INVITED COMMENTARY

Markers of bone turnover in the evaluation of the response to GH treatment in GH-deficient children

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Growth rate and final height are hard end-points when assessing the response to growth hormone (GH) treatment of growth-retarded children. Considering the pronounced variability of height measurements, a 6- to 12-month period of observation is needed to detect a response to GH. Only by employment of the more time-consuming and observer-dependent examination, knemometry (1), can a valid measure of short-term growth be obtained. Other methods to monitor the effects of GH treatment are therefore sought. Response is known to vary considerably and some children may, in practice, be non-responders, which makes short-term monitoring particularly important. With the prediction of growth response after short-term GH therapy, unnecessary inconvenience for non-responding children and their families, as well as expense for the community, may be avoided. The problem is of particular importance during treatment of children who are not clearly GH deficient (GHD), such as patients with Turner's syndrome, familial short stature or partial GH deficiency.

A study in short non-GHD prepubertal children has reported an inverse relationship between spontaneous GH secretion and growth response (2). Thus, an estimation of GH secretory capacity may help to select probable responders before the start of GH therapy. One of the most commonly used markers of GH therapy is insulin-like growth factor (IGF)-I. Serum IGF-I levels, which increase following GH administration, have been reported to be correlated with growth (3). The effect of GH on bone metabolism could be either direct or mediated through IGFs or IGF-binding proteins (IGFBP), and IGFBP-3 has also been proposed as a marker of the effects of GH in bone.

Recently, markers of bone metabolism have been introduced, and changes in their levels during GH treatment, in particular in its early phase, may be valuable indicators of therapeutic efficacy. GH stimulates bone turnover in GHD patients and in healthy subjects, as reflected by simultaneous increments in the levels of markers of bone formation and resorption in serum or urine (4, 5). Positive correlations have been reported between growth velocity and levels of the aminoterminal propeptide of type III collagen (PIIINP) (6), and of the carboxyterminal propeptide of type

I procollagen (PICP) (7), which both reflect bone formation. Early phases of the bone remodelling process generate the amino-terminal propeptide of type I collagen (PINP), being involved in the deposition of collagen, and PIIINP, reflecting extraosseous collagen formation. Type I collagen primarily relates to mineralized bone and soft tissue, whereas type III collagen primarily derives from soft connective tissue (8). The reduced bone turnover in GHD children may be causally associated with a diminished bone mineral density (BMD). To what extent changes in bone dynamics can be translated into increased final height, improved BMD or enhanced bone strength in adolescence and adulthood is, however, still uncertain.

In this issue of the *European Journal of Endocrinology*, Baroncelli *et al.* (14) report on the impact of GH on the dynamics of three different bone markers in GHD children (osteocalcin, PICP, and carboxyterminal telopeptide of type I collagen (ICTP)). Twenty-four children, who have received GH for 9 years on average, have been followed. The bone matrix protein osteocalcin (OC), reflecting extracellular matrix mineralization, and thus indicative of osteoblast function, and PICP, which is released during secretion of type I collagen, both reflect bone formation. ICTP is a marker of type I collagen breakdown during bone resorption. Levels of all three markers were reduced at baseline, and increased in response to GH therapy, with peak levels attained after 12 months.

Concentrations of the bone markers remained above baseline levels until final height was achieved. However, OC and PICP levels declined while ICTP levels remained stable during the entire observation period. This could suggest a preponderance of resorption relative to formation of bone following longer-term GH therapy. The synthesis of PICP has been reported to be down-regulated when bone matrix mineralization is achieved (9). Thus, the observed decrease in levels of formative bone markers might be explained by an enhanced BMD in response to GH treatment. On the other hand, as Baroncelli *et al.* state (14), ICTP reflects not only bone resorption, as it is also produced at extraosseous sites, and similarly PICP also derives from fibroblasts. Consequently, they warn against the use of the bone markers as quantitative indices of exclusively bone formation

and resorption respectively. Finally, data depending on total bone and collagen are also influenced by height and weight, and should therefore probably be corrected for body surface area, weight or urine creatinine (10).

Several other metabolic markers, reflecting bone formation and resorption, have become available during recent years. Serum levels of the bone-specific isoenzyme of alkaline phosphatase is an index of osteoblastic activity, reflecting extracellular matrix formation. Hydroxyproline, a marker of collagen breakdown, has been replaced by markers with improved specificity and sensitivity, allowing a more precise description of GH-induced bone turnover. The cross-links pyridinoline and deoxypyridinoline, which are formed in type I collagen, are excreted in the urine, and serve as specific markers of bone resorption. Other recently introduced markers of bone resorption are serum and urine levels of N-terminal telopeptide cross-links, and serum crosslap levels.

Concerning the dynamics of bone markers, the results of the present study are largely in accordance with previous reports in untreated GHD patients of reduced circulating levels of bone markers, which increase in response to GH therapy. In a number of these studies, levels of some of the markers also decreased after longer-term GH exposure. In a study in adult GHD patients, levels of PICP and ICTP increased during the initial 6 months of GH therapy, but had returned to baseline after 42 months, whereas BMD plateaued at a peak level after 36 months (11), indicating that the effect of GH was conserved despite 'normalized' bone marker levels.

Markers of bone metabolism have been reported to display pronounced inter- and intra-individual, circadian, and day-to-day variability (10). The present study has accounted for sampling conditions and possible circadian and day-to-day variations. These factors were found to be of minor importance in the results.

The decline in the growth rate observed during the 9-year study period might reflect a shorter period of pubertal growth in GHD children. Secondly, a decrease in bone turnover may occur with advancing puberty, in parallel with changes in circulating levels of sex hormones. In general, sex hormones increase bone marker levels (e.g. PICP, OC) (12). Down-regulation of markers of bone formation secondary to achievement of a steady-state level of bone matrix mineralization, as mentioned above, could be another explanation. Finally, sensitivity to the GH doses employed may have gradually waned.

The present study disappointingly failed to demonstrate any relationship between short-term (after 6 and 12 months of GH therapy) changes in bone marker levels and long-term growth rate or final height. A previous study reported positive correlations between levels of PIIINP and PICP after 3 months of GH treatment and relative height score at 12 months (13). The existence of a positive relation between short-term

changes in bone turnover and growth has been reported by many, but not all, studies. The hypothesis that levels of bone markers predict the long-term response to GH was not, however, supported by the present longer-term study. The authors suggest that other factors could influence longitudinal growth independently of the effects of GH on bone turnover. Sex hormones may be proposed as one of these factors. Although BMD measurements in growing children can be associated with errors, it would have been a strength of the present study if BMD data had been available, as a positive relationship might exist between changes in bone turnover and BMD.

Perhaps a realistic expectation would be that early changes in bone marker concentrations predict an essential part of the variability of growth seen in the early phase of GH therapy. Thereby, dynamics of bone turnover could serve as an instrument, giving clinicians an indication of individual responsiveness to GH, where clear increases or lack of changes represent the extreme limits of response.

The difficulties described in finding a single or a few parameters that enable a prediction of the response to GH treatment is to some degree parallel with the problem in unmasking doping with GH in sports by one sensitive and specific metabolic marker. In both cases, the employment of a combination of markers reflecting different aspects of GH action on, for example, bone, circulating GH isoforms and the IGF axis, may prove to be superior.

In summary, increased knowledge of the dynamics of bone turnover during short- and longer-term GH administration enhances the application of metabolic bone markers in monitoring response to treatment. Even though an optimal growth response to GH cannot be predicted solely by changed bone marker levels, other better indicators are not available. In order to ensure selection of appropriate candidates for GH treatment a precise diagnosis is necessary. Standard sampling procedures are prerequisites in order to take into account circadian and day-to-day variability and, furthermore, the impact of sex hormone status should be revealed. It may be suggested that the employment of a combination of different specific markers of bone resorption as well as bone formation may be complemented by markers reflecting the IGF axis.

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Received 8 March 2000

Accepted 14 March 2000