \)). Figures 3 and 4 show the linear correlation in boys and girls. Partial correlation between IGF-I and BMD, with age held constant, was significant for lumbar and radial BMD in girls, whereas in boys it was only significant for lumbar BMD (Table 2).

There was a significant correlation between serum IGF-I levels and age, weight, height, body surface and bone age (Table 3). After controlling for age, IGF-I still

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**Table 2.** Linear correlation coefficients of lumbar (L1–L4) and radius bone mineral density, auxological variables and serum IGF-I in 121 children (69 boys, 52 girls) aged 3–18 years.

<table>
<thead>
<tr>
<th></th>
<th>Simple</th>
<th></th>
<th>Partial (age constant)</th>
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<tbody>
<tr>
<td></td>
<td>L1–L4</td>
<td>Radius</td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>Age</td>
<td>0.70***</td>
<td>0.71***</td>
<td>0.76***</td>
<td>0.81***</td>
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<tr>
<td>Weight</td>
<td>0.70***</td>
<td>0.86***(a)</td>
<td>0.66***</td>
<td>0.86***(b)</td>
</tr>
<tr>
<td>Height</td>
<td>0.75***</td>
<td>0.73***</td>
<td>0.74***</td>
<td>0.82***</td>
</tr>
<tr>
<td>Body surface</td>
<td>0.75***</td>
<td>0.83***</td>
<td>0.72***</td>
<td>0.86***(a)</td>
</tr>
<tr>
<td>Bone age</td>
<td>0.70***</td>
<td>0.83***</td>
<td>0.70***</td>
<td>0.89***(b)</td>
</tr>
<tr>
<td>IGF-I</td>
<td>0.48***</td>
<td>0.63***</td>
<td>0.36**</td>
<td>0.59***</td>
</tr>
</tbody>
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*\( p < 0.05, \) **\( p < 0.01 \) and ***\( p < 0.001 \) (significance of correlation coefficients).

*\( p < 0.05, \) **\( p < 0.01 \) and ***\( p < 0.001 \) (versus boys).

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**Fig. 1.** Mean \((\pm\text{SEM})\) serum IGF-I concentrations in 69 boys (■) and 52 girls (▲) aged 3–18 years. (■) 10–11 years vs 12–13 years, \( p < 0.05; \) 10–11 years vs 14–15 years, \( p < 0.05; \) (▲) 10–11 years vs 12–13 years, \( p < 0.01; \) 10–11 years vs 14–15 years, \( p < 0.01; \) 12–13 years vs 14–15 years, non-significant.
correlated significantly with the auxological variables (Table 3).

The effect of age on BMD was mediated probably by associated changes in height, weight or pubertal status. We performed multiple regression analysis to resolve the independent contributions of the different variables studied on BMD. For lumbar BMD, chronological age, weight and Tanner stage were significant predictors in boys, whereas in girls, only weight and Tanner stage reached significance. For radial BMD, the best predictors were chronological age and body surface in boys and bone age and weight in girls. The ability of serum IGF-I

![Fig. 2. Serum IGF-I concentrations at different pubertal stages in 86 children (55 boys and 21 girls) aged 10–18 years (1: Tanner stage 1; 2: Tanner stage 2; 3: Tanner stage 3; 4: Tanner stages 4 and 5). Stages: 2 vs 1, p < 0.01; 3 vs 1, p < 0.01; 4 vs 1, p < 0.01; 4 vs 3, non-significant; 4 vs 2, non-significant.](image1)

![Fig. 3. Linear regression between bone mineral density (BMD) and serum IGF-I concentrations in 69 boys aged 3–18 years (see Table 2 for simple and partial correlation coefficients).](image2)
levels to predict BMD did not reach significance in any of the equations performed.

Serum calcium, phosphate and total protein levels were normal in all children.

Discussion

Our results on lumbar BMD in healthy children, as measured by DXA, confirm previous reports that show a steady increase in lumbar BMD with age and a steeper increase during puberty (8–13). Our finding of a greater lumbar BMD in girls than in boys between the ages of 12 and 13 years, probably due to the earlier onset of puberty in girls, also agrees with previous reports (8, 9).

The age-related changes in serum IGF-I concentration, shown in Fig. 1, are in line with the findings of Merimee et al. (27). These authors reported that in both males and females serum IGF-I levels increase progressively before puberty, peaking in boys at 15 years of age and in girls between 12 and 13 years of age, and that GH and IGF-I concentrations are greater in females than in males.

We did not study the relationship between growth velocity and serum IGF-I levels, but we did find maximal serum IGF-I levels in girls between 12 and 15 years of age, after the expected time of peak growth velocity (as reported by Tanner). Merimee et al. (27) showed that between 10 and 16 years of age the height velocity correlates with GH in girls but not in boys of a similar age, whereas in males the major pubertal growth spurt correlates with a rise in serum testosterone concentrations.

The BMD and IGF-I showed parallel age and early pubertal increases, but did not correlate with one another when age was adjusted for. Therefore, the question as to whether circulating IGF-I affects BMD still remains. Growth hormone stimulates the differentiation of chondroblast and osteoblast cell lineage through specific GH membrane receptors, whereas IGF-I enhances the proliferation of mature chondrocytes, osteoblast differentiation and matrix formation (28). Growth hormone, acting through IGF-I, increases renal calcitriol hydroxylase activity, calcitriol formation and phosphorus resorption and enhances bone mineral deposition (29–31). However, we found that serum IGF-I and BMD did not always increase in parallel. Serum IGF-I concentrations decrease after the pubertal peak, as reported previously (27, 32, 33), whereas a substantial increase in BMD occurs after menarche (9) and the attainment of peak bone mass occurs years after puberty has finished. During puberty, androgens and

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Table 3. Linear correlation coefficients of serum IGF-I levels and auxological variables in 108 children (63 boys, aged 3–15 years; 45 girls, aged 3–13 years).

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<th></th>
<th>Simple</th>
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<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>Age</td>
<td>0.42***</td>
<td>0.59***</td>
</tr>
<tr>
<td>Weight</td>
<td>0.50***</td>
<td>0.78****</td>
</tr>
<tr>
<td>Height</td>
<td>0.56***</td>
<td>0.69***</td>
</tr>
<tr>
<td>Body surface</td>
<td>0.55***</td>
<td>0.77***</td>
</tr>
<tr>
<td>Bone age</td>
<td>0.53***</td>
<td>0.66***</td>
</tr>
</tbody>
</table>

**p < 0.01 and ***p < 0.001 (significance of correlation coefficients).

* p < 0.05 (versus boys).
estrogens increase dramatically and both of these gonadal hormones, acting through osteoblast receptors, increase bone mineralization (34, 35). Johansen et al. (36) found that in normal males, the pubertal increase in serum testosterone occurs later than the increase in IGF-I and that testosterone levels are low at the time of the peak in serum IGF-I concentration. Sex hormone levels, unlike IGF-I, remain high after puberty, which may account for the attainment of peak bone mass years after puberty has finished. In agreement with this, Dhuper et al. (37) reported that in females ages 13–20 years, BMD correlated with an “estrogen score” (age of menarche, regularity of menses, Tanner breast stage and estradiol levels).

In the study presented here, the increase in BMD with the advancement of pubertal stage was less marked for the radius than for the lumbar spine. This is in agreement with the fact that turnover of bone mass is about eightfold more rapid in trabecular bone and changes in bone synthesis are more marked and noted earlier in trabecular than in compact bone (38). We have no previous reports with which to compare our results on radial BMD measured by DXA. One recent study conducted in 32 normal children aged 3–18 years, in which pubertal stage and comparison between sexes were not stated, shows an age-related increase in radial BMD (39).

Glastré et al. (8) reported a high correlation between lumbar BMD and auxological variables. Because both BMD and auxological variables increase with age, we have performed multiple correlations and partial correlations by holding age constant and have demonstrated that the correlation between BMD and the auxological variables is, in most cases, only explained in part by an effect of age. We conclude that, in healthy children, serum IGF-I levels are related weakly to BMD and that auxological variables are related more closely to bone mineralization than are circulating IGF-I levels.

References

30. Mann DR, Rudman CG, Akinbami MA, Gould KG. Preservation of bone mass in hypogonadal female monkeys with recombinant

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