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ALP, b-ALP, PICP and ICTP in children with growth hormone deficiency during the first year of growth hormone treatment

ALP, b-ALP, PICP i ICTP u dzieci z somatotropinową niedoczynnością przysadki w pierwszym roku leczenia hormonem wzrostu

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Key words
growth hormone treatment, bone turnover markers, children

Słowa kluczowe
leczenie hormonem wzrostu, markery obrotu kostnego, dzieci

S u m m a r y

Introduction. Measurement of biochemical markers of bone turnover is an easily accessible method of non-invasive evaluation of bone turnover. In pediatric endocrinology, bone formation and bone resorption markers are useful in predicting the effects of growth hormone therapy.

Aim. Evaluation of selected bone turnover markers and their usefulness in predicting the effects of treatment in children with growth hormone deficiency during the first year of growth hormone therapy.

Material and methods. The studied group consisted of 27 children with growth hormone deficiency during the first year of growth hormone therapy. In all children anthropometric measurements were performed at baseline and at 3, 6 and 12 months of treatment. Growth rate was calculated at baseline and after the first year of growth hormone treatment. Blood concentrations of ALP, b-ALP, PICP and ICTP were measured at baseline and at 3 and 6 months of treatment.

Results. Concentrations of all the measured markers of bone formation increased significantly at 3 months of treatment. The concentration of the bone resorption marker changed significantly at 6 months of treatment. A correlation between serum concentrations of ALP, PICP, ICTP and growth rate in the first year of growth hormone treatment was found.

Conclusions. After the start of growth hormone therapy bone metabolism accelerates significantly and a new balance between the processes of bone formation and bone resorption is established. Changes in levels of bone turnover markers correlate with growth rate in the first year of growth hormone treatment.

S t r e s z c z e n i e

Wstęp. Oznaczanie biochemicznych markerów obrotu kostnego jest łatwo dostępną nieinwazyjną metodą oceny metabolizmu kostnego. W endokrynologii wieku rozwojowego markery kościotworzenia i resorpcji kostnej są przydatne w prognozowaniu efektów leczenia hormonem wzrostu.

Cel pracy. Ocena wybranych markerów obrotu kostnego oraz ich przydatności w przewidywaniu efektów leczenia u dzieci z somatotropinową niedoczynnością przysadki w pierwszym roku leczenia hormonem wzrostu.

Materiał i metody. Badano 27 dzieci z somatotropinową niedoczynnością przysadki w pierwszym roku leczenia hormonem wzrostu. U wszystkich dzieci wykonywano pomiary antropometryczne przed rozpoczęciem leczenia oraz po 3, 6 i 12 miesiącach. Obliczono szybkość wzrastania przed leczeniem oraz w pierwszym roku leczenia hormonem wzrostu. We krwi oznaczano stężenia ALP, b-ALP, PICP i ICTP przed rozpoczęciem oraz po 3 i 6 miesiącach leczenia.

Wyniki. Stężenia wszystkich ocenianych markerów kościotworzenia wzrosły istotnie po 3 miesiącach leczenia. Stężenie markera resorpcji kostnej zmieniło się istotnie po 6 miesiącach leczenia. Wykazano korelację pomiędzy stężeniami ALP, PICP oraz ICTP a szybkością wzrastania w pierwszym roku leczenia hormonem wzrostu.

Wnioski. Po rozpoczęciu leczenia hormonem wzrostu następuje istotne przyspieszenie metabolizmu kostnego i ustalenie nowej równowagi pomiędzy procesami kościotworzenia i resorpcji kostnej. Zmiany markerów obrotu kostnego korelują z szybkością wzrastania w pierwszym roku leczenia hormonem wzrostu.

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INTRODUCTION

Measurement of biochemical markers of bone formation and bone resorption is an easily accessible method of non-invasive evaluation of bone turnover. Markers of bone formation are products of metabolic activity of osteoblasts and markers of bone resorption are products of type I collagen breakdown by osteoclasts. Markers of bone turnover are widely used in both children and adults. In pediatric endocrinology bone turnover markers are considered as useful tools for predicting effects of growth hormone (GH) therapy.

AIM

Evaluation of bone turnover markers and their usefulness in predicting the effects of treatment in children with growth hormone deficiency during the first year of growth hormone therapy.

MATERIAL AND METHODS

The studied group consisted of 27 children with growth hormone deficiency qualified for growth hormone treatment according to applicable criteria. This was a prospective study and covered a period of at least six months before and the first year of growth hormone treatment. The mean age in the studied group was 12.09 ± 3.08 years (5.08-16.0 years). After the first year of treatment pubertal development across the studied group did not exceed Tanner stage 3. Mean GH dose was 0.183 mg/kg/week (0.15-0.21 mg/kg/week). Permission to conduct the study was obtained from the Bioethics Committee of the Medical University of Warsaw. Evaluation of patients included anthropometric measurements and biochemical blood tests. Anthropometric measurements were performed according to current standards at baseline and at 3, 6 and 12 months of growth hormone treatment (1). Body height was standardized in accordance with growth charts published by the Institute for Mother and Child in 2001 for Warsaw children (2). Growth velocity before treatment was calculated based on data from the period of 6-18 months before the start of therapy. The following bone turnover markers were measured in the blood: three markers of bone formation, namely alkaline phosphatase (ALP), bone alkaline phosphatase (b-ALP), procollagen I carboxyterminal propeptide (PICP) and one marker of bone resorption cross-linked carboxyterminal telopeptide of type I collagen (ICTP). Measurements were made at baseline and at 3 and 6 months of treatment. ALP and b-ALP were measured on a Vitros 250 by dry chemistry using Ortho-Clinical Diagnostics reagents (Johnson & Johnson, China, Hong Kong) (reference ranges – prepubertal girls and boys: 150-420 U/L, pubertal girls: 70-560 U/L, pubertal boys: 130-530 U/L). PICP and ICTP μg/L were measured by radioimmunoassay (RIA) using UniQ PICP RIA kit and UniQ ICTP RIA kit (Orion Diagnostica, Finland, Espoo) (reference ranges – PICP: children aged 4-16 yrs 330 ± 130 μg/L, ICTP: prepubertal children 7-16 μg/L, pubertal girls 6-16 μg/L, pubertal boys 8-23 μg/L).

RESULTS

The mean growth velocity in the studied group before the start of GH treatment was 4.7 ± 0.97 cm/year (minimum 2.8, maximum 6.2). During the first year of treatment, mean growth velocity improved significantly to 9.3 ± 1.7 cm/year (minimum 7.2, maximum 12.7) ($p < 0.00001$). Mean ALP, b-ALP and PICP concentrations increased significantly at 3 months. Mean ICTP concentrations did not increase significantly until 6 months of treatment. Mean values of evaluated bone turnover markers are shown in table 1. Mean ALP concentrations increased from 215.1 ± 69.2 U/L at baseline to 295.5 ± 97.1 U/L at 3 months of treatment ($p = 0.001$), mean b-ALP concentrations increased from 66.0 ± 10.5% at baseline to 72.4 ± 6.2% at 3 months ($p < 0.01$), mean PICP concentrations increased from 381.9 ± 139.7 μg/L at baseline to 480.3 ± 157.9 μg/L at 3 months ($p < 0.05$). Changes in ALP, b-ALP and PICP concentrations in the following three months (a comparison between levels at 3 months and at 6 months of treatment) were not statistically significant (p = NS). Mean ICTP concentrations increased from 13.5 ± 2.9 μg/L at baseline to 18.2 ± 5.8 μg/L at 6 months of treatment ($p < 0.001$). Positive correlations between concentrations of ALP ($r = 0.41$, $p < 0.05$, fig. 1) at 3 months of treatment, PICP ($r = 0.55$, $p < 0.05$, fig. 2) at 3 months of treatment, ICTP ($r = 0.43$, $p < 0.05$, fig. 3) at 6 months of treatment and growth velocity in the first year of treatment were found. No such correlation was found for b-ALP.

Table 1. ALP, b-ALP, PICP and ICTP at the start of GH treatment and at 3 and 6 months of treatment.

Bone marker	At baseline	At 3 months	At 6 months
ALP (U/L)	215.1 ± 69.2	295.5 ± 97.1*	303.1 ± 118.5*
b-ALP (%)	66.0 ± 10.5	72.4 ± 6.2*	71.0 ± 11.3*
PICP (μg/L)	381.9 ± 139.7	480.3 ± 157.9*	469.9 ± 132.8*
ICTP (μg/L)	13.5 ± 2.9	17.9 ± 4.5	18.2 ± 5.8*

*statistically significant differences in comparison with baseline

DISCUSSION

The main objective of growth hormone therapy in children is to improve final height. This effect is primarily dependent on direct action of growth hormone on bone and its indirect action involving IGF-1. This includes influence on the growth plate, increasing bone mass and bone remodeling. A strong relationship has been found between GH/IGF-1 axis and concentrations of serum markers of bone turnover in healthy children and in children with growth hormone deficiency treated with growth hormone (3-6). Measurement of biochemical markers of bone turnover is an easily accessible method of non-invasive evaluation of bone turnover. Markers of bone formation are products of metabolic activity of osteoblasts and markers of bone resorption are products of type I collagen

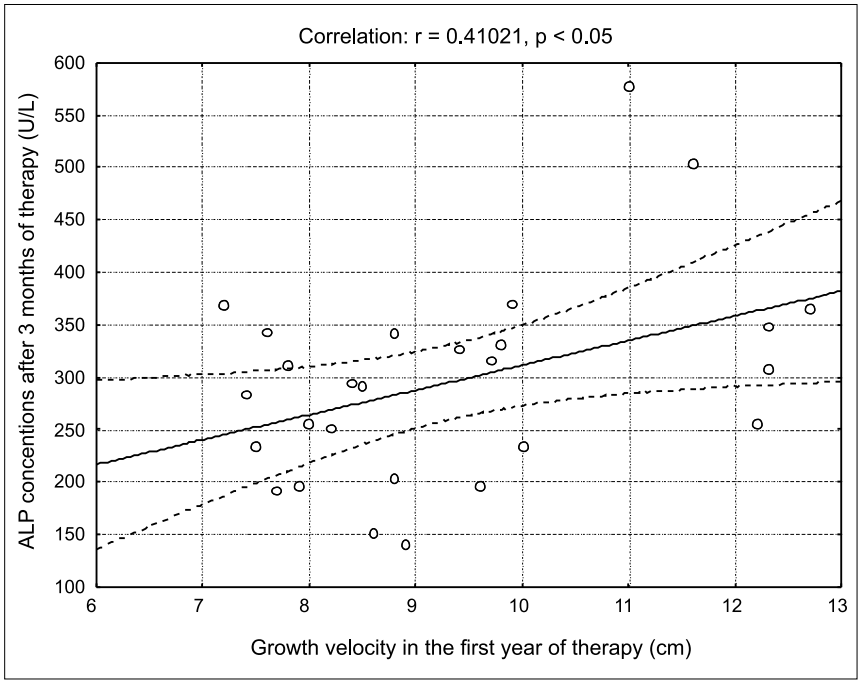

Fig. 1. Correlation between ALP after 3 months of therapy (U/L) and growth velocity in the first year of GH therapy (cm).

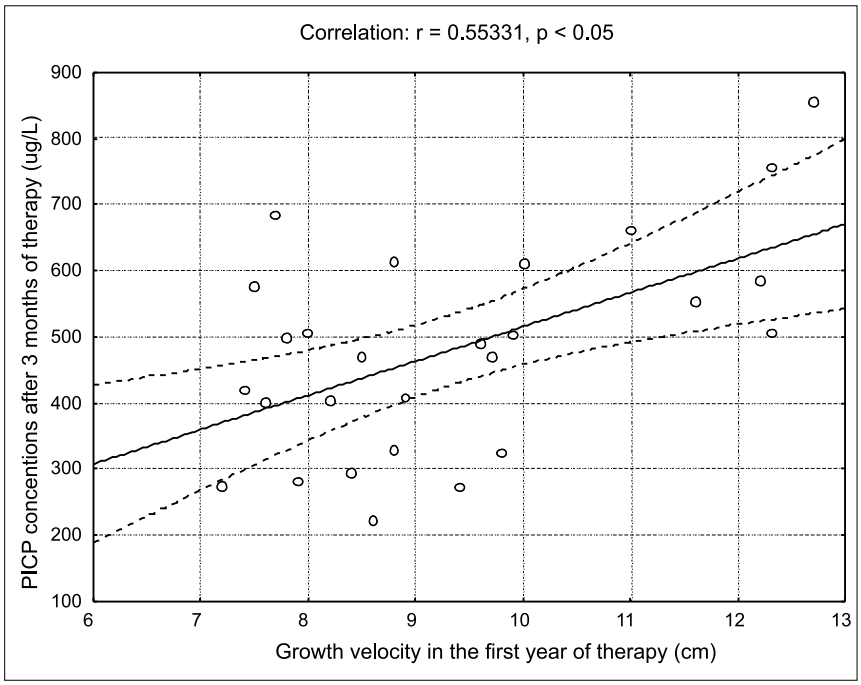

Fig. 2. Correlation between PICP after 3 months of therapy (μg/L) and growth velocity in the first year of GH therapy (cm).

breakdown by osteoclasts (7). Markers of bone formation are alkaline phosphatase (ALP), bone alkaline phosphatase (b-ALP), procollagen I carboxyterminal propeptide (PICP), procollagen I aminoterminal propeptide (PINP) and osteocalcin (OC). Bone resorption markers are cross-linked carboxyterminal telopeptide of type I collagen (ICTP), pyridinoline (PYD), deoxypyridinoline (DPD), collagen type I crosslinked N-telopeptide (NTX), collagen type I crosslinked C-telopeptide (CTX), tartrate-resistant acid phosphatase (TRAP) and hydroxyproline (Hyp) (7-10). Markers of bone turnover are widely used in both children and adults. It is useful in the diagnosis and monitoring of the course of treatment of patients with metabolic bone diseases such as osteoporosis (11), but also in other fields such as cardiology (12, 13), oncology (14, 15) and in critically ill patients (16). In pediatric endocrinology bone turnover markers are useful tools for predicting effects of growth hormone therapy. In Poland recombinant human growth hormone (GH) is licensed for short stature associated with growth hormone deficiency (GHD), Turner syndrome (TS), Prader-Willi syndrome (PWS) and chronic renal insufficiency (CRI) (17). In other countries GH is also licensed for

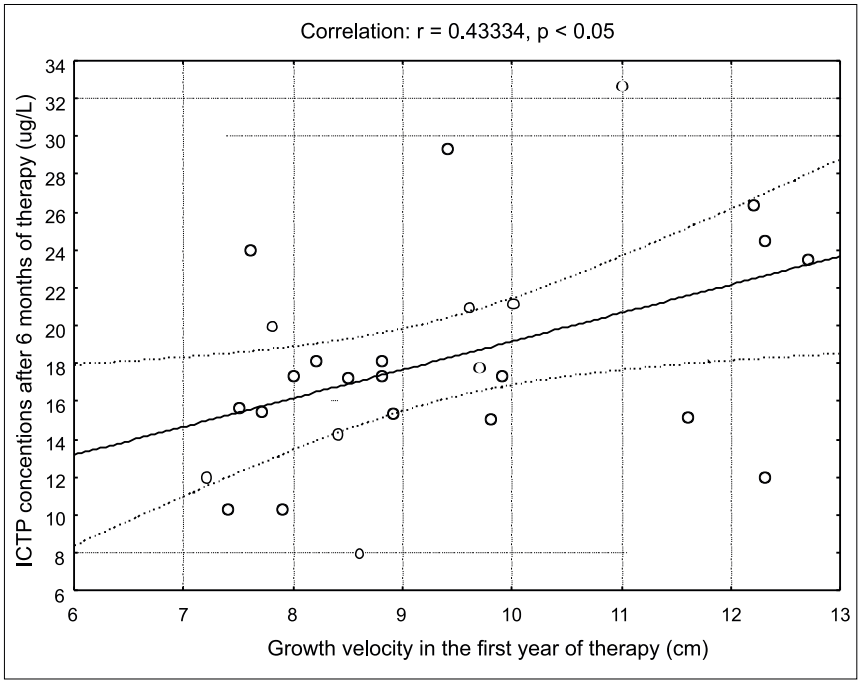

Fig. 3. Correlation between ICTP after 3 months of therapy (μg/L) and growth velocity in the first year of GH therapy (cm).

short stature associated with short stature homeobox-containing gene deficiency (SHOX-D) and being born small for gestational age (SGA) (18). Start of growth hormone therapy is associated with significant increases in growth velocity and bone metabolism, which correlate with an increment in the concentrations of bone turnover markers (3, 19-23).

The aim of our study was to evaluate changes in the concentrations of selected markers of bone formation and bone resorption in children with growth hormone deficiency in the first year of growth hormone treatment and to assess the relationship between these changes and the effects of GH treatment. We have shown that several months after the start of growth hormone therapy significant changes in the concentrations of bone turnover markers can be observed. In the case of markers of bone formation a significant increase can be seen as early as at 3 months of treatment, whereas in the case of the bone resorption marker ICTP it occurs later – at 6 months of treatment. Our study also confirmed the usefulness of the evaluated markers in predicting the effects of treatment achieved after one year of GH therapy, with the exception of b-ALP, but the data available in the literature confirms a high predictive value of this marker. Tobiume et al. measured the serum levels of b-ALP in 363 healthy children and in 20 GH-deficient children and found that b-ALP levels are a useful marker for bone formation because b-ALP levels increased when the growth rate accelerated during puberty or catch-up growth after the start of GH treatment. They suggest that serum b-ALP is a good predictor of the effects of GH therapy, because its serum level at 3 months of treatment correlates with growth velocity in the first year of GH therapy. They also found that serum b-ALP levels significantly correlate with PICP ($p < 0.0001$, $r = 0.447$) and OC ($p < 0.0001$, $r = 0.433$) (3). Korpal-Szczyrska et al. also consider serum b-ALP at 3 months of GH treatment to be a good early predictor of growth rate during the first 12 months of therapy in children with GHD ($p < 0.05$, $r = 0.77$) (19). Baroncelli et al. (24) analyse the dynamics of bone turnover in GH-deficient children during long-term treatment. They measured growth velocity and serum concentrations of OC, PICP and ICTP until final height. Osteocalcin reflects extracellular matrix mineralization, and thus indicates osteoblast function. PICP is released during secretion of type I collagen. ICTP is a marker of type I collagen breakdown during bone resorption. Concentrations of those markers were reduced at baseline in comparison with healthy prepubertal children and increased significantly ($p < 0.0001$) during the first year of treatment with a peak at 12 months. The change in the concentrations of OC, PICP and ICTP at 6 and 12 months of treatment with respect to the baseline values was not related to growth rate during long-term treatment or final height. After the first year of treatment, OC and PICP levels progressively decreased, whereas ICTP levels remained stable until final height (24). Most authors have analyzed bone turnover markers only in the first year of growth hormone therapy, usually in prepubertal patients, and have found a simultaneous increase in both markers of bone formation and bone resorption. In our study an increase in the concentration of ICTP was found as early as at 3 months of treatment, which is consistent with the results presented by other authors. However, a statistically significant increment occurred later than an increase in markers of bone formation and was statistically significant as late as at 6 months of treatment. This difference may

result from the selection of the studied patients (different stages of pubertal development) or the small size of the group, but the delayed increase in the concentration of ICTP may suggest that the processes of bone formation and resorption do not occur at the same rate and the balance between them is dynamic. This issue was pointed out by Laursen et al. (6) with reference to results published by Baroncelli et al. According to Laursen et al. (6) they could suggest a domination of resorption over formation of bone following longer-term GH therapy. Stein et al. reported that the synthesis of PICP is down-regulated when bone matrix mineralization is achieved (25). The observed decrease in levels of bone formation markers might be explained by an enhanced bone mineral density in response to GH treatment. On the other hand, as Baroncelli et al. state (24), ICTP does not only reflect bone resorption, because it is also produced at extraosseus sites, and similarly PICP derives from fibroblasts. Thus, they advise caution in the use of bone markers as quantitative indices of bone formation and resorption. The observations by Baroncelli et al. concerned long-term GH therapy, but similar differences can also be seen in the first few months of GH therapy. While analysing results of measurements of concentrations of bone turnover markers it should be taken into account that data depending on total bone and collagen metabolism are also influenced by height and weight, and should be corrected for body surface area, weight or urine creatinine (26). In light of the available research, it seems that the evaluation of bone turnover markers is a good method for monitoring and predicting the effects of GH treatment, but it should be remembered that the processes of bone metabolism do not only depend on the influence of GH and IGF1 on bone, but also on a number of other factors that can significantly modify bone turnover markers levels.

CONCLUSIONS

After the start of growth hormone therapy bone metabolism accelerates significantly and a new balance between the processes of bone formation and bone resorption is established. In the present study a significant increase in markers of bone formation was observed earlier than an increment in the concentrations of bone resorption marker ICTP. Changes in levels of bone turnover markers correlate with growth rate in the first year of GH treatment. Evaluation of bone turnover markers can be a useful tool for predicting response to GH therapy.

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received/otrzymano: 02.07.2014
accepted/zaakceptowano: 19.09.2014