Pubertal Changes in Biochemical Markers of Growth

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Key Words

Adolescents · Bone markers · Children · Growth hormone · Growth hormone deficiency · Leptin · Puberty

Abstract

Puberty is a crucial period of life during which dramatic hormonal changes induce notable modifications in linear growth, bone mass and body composition. These changes are associated with variations in some biochemical parameters such as markers of bone turnover and leptin, which may reflect changes in bone growth and fat mass, respectively. Children with growth hormone (GH) deficiency have reduced concentrations of bone markers, which increase during GH administration, while the levels of leptin decrease. There have been few studies analysing the behaviour of bone markers during puberty in GH-treated GH-deficient patients and no studies analysing the behaviour of leptin. Results from a longitudinal study showed that there was no change in serum osteocalcin, carboxy-terminal propeptide of type I procollagen, and cross-linked carboxy-terminal telopeptide of type I collagen levels during puberty in GH-treated GH-deficient children. Some studies have shown that changes in markers of bone turnover and leptin after short-term GH treatment may predict the growth response (at 6–12 months) to GH administration in GH-deficient children. At present, insufficient data are avail-

able for the clinical use of these parameters as markers of growth response during pubertal development and as predictors of long-term growth response to GH treatment in children with GH deficiency. Nevertheless, the use of more and possibly new markers might improve the accuracy of growth prediction models in the future.

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Introduction

Puberty is characterized by profound somatic changes, such as a notable increase in linear growth, modifications in body composition and attainment of reproductive capacity, all of which are regulated by changes in the endocrine milieu. The increase in sex steroids, in particular oestradiol, enhances spontaneous growth hormone (GH) secretion by more than two-fold in late puberty. Insulin-like growth factor I (IGF-I) and its major circulating binding protein, IGF-binding protein 3, also increase during puberty. The rises in the levels of sex steroids, GH and IGF-I are crucial for linear growth, acquisition of bone mass and muscle bulk [1]. In this review, the behaviour of biochemical markers that may reflect changes in bone turnover and fat tissues in both normal and GH-deficient patients will be discussed, in addition to their possible clinical value as markers of linear growth.

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Table 1. Values of bone markers at diagnosis and during treatment in children with GHD

Author	Reference	At diagnosis					During GH treatment Bone marker*
		OC	PICP	BAP	ICTP	PYR, DPYR	
Carey et al.	7		↓				↑
Delmas et al.	8	↓					↑
Johansen et al.	9	↓					↑
Sartorio et al.	10	↓					↑
Trivedi et al.	11		↓				↑
Zamboni et al.	12	↓					↑
Kanzaki et al.	13	↓					↑
Saggese et al.	14	↓	↓				↑
Kubo et al.	15				↓		↑
Fujimoto et al.	16					↓	↑
Rauch et al.	17					↓	↑
Tobiume et al.	18			N			↑
Tapanainen et al.	19		↓				↑
Vihervuori et al.	20		↓		N		↑
Boot et al.	21	N	N		N		↑
Baroncelli et al.	22	↓	↓		↓		↑

BAP = Bone alkaline phosphatase isoenzyme; DPYR = total deoxypyridinoline; ICTP = cross-linked carboxy-terminal telopeptide of type I collagen; OC = osteocalcin; PICP = carboxy-terminal propeptide of type I procollagen; PYR = total pyridinoline. ↓ = Decreased; ↑ = increased; N = normal.

* Refers to the same bone marker(s) assessed at diagnosis.

Changes in Bone Markers in Healthy Individuals during Childhood and Adolescence

Bone is a dynamic tissue that grows and remodels throughout life in response to physical load and the metabolic environment. In children and adolescents, biochemical markers of bone turnover reflect a combination of growth, modelling and remodelling of bone tissue.

Biochemical markers of bone formation, such as serum bone alkaline phosphatase isoenzyme, osteocalcin (OC), carboxy-terminal propeptide of type I procollagen (PICP), and markers for bone resorption, including cross-linked carboxy-terminal telopeptide of type I collagen (ICTP), show age-related changes with higher values during the first 2 years of life and puberty, and increases occurring earlier in girls than in boys [2–5]. These changes resemble the growth velocity curves. Urinary pyridinoline and deoxypyridinoline values peak in the second month of life and subsequently decrease until approximately 3 years of age. During puberty, pyridinoline and deoxypyridinoline increase in boys, while in girls, pubertal increase is observed in peptide-bound forms such as collagen type I cross-linked N-telopeptides [3, 5].

Van Coeverden et al. [6] showed in a recent study that serum levels of bone alkaline phosphatase isoenzyme, OC, amino-terminal propeptide of type I procollagen (PINP) and ICTP increased until maximum values were reached at pubertal stages G4 in boys and B3 in girls; sex steroids and IGF-I reached adult values at pubertal stage 4. These data suggest that measurement of bone marker concentrations may have a clinical value in assessing growth-related changes during childhood and adolescence.

Changes in Bone Markers in GH-Deficient Children and Adolescents

Some studies have shown that children with GH deficiency (GHD) have reduced bone marker values at diagnosis [7–22] (table 1). In addition, we found that the concentrations of PICP during 24 h, but not those of OC, were growth velocity- and GH-dependent in GH-deficient children [23]. These data suggest that GHD affects bone turnover and this may represent a cause of reduced bone mineral density in children with GHD [24].

Table 2. Predictive value of growth response during GH treatment in children with GHD assessed by bone marker measurement

Author	Reference	Bone marker type	Time of measurement of bone marker (months)	Time of assessment of growth velocity (months)	r	p
Johansen et al.	9	OC	3	12	–	<0.01
Trivedi et al.	11	PICP	3	12	0.87	<0.001
Kanzaki et al.	13	OC	1	12	0.66	<0.01
Saggese et al.	14	PICP	1 week	6, 12	0.61–0.72	<0.001
Kubo et al.	15	PICP	1	12	0.68	<0.05
Fujimoto et al.	16	PYR	1	6	0.58	<0.05
Rauch et al.	17	GAL-HYL	3	12	0.76	0.002
Tobiume et al.	18	BAP	3	12	0.53	<0.05
Tapanainen et al.	19	PICP	3	6	0.59	<0.05
Vihervuori et al.	20	OC, ICTP	1 week	12	0.61–0.67	<0.05
		PICP	3	12	0.50	<0.05
Spagnoli et al.	26	PYR, DPYR	1	12	0.82	<0.05
Schonau et al.	27	PICP, DPYR	1	12	0.77	<0.001
Baroncelli et al.	22	OC, PICP, ICTP	6, 12	12 up to final height	0.02–0.36	NS

BAP = Bone alkaline phosphatase isoenzyme; DPYR = total deoxypyridinoline; GAL-HYL = galactosyl-hydroxylysine; ICTP = cross-linked carboxy-terminal telopeptide of type I collagen; OC = osteocalcin; PICP = carboxy-terminal propeptide of type I procollagen; PYR = total pyridinoline.

Furthermore, some studies have demonstrated that GH treatment increases the values of bone markers [7–22] (table 1), suggesting that GH stimulates bone turnover. We observed that during GH treatment, bone marker values peaked at 12 months, probably reflecting the number and activity of the recruited osteoblasts (OC and PICP), and an increased action of osteoclasts on bone matrix or change in the activation frequency of new remodelling units (ICTP) [22]. After the first year of treatment, the mean levels of OC and PICP progressively declined, while the mean levels of ICTP remained stable until final height was achieved [22]. Similar results were reported by Boot et al. [21] after a 2-year follow-up. We did not, however, observe any changes in the levels of serum OC, PICP and ICTP in these patients during puberty [22]. In children with GHD, the increased bone turnover may reflect stimulation of linear growth and recovery of bone mineral density [21, 24].

The dynamics of bone markers during long-term GH treatment may suggest the occurrence of a progressive prevalence of bone resorption over bone formation, but it must be noted that bone markers provide only a qualitative assessment of bone formation or resorption, and that their serum levels cannot be directly translated into rates of bone formation or resorption [25]. Comparing the

degree of variation of markers of bone formation with that of markers of bone resorption may not be justified because they probably reflect different aspects of growth. Indeed, a small change in one marker may be more important than a large change in another marker.

Bone Markers and Growth Response to GH Treatment in GH-Deficient Children

Some studies in GH-deficient children have shown that an increase in biochemical markers of bone turnover during the first weeks or months of GH treatment predicted growth rate within 6 or 12 months of therapy [9, 11, 13–20, 22, 26, 27] (table 2). This suggests that their measurement may be a useful tool in assessing responsiveness to GH treatment. We failed, however, to demonstrate any relationship between short-term (after 6 and 12 months of GH therapy) changes in bone markers (OC, PICP and ICTP) and long-term growth rate or final height in children with GHD [22]. Nonetheless, other factors may influence linear growth independently of the effect of GH on bone turnover. It should be considered that the bone markers we examined are not specific markers of longitudinal growth, which is primarily a function of

growth plate cartilage activity [4]. In GH-deficient children, therefore, growth response to GH treatment cannot be predicted solely by changes in the levels of bone markers during treatment. The predictive power of bone markers on long-term GH treatment may be improved by their inclusion into a more complex prediction model that takes into account clinical findings, other biochemical parameters and additional biochemical bone markers.

Leptin: A Marker of Fat Mass

Adipocytes express and secrete leptin, a protein encoded by the *ob* gene, which is involved in the regulation of satiety and body fat [28]. In healthy children and adolescents, leptin is related to body mass index (BMI). In particular, a strong exponential relationship in girls, but a weak association in boys, has been reported [29]. By stratifying the analysis according to pubertal stages, the association between blood leptin and BMI was shown to be similar at pubertal stages 1 and 2 in boys and girls. As pubertal development proceeded, the levels of leptin at a given BMI decreased in boys and increased in girls [29]. Thus, it appears that after pubertal stage 2, there is a sexual dimorphism in the levels of serum leptin and that this sex difference is especially evident in late puberty. The lower levels of leptin found in boys in late puberty may be explained, in part, by a suppressive effect of the increasing concentrations of circulating androgens, as demonstrated by studies on hypogonadal men receiving androgen replacement therapy [30, 31]. In addition, it was observed that oestradiol concentrations correlated positively with leptin levels in pubertal girls, while testosterone concentrations correlated negatively with blood leptin [32]. By associating leptin levels with percentage body fat, measured by electric impedance, Blum et al. [29] found a strong correlation in both boys and girls, suggesting that fat mass is the main regulator of leptin levels and that BMI correlates with leptin because it reflects fat mass in a certain way. These data suggest that the reference range of leptin should include BMI and pubertal stage.

Changes in Leptin in GH-Deficient Children

It has generally been observed that GH administration decreases serum levels of leptin in GH-deficient children [33, 34]. In one study, Matsuoka et al. [34] showed that GH administration to children with GHD was associated with a reduction in leptin levels to approximately 79% of

baseline values after 10 days of treatment. Absolute levels of leptin showed a high correlation with absolute total body fat at the start and end of the study; a moderate correlation was observed between the 1-year change in total body fat and leptin. When blood leptin was expressed per unit fat mass, however, there was no difference between mean values at the start and after 1 year of GH treatment, suggesting that GH does not have an independent effect on leptin other than via a reduction in fat mass [34]. Other investigators, however, reported that GH may have a direct effect on leptin production, metabolism or clearance because the levels of leptin declined before changes in body composition occurred [35].

GH-induced changes in circulating leptin make this protein a possible metabolic marker of growth response to GH. Kriström et al. [33] studied the behaviour of serum leptin levels and height standard deviation score (SDS) in 150 short children with a broad range of GH secretory capacity, 86 of whom had GHD. All patients were treated with GH and were followed for at least 1 year. Changes in height SDS after 1 year of GH treatment correlated positively with levels of serum leptin at the start of GH therapy and negatively with serum leptin levels after 3 months of GH administration. By adding baseline concentrations of serum leptin to other pre-treatment variables, such as growth pattern before the age of 2 years, IGF-I SDS and GH peak in the arginine–insulin tolerance test, the power of the model to explain variations in growth response to GH improved from 46 to 58%. Thus, both pre-treatment and short-term changes in the levels of serum leptin in response to GH administration may be useful markers for the prediction of first-year growth response.

Leptin and Bone Markers

Recently, it was discovered that leptin may regulate osteoblast activity both indirectly and directly. Intravenous infusion of leptin for 20 days in *ob/ob* mice and in wild-type mice caused a decrease in bone mass and volume through the hypothalamus [36], while intraperitoneal infusion over the same period increased femoral length in these mice [37]. It was hypothesized that the local environment may provide bone cells with signals favouring constant growth, whereas the central negative signal determines the density and length regulated by energy metabolism and leptin [38]. Functioning receptor isoforms for leptin were found in rat osteoblasts [39]. It was also reported that leptin may inhibit osteoclast generation in cultures of human peripheral blood mononuclear cells

[40], while acting as a growth factor on the chondrocytes of skeletal growth centres in mice [41].

In healthy men, serum leptin levels correlated negatively with markers of bone formation and positively with markers of bone resorption, suggesting that leptin may stimulate bone resorption in adulthood [42]. In contrast, levels of leptin correlated negatively with markers of bone resorption in fetal blood, suggesting that leptin might promote bone formation during fetal life [43]. This contrasting behaviour may, however, reflect differences in age, metabolism and endocrine milieu.

Conclusions

In summary, GH status and GH treatment influence bone marker values. They may predict short-term growth response to GH treatment, but not long-term growth response or final height, when examined using univariate analysis. Moreover, GH treatment does not influence levels of bone markers during puberty. Serum levels of leptin may predict short-term growth response to GH treatment, but no data are available to consider leptin as a predictor of long-term growth response in GH-treated GH-deficient children.

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