The effect of two different GH dosages on final height and bone geometry

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Abstract

Background: Growth hormone (GH) has a strong positive influence on bone, stimulating both bone elongation and increase in size. The aim of the study was to compare the effect of two different GH dosages on final height and bone geometry in two groups of GH-deficient children.

Methods: We evaluated 121 children (86 m, 35 f). Group 1 (77 patients) treated with GH at a mean dose of 0.16 mg/kg/week and group 2 (44 patients) at 0.3 mg/kg/week. Bone geometry was evaluated at final height from a digitalized X-ray of the left hand considering the following parameters: metacarpal index (MI), cross-sectional area (CSA), cortical area (CA) and medullary area (MA).

Results: At baseline, group 2 was shorter than group 1 (−1.54 vs −1.01 SDS; p < 0.005), while at final height there was no difference. Height gain was significantly greater in group 2 than in group 1 (1.62 vs 1.13 SDS; p < 0.001). Bone geometry: MI was significantly greater in group 2 (0.62 vs 0.55; p < 0.001) as well as CA (46.87 vs 42.69 cm²; p < 0.005), while MA was significantly lower in group 2 (8.48 vs 11.65 cm²; p < 0.002).

Conclusion: Higher GH doses elicit a significantly greater statural gain and a greater bone cortical area.

Keywords: GH treatment, Bone geometry, Children, Final height, GH dosage
other endocrine disorders. Seventy seven children (57 M, 20 F) age 9.9 ± 3.6 were treated in Pavia with a weekly rGH dosage of 0.16 mg/Kg for a mean period of 6.07 ± 3.2 years (group 1) while forty four children (29 M, 15 F), age 10.3 ± 3.1 were treated in Bolzano with a weekly rGH dosage of 0.3 mg/Kg for a mean period of 5.8 ± 2.7 years (group 2).

The male/female ratio in the two groups was not different (0.66 vs 0.74; NS). They were all regularly followed-up until final height (bone age >15 years in girls and >17 years in boys according to the method of Greulich and Pyle [11]. Height and BMI were converted to standard deviation score (SDS) according to the Italian Standards [12]. However, in order to also take the patient’s genetic potential for growth into account, height was expressed as parentally adjusted height-SDS, i.e. the difference between height-SDS for chronological age and target height-SDS (average height of both parents plus 6.55 cm for boys and minus 6.55 cm for girls).

The difference between the parentally adjusted height-SDS on attainment of adult stature and the one before starting treatment was defined as relative height gain. The auxological features of the patients are reported in Table 1 (raw data) and Table 2 (parentally adjusted).

**Bone geometry**

We used the digitalised X-rays (Dicom files) taken for the assessment of bone age, for the evaluation of bone geometry. The following parameters were evaluated at the level of the 2nd metacarpal bone at its narrowest site, as previously described: outer (D) and inner (d) diameter, metacarpal index (MI = D-d/D: mm), which is a relative measure of the thickness of the 2nd metacarpal cortical bone, total cross sectional area (TCSA: mm²), cortical area (CA: mm²) and medullary endocortical area (MA: mm²). TCSA, CA and MA are not directly measured with this technique, but calculated assuming that the bone is cylindrical. Bone strength was calculated at the metacarpus: it is dependent upon the material property of the metacarpal bones (which cannot be directly measured in vivo) and the cross-sectional moment of inertia which is a function of the fourth power of the cortical ring. By assuming a constant material property, a Bending Breaking Resistance Index (BBRI-1) can be calculated as follows: outer diameter (D) to the fourth power minus inner diameter (d) to the fourth power divided by D [D⁴-d⁴/D]. Furthermore, considering that due to anatomical irregularities, the outer and the inner circumferences are not exactly homogenous, we tried to overcome this problem by calculating the bone strength using the corresponding areas instead of the diameters (BBRI-2), according to the formula: (CSA²-MA²)/√CSA).

**Statistical analysis**

The data were normally distributed and are reported as mean ± SD. Student’s paired and unpaired t-test were used to verify differences within and between groups, after adjusting for height and sex. Simple correlations were used to investigate the association between the different parameters. A P value of less than 0.05 indicated statistical significance. The SAS Enterprise Guide 4.3statistical software (SAS Institute Inc. Cary, NC, 27513, USA) was used for these analyses.

**Results**

**Auxology:** parentally-adjusted height-SDS was significantly higher in group 1 at the beginning of treatment than in group 2 (−1.01 ± 0.83 vs −1.54 ± 1.14; p < 0.005), while no difference between the 2 groups (0.11 ± 0.94 vs 0.15 ± 1.0;NS) was observed at the end of treatment. Group 1 (−1.01 ± 0.83 vs 0.11 ± 0.94; p < 0.01) and group 2 (−1.54 ± 1.14 vs 0.15 ± 1.0; p < 0.001) significantly improved their parentally-adjusted height-SDS, but height gain was significantly higher in group 2 than in group 1 (1.13 ± 0.70 vs 1.62 ± 0.69; p < 0.001) (see Table 2).

Bone geometry: at final height, group 2 showed a greater MI (0.55 ± 0.07 vs 0.62 ± 0.07; p < 0.001), a greater CA (42.69 ± 8.39 vs 46.87 ± 9.39 mm²; p < 0.005) but a significantly lower MA (11.65 ± 4.65 vs 8.48 ± 3.87 mm²; p < 0.002). There was no difference in total cross sectional area (see Table 3 and Fig. 1). BBRI-1 (556.11 ± 167.69 vs 584.66 ± 177.30 mm³; NS), BBRI-2 (389.78 ± 116.57 vs 406.64 ± 123.32 mm³; NS).

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**Table 1 Clinical data**

|                | Number of subjects | Age at the beginning of treatment (yr) | BMI-SDS at the beginning of treatment | Height SDS at the beginning of treatment |
|----------------|--------------------|----------------------------------------|---------------------------------------|-----------------------------------------|
| Group 1        | 77                 | 9.89 ± 3.62                            | −1.5 ± 2.19                           | −1.76 ± 0.77                            |
| Group 2        | 44                 | 10.29 ± 3.13                           | −0.23 ± 1.16                          | −1.97 ± 0.99                            |

**Table 2 Parently adjusted height SDS and relative height gains**

|                | Height 1 (SDS) | Height 2 (SDS) | GAIN |
|----------------|---------------|---------------|------|
| Group 1        | −1.01 ± 0.83  | 0.11 ± 0.94   | 1.13 ± 0.70 |
| Group 2        | −1.54 ± 1.14  | 0.15 ± 1     | 1.62 ± 0.69  |

*a Group 1 vs Group 2 p < 0.005
*b Group 1 vs Group 2 p < 0.001
*c Height 1 vs Height 2 p < 0.001
*d Height 1 vs Height 2 p < 0.01
Correlations
CA was positively correlated with final height \( r = 0.40, p < 0.001 \), height gain \( r = 0.22, p < 0.05 \), final BMI, CSA \( r = 0.92, p < 0.0001 \) and BBRI. MI was positively correlated with BMI at baseline \( r = 0.38, p < 0.0005 \) and at final height \( r = 0.39, p < 0.0005 \) and negatively with MA \( r = -0.82, p < 0.001 \) and CSA \( r = -0.24, p < 0.05 \). MA was negatively correlated with BMI at baseline \( r = -0.29, p < 0.01 \) and at final height \( r = -0.28, p < 0.01 \) and positively with final height \( r = 0.31, p < 0.005 \) and BBRI \( r = 0.57, p < 0.001 \).

Discussion
The major outcome of this study is the confirmation that higher doses of GH elicit a significantly greater statural gain and improvement of the bone geometry. The greater height gain achieved by the children receiving the higher GH dosage is in agreement with previous reports [10, 13–15], emphasizing the advantage of using higher GH doses. Although 0.3 mg/Kg/week is a slightly higher dose than that usually employed in isolated GHD, it is in agreement with the recommendations of the GH Research society [16].

Statural growth is mainly the result of bone elongation under the influence of GH which, moreover, also stimulates the width growth of the bones leading to an increased size. In this study we were able to confirm the positive influence of GH on bone, since the group of children treated more intensively accrued more cortical bone compared to the other group. This finding is also supported by the positive correlations found between cortical area and final height, height gain, cross sectional area and BMI, which are all GH-dependent parameters.

In agreement with our findings, a previous study on adults with growth hormone (GH) deficiency, also showed the strong positive effect of GH treatment on cortical bone, which was exerted by stimulating both periosteal and endosteal bone apposition.

Furthermore, we found a smaller medullary area in group 2 at final height \( p < 0.002 \), suggesting that higher dose of GH could induce a clearer effect on the endosteal side (the smaller the area, the clearer the effect) than on the periosteal side of the bone.

MI and CA were therefore significantly higher in group 2 (higher dose GH), strengthening the advantage of using the higher GH dose. However, these geometrical advantages, possibly due to the low number of subjects, were not sufficient to produce a significant improvement in BBRI, although a trend was observed.

One cannot exclude the possibility that another possible explanation for all these geometrical remarks might be that the children in group 2 were significantly shorter at baseline and so, presumably, they also had smaller bones. In this case, the CSA might prove to be increased more efficiently under higher GH dose. Unfortunately, we were not able to calculate the relative gain in the different parameters of bone geometry in the two groups since in many patients the X-rays taken at the beginning of the treatment with GH were not available. Another possible explanation might have been an overrepresentation of females in group 2, since females are known to have a greater endocortical acquisition during puberty. The male/female ratio in the two groups was however not different and differences in sex and height have been taken into account in statistical analysis.

In our study we did not measure for technical reasons bone mineral density at the lumbar spine, which is an

| Table 3 | Bone geometry and bone strength in the two groups |
|---------|-----------------------------------------------|
| MI      | CA (mm²) | MA (mm²) | CSA (mm²) | BBRI-1 (mm³) | BBRI-2 (mm³) |
| Group 1 | 0.55 ± 0.07 | 42.69 ± 8.39 | 11.65 ± 4.65 | 54.34 ± 11.66 | 556.11 ± 167.69 | 389.78 ± 116.57 |
| Group 2 | 0.62 ± 0.07\(^a\) | 46.87 ± 9.39\(^b\) | 8.48 ± 3.87\(^c\) | 55.35 ± 11.14 | 584.66 ± 177.30 | 406.64 ± 123.32 |

\(^a\) Group 1 vs Group 2 \( p < 0.001 \)
\(^b\) Group 1 vs Group 2 \( p < 0.005 \)
\(^c\) Group 1 vs Group 2 \( p < 0.002 \)

Fig. 1 Bone geometry in the two groups
important marker of peak bone mass, however, bone geometry measured at metacarpal level is strongly related with bone status in other sites [17–19].

One limit of this paper is the fact that the diagnosis of GHD was based on a level of GH after pharmacological stimulation of less than 10 μg/l while now, in Italy, a value of 8 μg/l is considered as more appropriate. This might have allowed the inclusion of some short normal children, according to the new criteria.

Conclusion
We confirm the beneficial effects of larger doses of growth hormone on both height gain and bone accretion.

The study protocol followed the ethical principles outlined by the Helsinki Declaration. Adequate information about the protocol supported the decision-making by the parents.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
FL have been involved in drafting the manuscript have made substantial contributions to acquisition of data, analysis and interpretation of data. MB have made substantial contributions to conception and design and acquisition of data and revising the manuscript critically for important intellectual content. SL have made substantial contributions to acquisition of data and interpretation of data. GF have been involved in drafting the manuscript and revising it critically for important intellectual content. GR conceived of the study, participated in its design and coordination and helped to draft the manuscript, he revised it critically and have given final approval of the version to be published.

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References
1. Brexen K, Hansen TB, Hauge E, Vahl N, Jorgensen JO, Christiansen JS, et al. Growth hormone treatment in adults with adult-onset growth hormone deficiency increases iliac crest trabecular bone turnover: a 1-year, double-blind, randomized, placebo-controlled study. J Bone Miner Res. 2000;15(2):299–300. doi:10.1359/jbmr.2000.15.2.299.
2. Ueland T, Bollerslev J, Flyvbjerg A, Hansen TB, Vahl N, Moselund L. Effects of 12 months of GH treatment on cortical and trabecular bone content of IGFs and OPG in adults with acquired GH deficiency: a double-blind, randomized, placebo-controlled study. J Clin Endocrinol Metab. 2002;87(6):2760–3. doi:10.1210/jcem.87.6.8549.
3. Baroncelli G, Bertelloni S, Sodini F, Saggese G. Longitudinal changes of lumbar bone mineral density (BMD) in patients with GH deficiency after discontinuation of treatment at final height; timing and peak values for lumbar BMD. Clin Endocrinol (Oxf). 2004;60(2):75–84.
4. Isaksson OG, Lindahl A, Nilsson A, Isgaard J. Mechanism of the stimulatory effect of growth hormone on longitudinal bone growth. Endocr Rev. 1987;8(4):242–38. doi:10.1210/edrv-8-4-242.
5. Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Soothweg MC. Growth hormone and bone. Endocr Rev. 1998;19(1):75–99. doi:10.1210/edrv.19.1.0324.
6. Walenkamp MJ, Wit JM. Genetic disorders in the GH-IGF-1 axis in mouse and man. Eur J Endocrinol. 2007;157 Suppl 1:S15–26. doi:10.1530/EJE-07-0148.
7. Yakar S, Courtland HW, Clemmons D. IGF-1 and bone: New discoveries from mouse models. J Bone Miner Res. 2010;25(12):2543–52. doi:10.1002/jbmr.234.
8. Mohan S, Baylink DJ. Role of growth hormone/insulin-like growth factor axis. In: Glowacki J, Rosen CJ, Bleizfkan JP, editors. The aging skeleton. San Diego: Academic; 1999. p. 209–19.
9. Olson LE, Ohlsson C, Mohan S. The role of GH/IGF-I-mediated mechanisms in sex differences in cortical bone size in mice. Calcif Tissue Int. 2011;88(1):1–8. doi:10.1007/s00223-010-9436-2.
10. Radetti G, D’Addato G, Gatti D, Bozzola M, Adami S. Influence of two different GH dosage regimens on final height, bone geometry and bone strength in GH-deficient children. Eur J Endocrinol. 2006;154(3):479–82. doi:10.1530/eje.1.02113.
11. Greulich WW, Pyle SI. Radiographic Atlas of Skeletal Development of the Hand and Wrist. 1959.
12. Cacciari E, Milani S, Baldasso A, Spada E, Bona G, Cavallo L, et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). J Endocrinol Invest. 2006;29(7):581–93. doi:10.1007/s80344-156.
13. Radetti G, Buzzi F, Paganini C, Plotra A, Felippai B. Treatment of GH-deficient children with two different GH doses: effect on final height and cost-benefit implications. Eur J Endocrinol. 2003;148(5):515–8.
14. Wit JM, Rekers-Mombarg LT, Cutler GB, Crowe B, Beck TJ, Roberts K, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr. 2005;146(1):45–53. doi:10.1016/j.pediatrics.2004.08.055.
15. Coelho R, Brook CG, Preece MA, Stanhope RG, Dattani MT, Hindmarsh PC. A randomised study of two doses of biosynthetic human growth hormone on final height of pubertal children with growth hormone deficiency. Horm Res. 2008;70(2):85–8. doi:10.1159/000139149.
16. Growth Hormone Research S. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990–3. doi:10.1210/jcem.85.11.6984.
17. Wilczek ML, Kalvesten J, Alguini J, Beiki O, Brismar TB. Digital X-ray radiography of hand or wrist radiographs can predict hip fracture risk—a study in 5,420 women and 2,837 men. Eur Radiol. 2013;23(3):1383–91. doi:10.1007/s00330-012-2709-0.
18. Forsblad-d’Elia H, Carlsten H. Bone mineral density by digital X-ray radiography is strongly decreased and associated with joint destruction in long-standing rheumatoid arthritis: a cross-sectional study. BMC Musculoskelet Disord. 2011;12:242. doi:10.1186/1471-2474-12-242.
19. Adami S, Zambonari N, Gatti D, Zanfisi C, Braga V, Boggini M, et al. Computed radiographic absorptiometry and morphometry in the assessment of postmenopausal bone loss. Osteoporos Int. 1996;6(1):8–13.