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Monitoring serum insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), IGF-I/IGFBP-3 molar ratio and leptin during growth hormone treatment for disordered growth

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Summary

OBJECTIVE Serum IGF-I levels are monitored during GH replacement treatment in adults with GH deficiency (GHD) to guide GH dose adjustment and to minimize occurrence of GH-related side-effects. This is not routine practice in children treated with GH. The aim of this study was to evaluate changes in (1) serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio, and (2) serum leptin, an indirect marker of GH response, during the first year of GH treatment in children with disordered growth.

DESIGN An observational prospective longitudinal study with serial measurements at five time points during the first year of GH treatment was carried out. Each patient served as his/her own control.

PATIENTS The study included 31 patients, grouped as (1) GHD ($n=20$) and (2) non-GHD (Turner syndrome $n=7$; Noonan syndrome $n=4$), who had not previously received GH treatment.

MEASUREMENTS Serum IGF-I, IGFBP-3 and leptin levels were measured before treatment and after 6 weeks, 3 months, 6 months and 12 months of GH treatment, with a mean dose of 0.5 IU/kg/wk in GHD and 0.7 IU/kg/wk in non-GHD groups. IGF-I, IGFBP-3 and the calculated IGF-I/IGFBP-3 molar ratio were expressed as SD scores using reference values from the local population.

RESULTS In the GHD group, IGF-I SDS before treatment was lower compared with the non-GHD (-5.4 ± 2.5 vs. -1.8 ± 1.0 ; $P<0.001$). IGF-I (-1.8 SDS ± 2.2) and IGFBP-3 (-1.1 SDS ± 0.6) levels and their molar ratios were highest at 6 weeks and remained relatively constant thereafter. In the non-GHD group, IGF-I levels increased throughout the year and were maximum at 12 months (0.3 SDS ± 1.4) while IGFBP-3 (1.1 SDS ± 0.9) and IGF-I/IGFBP-3 molar ratio peaked at 6 months. In both groups, IGF-I SDS and IGF-I/IGFBP-3 during treatment correlated with the dose of GH expressed as IU/m²/week (r -values 0.77 to 0.89; $P=0.005$) but not as IU/kg/week. Serum leptin levels decreased significantly during GH treatment in the GHD (median before treatment 4.0 μ g/l; median after 12 months treatment 2.4 μ g/l; $P=0.02$) but not the non-GHD (median before treatment 3.0 μ g/l; median after 12 months treatment 2.6 μ g/l). In the GHD group, serum leptin before treatment correlated with 12 month change in height SDS ($r=0.70$, $P=0.02$).

CONCLUSIONS The pattern of IGF-I, IGFBP-3 and their molar ratio during the first year of GH treatment differed between the GHD and non-GHD groups. Calculation of GH dose by surface area may be preferable to calculating by body weight. As a GH dose-dependent increase in serum IGF-I and IGF-I/IGFBP-3 may be associated with adverse effects, serum IGF-I and IGFBP-3 should be monitored routinely during long-term GH treatment. Serum leptin was the only variable that correlated with first year growth response in GHD.

GH has been used for over 25 years as replacement for GH deficiency (GHD) in children and for over 10 years to promote growth in conditions such as Turner syndrome. The best dose and regimen, the most accurate short-term parameter of treatment success and reliable indicators of potential side-effects have yet to be definitively determined. GH induces hepatic and local tissue production of IGF-I and raises IGF-I and IGFBP-3 levels (the principal carrier protein of IGF-I) in serum. In GHD adults, GH dose-dependent changes in serum IGF-I, serum IGFBP-3 and adverse effects

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have been observed (de Boer *et al.*, 1996; Johannsson *et al.*, 1997), and serum IGF-I levels are monitored during treatment to guide GH dose adjustment and to minimize occurrence of adverse effects. The recommended target serum IGF-I range during treatment in adults varies among investigators (± 1 SD or ± 2 SD of age-related normal range) (de Boer *et al.*, 1996; Bülow *et al.*, 1999; Murray *et al.*, 1999) and the optimal range has not been defined. Serum IGF-I and IGFBP-3 concentrations are not routinely monitored during GH treatment in children, and the dose of GH tends to be adjusted according to the growth response.

The aim of this study was to evaluate changes in serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio over the first year of GH treatment in children to assess GH sensitivity and the possible role of these peptides as markers of compliance or overtreatment. Serum leptin is another potential marker, albeit indirect, of GH response. A fall in plasma leptin and fat stores associated with GH treatment has been reported in GHD adults (Florkowski *et al.*, 1996; Janssen *et al.*, 1997) and children (Rauch *et al.*, 1998; Kriström *et al.*, 1998; Matsuoka *et al.*, 1999). We therefore examined the changes in serum leptin concentrations during GH replacement and in relation to changes in growth and body mass index.

Subjects and methods

The study included 31 children (age 1.7–15.9 years; 14 girls) with disordered growth, not previously treated with GH, recruited from three centres. They were categorized into two groups: (1) 20 children (seven girls) with GHD (15 with isolated GHD and five with multiple pituitary hormone deficiency), and (2) 11 children with non-GHD (seven with Turner syndrome and four with Noonan syndrome). In addition to typical phenotypic features and appropriate auxological characteristics, the diagnosis of GHD was based on peak stimulated GH level less than 15 mU/l ($n = 18$) or peak stimulated GH level 15–17 mU/l and pituitary stalk transection on MRI ($n = 2$). GHD was idiopathic ($n = 13$) or associated with craniopharyngioma ($n = 3$), radiotherapy ($n = 3$) or septo-optic dysplasia ($n = 1$). The diagnoses of Turner syndrome and Noonan syndrome were confirmed by karyotype and experienced clinicians, respectively. None of the female patients received oestrogen during this period. The clinical characteristics of the two groups are shown in Table 1. Ethical committee approval and consent were obtained prior to the study from all children (if old enough) and their parents.

Recombinant human GH was administered subcutaneously before bedtime, 6 or 7 days a week, at a dose of 0.5 (SD 0.1)

Table 1 Clinical and biochemical characteristics of the 20 children with GH deficiency (GHD) and 11 children with non-GHD (Turner syndrome and Noonan syndrome). Data are presented as median, mean, SD and range

	GHD				Non-GHD			
	Median	Mean	SD	Range	Median	Mean	SD	Range
Before GH treatment								
Age (years)	9.3	9.1	3.7	3.4 to 15.2	9.8	9.4	4.0	1.7 to 15.9
Bone age (years)	4.6	6.3	3.5	1.5 to 13.0	10.2	9.3	3.8	3.0 to 13.0
Serum IGF-I ($\mu\text{g/l}$)	32	88	99	11 to 386	150	198	115	100 to 381
IGF-I SDS	-5.4	-5.4	2.5	-10.7 to -1.4 ^a	-1.9	-1.8	1.0	-3.0 to -0.1 ^a
Serum IGFBP-3 ($\mu\text{g/l}$)	1.3	1.3	0.5	0.5 to 1.9	1.6	1.5	0.3	0.9 to 2.0
IGFBP-3 SDS	-2.2	-2.0	0.7	-2.9 to 0	-1.8	-1.9	0.7	-3.0 to -1.0
Serum IGF-I/IGFBP-3 ratio	0.2	0.4	0.4	0.03 to 1.9	0.6	0.7	0.4	0.3 to 1.4
IGF-I/IGFBP-3 ratio SDS	-1.4	-1.4	0.9	-2.9 to 1.6	-0.9	-0.3	1.1	-1.3 to 1.8
Serum leptin ($\mu\text{g/l}$)	4.0	9.1	11.7	3.0 to 37.4	3.0	3.2	0.9	2.3 to 4.4
Height velocity (cm/year)								
Before	3.9	4.0	1.2	2.5 to 7.2 ^b	4.7	4.4	1.0	2.9 to 5.6 ^c
First 12 months	9.6	9.9	2.6	7.0 to 15.4 ^b	7.5	7.5	1.6	4.6 to 10.8 ^c
Height SDS								
At start	-2.9	-2.8	1.4	-6.0 to 0.1 ^d	-2.5	-2.7	0.9	-4.1 to -1.6 ^c
At 12 months	-2.0	-1.9	1.4	-5.1 to 1.0 ^d	-2.1	-2.2	0.7	-3.4 to -1.3 ^c
BMI SDS								
At start	0.3	0.6	1.5	-1.9 to 4.1 ^f	0	0.1	1.4	-2.9 to 2.2
At 12 months	-0.3	0.1	1.5	-3.7 to 3.1 ^f	0.1	0	1.1	-1.5 to 1.8

^{a-d} $P < 0.001$; ^e $P = 0.01$; ^f $P = 0.03$.

IU/kg/week in GHD and 0.7 (SD 0.1) IU/kg/week in non-GHD patients. The mean dose of GH expressed according to body surface area was 15.3 IU/m²/wk (SD 3.3, range 10.0–21.2) for the GHD and 19.8 IU/m²/wk (SD 4.8, range 13.3–29.2) for the non-GHD group.

Height, weight, serum IGF-I, IGFBP-3 and leptin levels were measured before and at four time points (6 weeks, 3 months, 6 months, 12 months) after commencing GH treatment. Height, weight and BMI (weight/height²) were converted to SD scores using 1990 UK standards (Cole *et al.*, 1995; Freeman *et al.*, 1995). Blood samples for serum IGF-I, IGFBP-3 and leptin were taken approximately 14–16 h after the last dose of GH.

Biochemical assays

Serum IGF-I was measured by a previously reported in-house radioimmunoassay (RIA) method (Gill *et al.*, 1997). The sensitivity of the assay was 0.8 µg/l and the intra- and interassay CVs were 4.0–5.7% and 5.2–7.4%, respectively. Serum IGFBP-3 was measured using a commercial double antibody RIA (Bioclone Australia Ltd, Sydney, Australia). The sensitivity of the assay was 3.5 µg/l and the intra- and interassay CVs were 4.3% and 6.6%, respectively. For calculation of the molar ratio between IGF-I and IGFBP-3, the following molecular masses were used: IGF-I 7.5 kD and IGFBP-3 42.0 kD. Values for IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio were expressed as age, sex and puberty specific SD scores using reference values obtained from our local population of healthy children (Hall *et al.*, 1998; Hall *et al.*, 1999). Serum leptin was measured using a commercial RIA (Linco, St Charles, MO, USA). The limit of detection of the assay was 0.5 µg/l. The intra- and interassay CVs ranged from 3.4 to 8.3% and 3.6–6.2%, respectively, over a leptin concentration range of 4.9–25.6 µg/l.

Statistical analysis

Values at different time points were compared by one-way repeated analysis of variance, followed by paired *t*-tests with a Bonferroni correction where significant ($P < 0.05$) differences were found. Leptin concentrations were log-transformed prior to analyses. Relationships between variables were evaluated by Pearson correlations and linear regression analysis.

Results

Growth response to GH treatment

Height velocity during the first year of GH treatment was significantly greater than that prior to treatment in both groups (Table 1). Change in height SDS in response to GH treatment showed wide variation in both groups. Mean change in height SDS during the first year of GH treatment was significantly

higher ($P = 0.05$) in the GHD group (0.8; SD, 0.5) than the non-GHD group (0.5; SD, 0.3). Mean change in BMI SDS during this period was also significantly greater ($P = 0.05$) in the GHD group (−0.5; SD, 0.7) compared to the non-GHD group (−0.06; SD, 0.7).

Pretreatment serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio

Pretreatment serum IGF-I SDS but not IGFBP-3 SDS was lower in the GHD compared with the non-GHD group ($P < 0.001$) (Table 1). Serum IGF-I levels were below −2 SDS in all but one patient with GHD (−1.4 SDS). IGF-I/IGFBP-3 molar ratios were below −2 SDS in five patients with GHD but within 2 SDS in all non-GHD patients.

Changes in serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio during GH treatment

GHD group. Serum IGF-I and IGFBP-3 levels increased significantly during treatment in the GHD group (Fig. 1a, b). The major increment in IGF-I in the GHD group was achieved by 6 weeks (Fig. 1a, b). IGF-I SDS increased at least 1.0 SDS in all but one patient (a 4-year-old boy: IGF-I SDS before and on GH −5.7 and −5.6, respectively). However, mean IGF-I SDS remained in the low normal range and levels did not increase above −2.0 SDS of the reference values in 7 of the 20 patients. The pattern of changes in IGFBP-3 levels (Fig. 1b) and IGF-I/IGFBP-3 molar ratios (Fig. 1c) was similar to that in IGF-I.

Non-GHD group. In the non-GHD group, IGF-I levels increased progressively throughout the year and reached a maximum at 12 months (Fig. 1d) while IGFBP-3 (Fig. 1e) and IGF-I/IGFBP-3 molar ratio (Fig. 1f) peaked at 6 months.

Relationship between serum IGF-I and IGFBP-3 and the growth response to GH treatment

Neither serum IGF-I, IGFBP-3, IGF-I/IGFBP-3 molar ratio nor the changes in values during treatment were predictive of annual height gain in either group. However all four GHD patients with change in IGF-I at 6 weeks < 2.5 SDS had a poor increment in height over 12 months' treatment of < 0.75 SDS (Fig. 2). Of the GHD patients with change in IGF-I at 6 weeks ≥ 2.5 SDS, 31% had a poor increase in height over 12 months of < 0.75 SDS while 69% had an increment ≥ 0.75 SDS.

Relationship between serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio and the dose of GH

During GH treatment, IGF-I SDS and IGF-I/IGFBP-3 molar

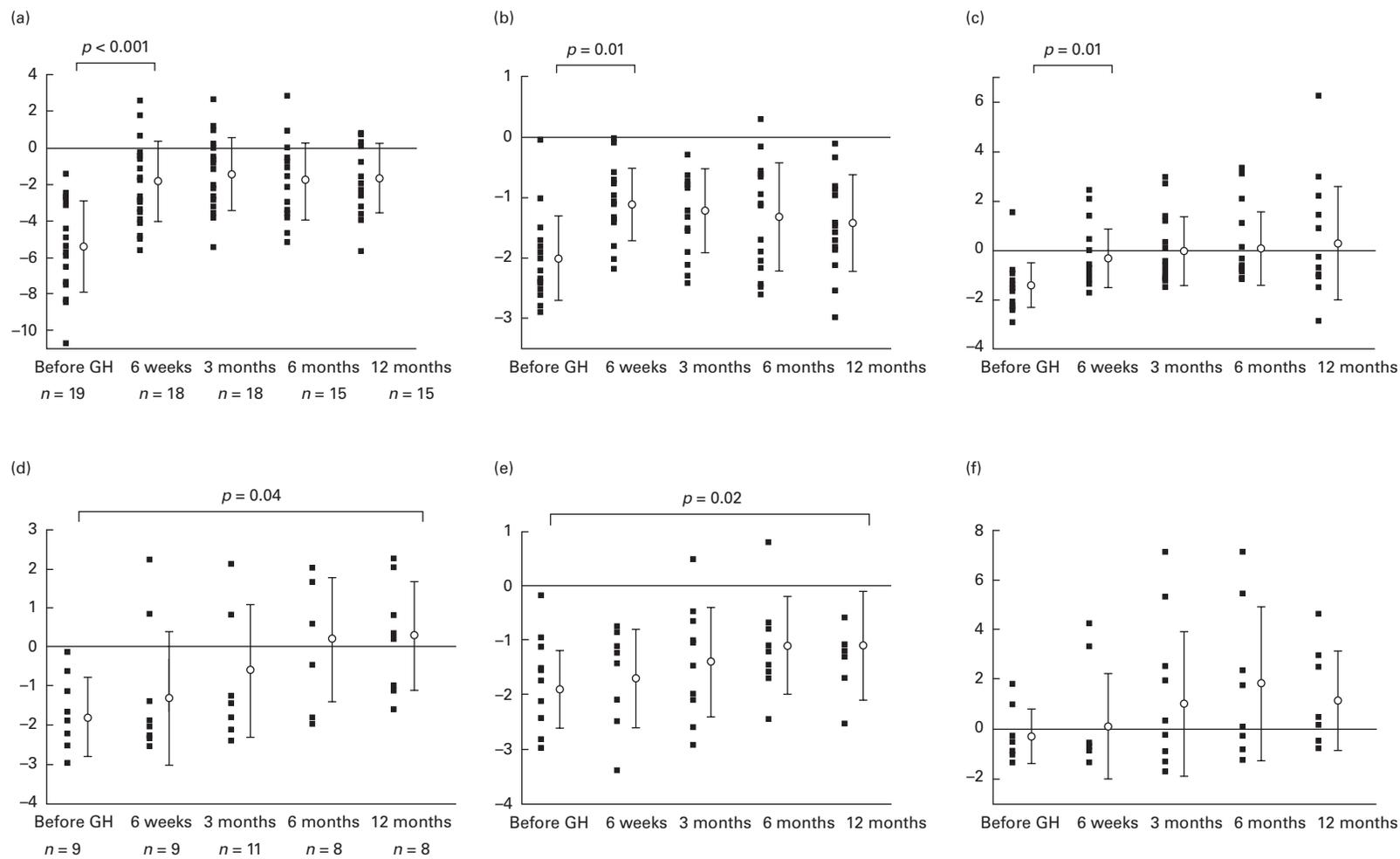


Fig. 1 Serum IGF-I (a and d), IGFBP-3 (b and e) and IGF-I/IGFBP-3 molar ratio (c and e) before and during treatment with GH in (a-c) GHD and (d-f) non-GHD groups. Values are expressed as SDS. Mean and standard deviation are shown by the mean and error bar plots.

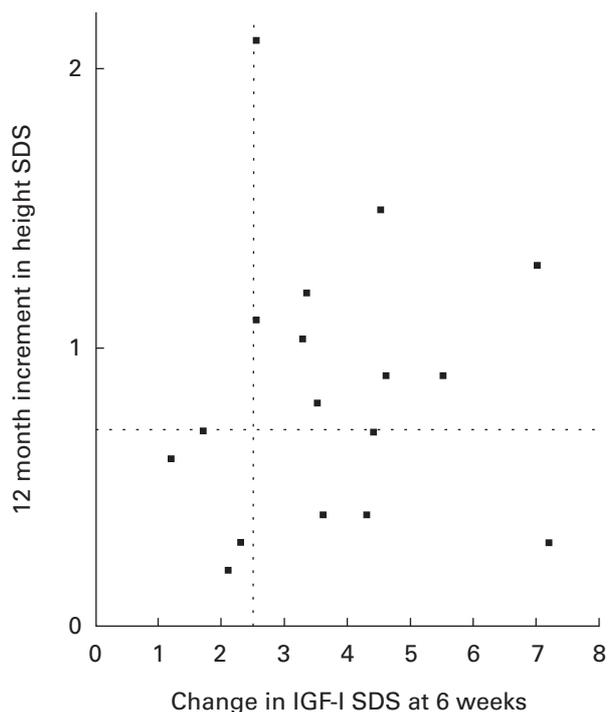


Fig. 2 Relationship between change in serum IGF-I at 6 weeks and increment in height SDS during 12 months' GH treatment in patients with GHD. The dotted lines represent the cut-offs for change in serum IGF-I at 6 weeks (2.5 SDS) and 12 month increment in height (0.75 SDS).

ratio correlated positively with GH dose/m²/week, but not dose/kg/week, in both study groups. The relationship was strongest at 3 months (GHD: IGF-I SDS $r=0.77$, $P<0.001$; IGF-I/IGFBP-3 $r=0.89$, $P<0.001$. Non-GHD: IGF-I SDS $r=0.78$, $P=0.005$; IGF-I/IGFBP-3 $r=0.87$, $P<0.001$). The relationship between GH dose and IGFBP-3 SDS was not significant in either group.

Exceptionally high and low biochemical values in individual patients

In the GHD group, the highest IGF-I/IGFBP-3 molar ratio (6.3 SDS) was seen in an 11-year-old girl with isolated GHD and coexisting asthma after her dose of inhaled beclomethasone dipropionate was halved from 1600 $\mu\text{g}/\text{day}$ to 800 $\mu\text{g}/\text{day}$ at 3 months (change in height SDS with GH replacement was 0.6 SDS; dose of GH 18.5 IU/m²/week). One 12-year-old patient with craniopharyngioma had high IGF-I (2.9 SDS) and IGF-I/IGFBP-3 molar ratio (3.4 SDS) during treatment (dose 18.4 IU/m²/week), when his height SDS increased by 1.3 SDS.

IGF-I levels (2.3, 2.1, 2.1 SDS) and corresponding IGF-I/IGFBP-3 molar ratios (5.3, 7.2, 5.4 SDS) were greater than

+2.0 SDS in 3 girls with Turner syndrome during GH treatment (dose 29.2, 24.3 and 21.6 IU/m²/week). Their change in height SDS with treatment was 0.1, 0.3 and 0.6 SDS, respectively.

IGF-I and IGFBP-3 SD scores after commencing GH treatment were lower than pretreatment values in two girls with Turner syndrome (GH dose 13.3 and 18.8 IU/m²/week; increase in height 1.3 and 0.3 SDS, respectively).

Serum leptin before and during GH treatment

Sufficient sample volumes to measure serum leptin were available from 11 and four unselected children with GHD and non-GHD, respectively. Serum leptin levels decreased significantly during GH treatment in the GHD (being lowest at 12 months: median 2.4, interquartile range 2.3–3.0 $\mu\text{g}/\text{l}$; $P=0.02$) but not the non-GHD group (median at 12 months 2.6, interquartile range 2.1–3.5 $\mu\text{g}/\text{l}$). In the GHD group, serum leptin concentration before treatment correlated with BMI SDS at the start ($r=0.77$, $P=0.01$), serum IGF-I SDS after 6 week ($r=0.77$, $P=0.006$), IGF-I/IGFBP-3 after 6 week ($r=0.74$, $P=0.009$) and change in height SDS ($r=0.70$, $P=0.02$) but not change in BMI during 12 months' treatment.

Discussion

The pattern of serum IGF-I and IGFBP-3 levels, and IGF-I/IGFBP-3 molar ratio during the first year of treatment differed between the GHD and non-GHD groups. It may be explained by the differences in GH secretory status, GH responsiveness, pretreatment IGF-I and IGFBP-3 levels and modulation by GHBP (GH receptor). The positive relationship between the dose of GH and serum IGF-I but not serum IGFBP-3 suggests that IGF-I is more sensitive to GH than IGFBP-3. The increase in IGF-I/IGFBP-3 molar ratio with increasing dose of GH may reflect an increase in bioavailable IGF-I.

Our observation of a reduction in serum leptin levels during GH replacement in GHD children complements previous studies (Kriström *et al.*, 1998; Rauch *et al.*, 1998; Matsuoka *et al.*, 1999). It raises the possibility of biological endpoints other than growth, such as body composition, and is likely to be a reflection of decreased fat mass: a relationship between the reduction in serum leptin and change in total body fat (estimated by dual-energy X-ray absorptiometry) during GH treatment has been reported (Matsuoka *et al.*, 1999). Our observations and those of Kriström *et al.* (1998) suggest that basal leptin concentration is correlated to the growth promoting effect of GH. A number of observations indicate a potential link between leptin/body fat, GH receptor expression and response to GH (Martha *et al.*, 1992; Bjarnason *et al.*, 1997; Florkowski *et al.*, 1999).

Leptin levels during GH treatment have not previously been reported in Turner syndrome or Noonan syndrome. The lack of complete data on all patients at all time points may have precluded us from identifying a significant fall in leptin levels during treatment. On the other hand, as there was little change in BMI during GH treatment, it is likely that leptin levels do not change significantly in these syndromes.

In GHD adults, considerable variability in responsiveness to GH, and relationships with GH dose, pretreatment GHBP levels, age and gender have been observed for different GH effects (including increase in serum IGF-I (Bengtsson *et al.*, 1993; Bülow *et al.*, 1999), serum IGFBP-3 (de Boer *et al.*, 1996; Chipman *et al.*, 1997), changes in body composition (Johannsson *et al.*, 1996) and glucose tolerance (Beshyah *et al.*, 1995). The growth response to GH (Sherman *et al.*, 1987; Schwartz *et al.*, 1990; Martha *et al.*, 1992; Blethen *et al.*, 1993; Kriström *et al.*, 1995; Kriström *et al.*, 1997; Kriström *et al.*, 1998; Ranke *et al.*, 1999) has been the main issue in children and adverse effects (Blethen & MacGillivray, 1997) of treatment have received less attention. In our study, serum leptin concentration before treatment was the only variable that correlated with the first year growth response to GH in children with GHD. The relatively small number of subjects may have precluded us from identifying other important explanatory variables. Unlike Schalch *et al.* (1982); Mandel *et al.* (1995) and Kriström *et al.* (1997), but in keeping with other investigators (Rosenfeld *et al.*, 1981; Dean *et al.*, 1982), we did not find changes in IGF-I nor IGFBP-3 to be major correlates of growth rate during GH replacement in patients with GHD. But we did show that a satisfactory growth response did not occur if the IGF-I response to treatment was low.

The increase in serum IGF-I and IGFBP-3 concentrations, and IGF-I/IGFBP-3 molar ratios observed during GH treatment has a number of implications. First, titrating the dose of GH to maintain serum IGF-I and IGFBP-3 within age dependent normal ranges is physiologically sound and analogous to monitoring replacement treatment for other endocrine deficiencies such as hypothyroidism. High values in some children but minimal response in others illustrates the need for individualized GH dosage. Second, as we observed in one patient with GHD and two girls with Turner syndrome, monitoring IGF-I levels during GH treatment offers the possibility of identifying noncompliance. Third, GH dose-dependent changes in IGF-I and IGFBP-3 may be associated with adverse effects in children and safety needs to be considered for GH replacement in GHD as well as for pharmacological treatment in non-GHD as treatment is likely to be continued for many years (Baens-Bailon *et al.*, 1992; MacGillivray *et al.*, 1998). Although we found that girls with Turner syndrome were more likely to have abnormally high IGF-I levels during GH treatment, one patient with GHD also

had high IGF-I concentrations despite a conventional replacement dose of GH. Potential fears related to longterm cancer risk have been well publicised (Chan *et al.*, 1998; Hankinson *et al.*, 1998; Orme *et al.*, 1998; Yu *et al.*, 1999). As the oncogenic potential is likely to be greatest in patients with high IGF-I and low IGFBP-3 concentrations (Hankinson *et al.*, 1998; Petridou *et al.*, 1999; Yu *et al.*, 1999) it seems prudent to monitor IGF-I and IGFBP-3 levels during GH treatment in children.

The change in serum IGF-I and IGFBP-3 in response to GH, as an index of the extent of GH responsiveness and the potential for adverse effects, may facilitate decision making, especially when treatment with higher doses is contemplated in children demonstrating poor growth with conventional doses. Monitoring is likely to be easy in practical terms with the availability of IGF-I and IGFBP-3 measurements from finger prick blood spots but raises a number of questions which will need to be addressed by further studies: how frequently serum IGF-I and IGFBP-3 levels should be monitored, and when and how the dose of GH should be modified with reference to these levels and an individual child's growth response.

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