BONE MINERAL DENSITY IN CHILDREN WITH GROWTH HORMONE DEFICIENCY TREATED WITH RECOMBINANT HUMAN GH

Corina Paul[1], I Popa[1], I Velea[1], D Onet[2], Loredana Negru Todorescu[1], B Cismas[1]
[1]2nd Clinic of Pediatrics, University of Medicine and Pharmacy "V. Babes" Timisoara, Romania
[2]Department of Radiology – University of Medicine and Pharmacy "V. Babes" Timisoara, Romania

Abstract

It is known that growth hormone deficit (GHD) in children is associated with decreased bone mineral density and improves with substitutive treatment.The aim of the present paper was to evaluate bone mineral density BMD in GHD children treated with rhGH. The studied lot included 45 children with GHD treated with growth hormone, followed-up in Clinic II Pediatrics between 1997-2004.
Our results are concordant with the literature data showing that BMD is decreased in GHD children and rhGH improves BMD after the first year of treatment.
Key words: Growth hormone deficit, bone mineral density, child.

Background

Data concerning bone markers in monitoring treatment with recombinant human growth hormone (rhGH) are still unclear. Although, numerous studies aim to establish a relationship between rhGH treatment and bone density in children. Beside its wellknown effects on linerar growth in childhood and adolescence, growth hormone exerts also, direct and indirect effects upon bone homeostasis and remodeling. Growth hormone deficit with childhood onset, influences not only linear growth but also bone mineral cumulation, so having, an important role in providing the proper bone density at each age (1).

The bone is an active tissue that is remodeling constantly, the old tissue being replaced by new tissue. In childhood and adolescence, the linear growth means also bone tissue cumulation, both through periostal aposition and growth plates calcification (2). Condrocytes are modulating the bone formation, the remodeling of preexistent mineralized tissue and also of the new bone, being specific in the growing child. Biochemical markers of the bone turnover (alkaline phosfatase, osteocalcin, urinary hydroxiproline, calciuria) are not specific to each process, in children, these markers being correlated also with growth velocity. Thus, these markers increase significantly in the accelerate growth periods, like the first year of life and puberty (2,3).

A significant cumulation of bone mass characterises mostly puberty and adolescence, when aproximately 25% of the total bone mass is achieved, thus, around the age 18, a percentage of 90 % of the peak bone mass (which is complete around the age 25-30) is attained (4). Bone turnover, is influenced by numerous local and general, nutritional and environmental factors, an important role being atributed to the hormonal factors.

From the dietary factors, an important role have calcium and protein intake and also vitamin D, which are essential for growth (5,6). The hormonal factors involved are GH and IGF1, thyroid hormones, glucocorticoids (before puberty) and sex steroids (in puberty and postpuberty). These are acting at different levels of the bone structures, corresponding to their specific bone receptors (fig. 1) (7).

On the other hand, experimental studies proved that exogenous glucocorticoids administration with a therapeutic aim, has a negative effect on the bone mass, inducing osteopenia, while the association of GH therapy is benefical, counteracting the negative effect of the glucocorticoids, through cortical bone mass cumulation (8,9).

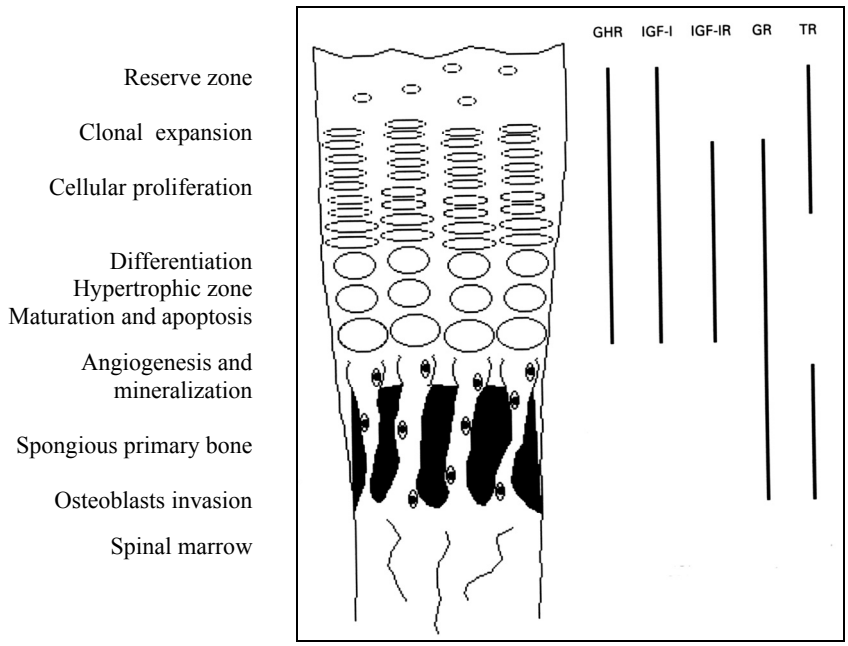
Material and method

The studied lot included 45 children with growh hormone deficiency (GHD), treated with rhGH folowed-up in Clinic II Pediatrics Timisoara between 1997-200. Children were aged between 3 – 15 years (mean age 10,5 ± 3,6), 29 male and 16 female (sex ratio 1,8). The diagnosis criteria for GHD included: height reduced for age (2 DS below the mean), slow height velocity (< 25th centile), delayed bone age, subnormal GH response at 2 provocative tests.

For the evaluation of bone mass density (BMD) we used the dual energy X ray absorbtiometry (DEXA) method in 21 children (aged over 12 years). Results were corelated with the alkaline phosphatse serum levels determined at every visit. In all cases serum calcium and magnesium were also measured.

Results and Discussions

DEXA evaluation showed lumbar osteoporosis and coxofemural osteopenia (fig. 2) in 10 cases (22 %), lumbar osteopenia in 6 cases (13,3%). BMD was normal in 5 cases (11,1%). (fig. 3). Of the 10 cases with lumbar osteoporosis, 2 cases were treated also with thyoid hormones (thyroxine), 4 cases were on plurihormonal therapy (thyroxine, corticoids, and sex steroids – in the last year of treatment) and 4 were in the first year of rhGH treatment, facts that could explain our findings.



Legend: GHR = GH receptor, IGF – IR = IGF1 receptor
GR = glucocorticoids receptor, TR = T3 receptor

Fig. nr. 1 – The action level of hormones in the bone (7).

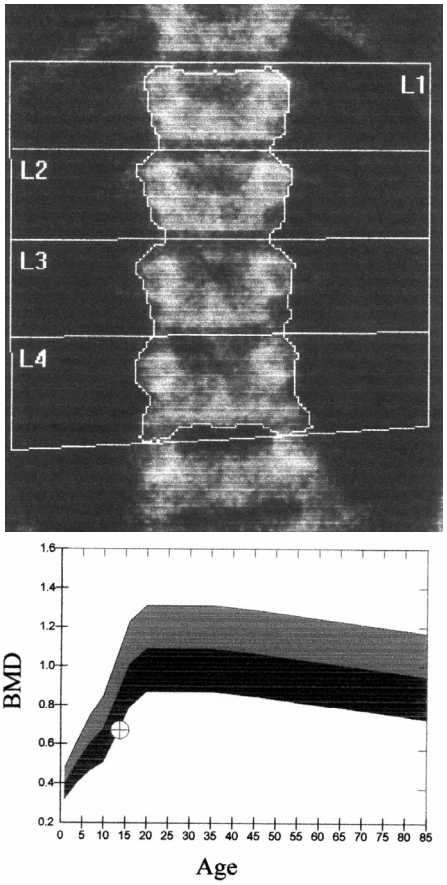


Fig. 2a. - Lumbar osteoporosis.

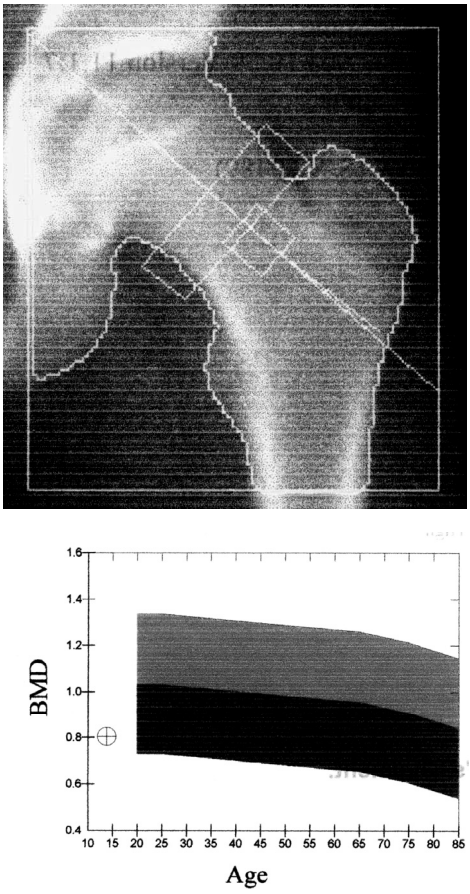


Fig. 2b. - Coxofemural osteopenia.

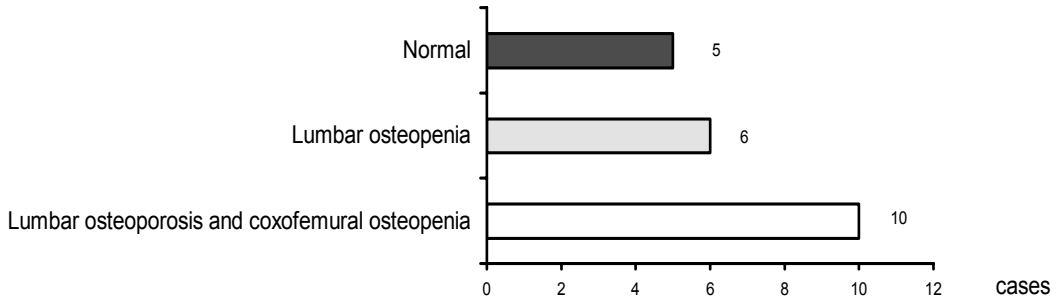


Fig. nr. 3 - Bone Mass Density evaluated by DEXA

Of the 6 patients with lumbar osteopenia, one received also treatment with L-Thyroxine, while 5 were in the second year of rhGH treatment.

Alkaline Phosphatase (APh), determined throughout the treatment period, showed an increase of the serum level above the cut-off normal level in 26 patients, after the first year of treatment (fig. 4), underlying the increase of the bone turnover, with the rhGH treatment. Moreover, in 14 of 26 patients the serum total and ionized calcium was decreased.

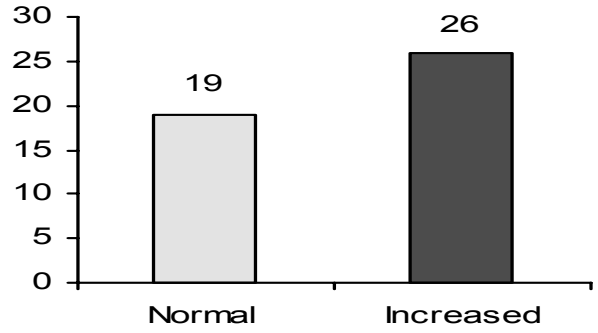


Fig. nr. 4 - Alkaline phosphatase after 1 year of rhGH treatment.

Considering the hypocalcemia and the increased APh, we supplemented the diet with calcium and D vitamin in all these patients. After two years of treatment, serum APh normalised in 15 of the 26 cases, remaining increased in 9 patients (fig. 5).

This aspect is corelating with the literature data, showing that after 6 months of rhGH therapy, bone density starts to recover, with an increase of the bone mineralization and, consecutively, of the bone density.

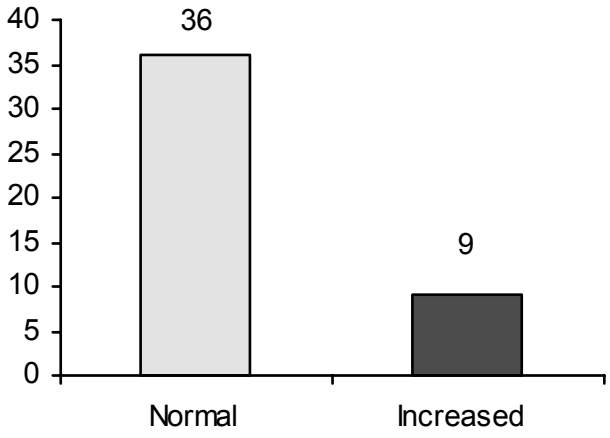


Fig. 5 - Alkaline phosphatase after 2 years of rhGH treatment.

These are still increased in the last year of treatment (at the time of DEXA evaluation) in the 4 cases with plurihormonal treatment (rhGH + thyroxine + corticoids + sex steroids) in whom the evaluation showed osteoporosis (fig. 6).

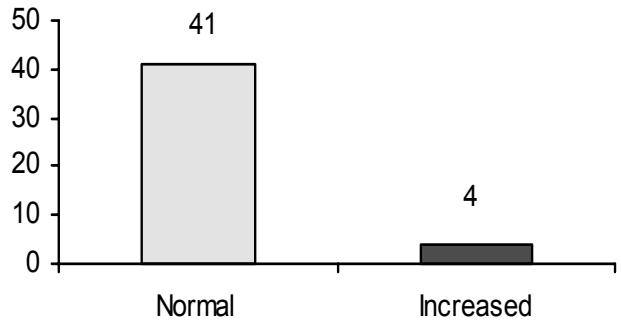


Fig. 6 - Alkaline phosphatase in the last year of rhGH treatment.

Our findings could be explained through many hypothesis. It is known that growth hormone deficit (GHD) in children is associated with decreased bone turnover and mineral density (10). Moreover, previous studies have proved that the initiation of growth hornmone therapy increases bone turnover and, in the same time, diminishes bone density in the first 6 months of treatment, reflecting the gap between the accelerated bone growth and the slower bone mineralization.

Bone turnover seems to be more accelerated in the trabecular than in the cortical bone, fact that explains the stadial correction of the bone density with the treatment, first in the vertebral bodies and only later in the whole body (11,12).

Previous studies have shown that in the first 6 months of treatment, bone density starts to improve, so that after 2 years of therapy, the bone density attains the normal parameters for age and height (12).

This favourable effect of the rhGH therapy on the bone mass, was proven in several studies, but it seems that, in patients receiving suboptimal doses of rhGH, bone density is decreased, before reaching the peak bone mass, sustaining the need of continuing rhGH therapy in these patients, even after attaining the final height, in order to obtain the correction of the bone density.

Worth mentioning that, with all the advantages of the hormonal therapy with rhGH, attainment of the peak bone mass, involves at first, a proper nutritional intake, especially regarding the calcium, D vitamin and protein intake.

D vitamin deficiency is frequent in the population from our country, both because of the weather (insufficient sunny season) and the lack of supplementation with D vitamin, and is responsible for a defficient bone mineralization in a significant number of healthy children and adults. This process will be accentuated in GHD children with or without treatment. In our patients the defficiency in D vitamin intake was associated with that regarding calcium supplements and a rational diet.

In the patients found with osteopenia, this might be explained through the associated effect of the therapy with rhGH, and, in one case, LT4, respectively. Moreover, worth mentioning that 4 of the patients with osteopenia were in the first 2 years of treatment, fact that permits the hypothesis of an insufficient period for the recovery of bone density with the substitutive treatment.

In the patients with osteoporosis, we consider that in the occurence of these modifications all hormonal factors were involved. Considering the unfavourable effect of corticotherapy on the bone density we consider that one of the determinant factors in the occurence of osteoporosis found in the 4 cases with plurihormonal substitution was represented by the association of glucocorticoids in the therapeutic scheme.

On the other hand, in these cases (all females) should be considered also the delayed puberty. It is wellknown the marqued effect of estrogens, at puberty, on the regulation, absorbtion and deposition of calcium in the bone, aiming to attain the optimal bone density and to prevent osteoporosis in adulthood. Moreover, we observed that the administration of low doses of estrogens in girls with hypogonadism determins a significant increase of the absorbtion and retention of calcium and also the decrease of calcium turnover in the whole body (13).

In the 4 cases with osteoporosis, considering the fact puberty was induced with some delay, aiming for a height gain as good as possible, before entering puberty, the lack of sex hormons and also the rapid growth induced by the rhGH treatment, would represent another explanation for the decrease of the bone density. Previous to the DEXA evaluation, the duration of estrogen therapy in these patients (few months), was not sufficient to exert a favourable effect on the bone mass.

We cannot get over the thyroid hormone therapy and their effect on the bones, having in view previous studies showing that under the circumstances of a substitutive long-term treatment, these hormones stress out the bone turnover, determining a decrease of the bone density, the effect being marqued more in the cortical than in the trabecular bone (14,15).

As a conclusion, we might say that bone modifications found in our patients, explained by the numerous factors involved, are concordant with the results reported by other authors showing a decreased bone density

in some GHD patients treated with rhGH comparatively with subjects of same chronological and bone age. Moreover, in these patients, bone turnover markers increase, attaining a peak at the end of the first year of treatment, decreasing than progresively and reaching the normal later (12,16,17), modification observed also in our patients.

Conclusions

1. Bone density is decreased in GHD children
2. Growth hormone treatment ensures the recovery of the bone mineral density after the first year of treatment
3. Glucocorticoids and levothyroxine increases the bone metabolism modifications induced by rhGH, at the initiation of the therapy
4. Osteoporosis and osteopenia are most frequently encountered in children with GHD, following multihormonal substitutive therapy

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Correspondence to:

Corina Paul
E. Celebi Street, No.1-3,
Timisoara 300226,
Romania
E-mail: corinapaul7@yahoo.com