INVITED COMMENTARY

Growth prediction with biochemical markers and its consequences

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In this issue of the European Journal of Endocrinology Tapanainen et al. (1) report on new collagen metabolites in the prediction of response to growth hormone therapy in short children. They analyse the collagen synthesis marker of collagen type I (P1CP) and collagen type III (P3NP) and describe significant correlations between these markers in the early treatment phase and the relative height increase over the first 6 and 12 months of therapy. These data are in accord with the well-known growth dependency of the activities of several biological bone and collagen markers such as alkaline phosphatase and osteocalcine.

Two peaks of high activity of these markers are typically seen during the first 2 years of life and during the pubertal growth spurt. During these two phases growth velocity and bone turnover are also highly stimulated. Overall the serum levels and activities of the various biochemical markers of bone and collagen metabolism are four to five times as high as in adults. These elevated activities are mainly due to growth and remodelling processes in the epiphyseal growth plates. Various hormones and biomechanical forces regulate cell activity in the growth plates. Chondrocytes synthesize the cartilage matrix composed of proteoglycans and collagen. In the lower hypertrophic zone of the growth plates, cartilage cells degenerate releasing calcium and alkaline phosphatase. This process leads to the mineralization of the cartilage matrix. In the metaphyseal junction osteogenic cells differentiate and deposit first osteoid (primary spongiosa). During this process, the osteoblasts synthesize collagen type I, which is the predominant collagen in bone, and alkaline phosphatase, osteocalcine and many other bone proteins. The primary spongiosa is directly resorbed by osteoclasts, following extensive synthesis of so-called secondary spongiosa. During this remodelling process, various segments of mature collagen structures such as the matrix crosslink components pyridinoline and deoxypyridinoline, N- and C-terminal telopeptides and the main amino acids of collagen (hydroxyproline and the glycosylated forms of hydroxylysine) are released. The activities of the osteoblasts and the osteoclasts are coupled in this internal remodelling process. Further very important adaption processes of the bone occur in the cortical bone during growth. Cortical bone must continually adapt itself to the growth-dependent changes and to biomechanical forces. During growth, especially during puberty, muscle strength also increases markedly. Correspondingly, osteoblasts of the periost are activated to synthesize lamellar bone structures. Depending on the growth phase and biomechanical usage, there is either endosteal osteoclastic bone resorption or, even more diaphysial osteoclastic bone formation, which leads to a thickening of cortical bone. This process, in which osteoblasts and osteoclasts are not coupled, is referred to as modelling.

For the investigator of biochemical markers, it is important to know the three most important bone processes of growth, remodelling and modelling in order to interpret and evaluate data. In any case, the activities or levels of biochemical markers describe the summing up of these three processes.

A further problem is the tissue specificity of the various biochemical parameters. Collagen type I is the main collagen of bone, but it is also synthesized in many other tissue types. In contrast, only traces of collagen type III can be detected in bone. Changes in the synthesis markers of collagen type III probably correspond to growth in other tissues, like skin, vessels, ligaments etc. Furthermore, many collagen and bone markers show a pronounced circadian rhythm. The parameters of bone resorption are often increased during the night, especially during the early morning hours, in comparison to daytime values. Osteoblastic (bone formation) markers show, on the other hand, higher activities in the afternoon in comparison to morning or night. Depending on the type of marker, strict standardization of sampling conditions is necessary. Many parameters also have a high day-to-day variability. For many parameters, the question of direct dependency on the total mass of bone and collagen, which is dependent on height and weight, still has to be clarified. In these cases, normalization to area of body surface, weight or urine creatinine concentrations should be carried out. Otherwise one will find decreased biological markers related to chronological age in many children with short stature (i.e. low bone mass), even in the case of normal growth rates. These limitations explain the high variability of bone and collagen markers during childhood and adolescence.

During the last 10 years many research groups, including the one of Tapanainen (1), have given special...
attention to new parameters of collagen metabolism in children with growth disorders and under treatment with growth hormone (2–8). Many papers have described correlation coefficients between 0.7 and 0.8 for the relationship between activities of biochemical markers and growth during the first year of growth hormone treatment. We were able to verify these results in investigations of healthy children by analysis of the collagen resorption marker galactosyl-hydroxylysine in urine (9). On the basis of data from the literature and the available data from Tapanainen, one can speculate that at best about 60–70% of the variability of growth during the first year of growth hormone therapy can be predicted by analysis of biochemical markers within the early phase (1–3 months) of therapy. Improvement might be possible if the above mentioned limitations are given more consideration.

One could speculate whether a combination of cellular activity markers with the growth parameters such as insulin-like growth factor-I or insulin-like growth factor-binding protein-3 would lead to a significant improvement. A combination of biochemical markers during the early phase of growth hormone therapy with auxiological data before therapy (growth velocity, deviation from the genetic target height) would also be plausible. Future work must show if multi-variant analysis or the development of a score will make possible a more certain prediction of growth (10).

**Consequences?**

Such extensive analyses and calculations only make sense if they result in diagnostic or therapeutic consequences. The goal of determining biochemical parameters and other predictive factors is to distinguish between patients, especially between those who will benefit from growth hormone therapy and so-called non-responders. The fundamental problem is, however, that for many indications (Ulrich–Turner syndrome, familial short stature etc.), successful or unsuccessful growth development during therapy has not been characterized. One of the main tasks of paediatric endocrinology is therefore to establish stricter standards for the evaluation and interpretation of manipulated growth, especially in the first year of therapy. A definition of responder and non-responder during the first treatment year is mandatory, especially for non-endocrine growth disorders. When these problems are better resolved, biochemical markers will surely represent an important decision maker in the early evaluation of growth, not only under growth stimulating therapies but also for the detection of side-effects (steroids). The results of growth hormone therapy in children without endocrine disorders vary so greatly that it presents a challenge to separate very early responders from non-responders.

This is not merely a financial matter. There is also an enormous psychological burden when a patient with short stature realizes after 1 to 2 years of therapy that even daily injections have not helped him or her. In addition, if therapy could be stopped earlier in non-responders, the mean growth increase of the responder group would, of course, improve.

It can be summarized that biochemical markers of bone and collagen metabolism currently describe growth response during the early phase of therapy better than other indicators. For meaningful future use, however, the growth development of responders and non-responders during the first year of treatment must be clearly defined, especially for non-endocrine growth disorders. This is the basic requirement to describe sensitivity and specificity of early prediction of successful growth stimulation.

**References**


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