

ORIGINAL ARTICLE

High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with idiopathic short stature

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Background: Long term growth hormone (GH) treatment in children with idiopathic short stature (ISS) results in a relatively small mean gain in final height of 3–9 cm, which may not justify the cost of treatment. As it is unknown whether GH treatment during puberty adds to final height gain, we sought to improve the cost–benefit ratio, employing a study design with high dose GH treatment restricted to the prepubertal period.

Aims: To assess the effect of short term, high dose GH treatment before puberty on growth, bone maturation, and pubertal onset.

Methods: Five year results of a randomised controlled study are reported. Twenty six boys and nine girls were randomly assigned to a GH treatment group (n = 17) or a control group (n = 18). Inclusion criteria were: no signs of puberty, height less than –2 SDS, age 4–8 years for girls or 4–10 years for boys, GH concentration >10 µg/l after provocation, and normal body proportions. To assess GH responsiveness, children assigned to the GH treatment group received GH treatment for two periods of three months (1.5 IU/m²/day and 3.0 IU/m²/day), separated by three month washout periods, during the first year of study. High dose GH treatment (6.0 IU/m²/day) was then started and continued for at least two full years. When puberty occurred, GH treatment was discontinued at the end of a complete year's treatment (for example, three or four years of GH treatment).

Results: In response to at least two years on high dose GH treatment, mean (SD) height SDS for chronological age increased significantly in GH treated children from –2.6 (0.5) to –1.3 (0.5) after two years and –1.4 (0.5) SDS after five years of study. No changes in height SDS were observed in controls. A rapid rate of bone maturation of 3.6 years/2 years in treated children compared to 2 years/2 years in controls was observed in response to two years high dose GH treatment. Height SDS for bone age was not significantly different between groups during the study period. GH treated children entered into puberty at a significantly earlier age compared to controls.

Conclusions: High dose GH treatment before puberty accelerates bone age and induces an earlier onset of puberty. This may limit the potential therapeutic benefit of this regimen in ISS.

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Although it is assumed that growth hormone (GH) secretion is normal in children with idiopathic short stature (ISS),¹ many studies have shown that the administration of GH increases height velocity.^{2–4} However, bone maturation may accelerate, with possible limiting effects on final height. In the absence of large, randomised control studies, there is no certainty as to the effect on final height which is now estimated to be increased by between 3 and 9 cm.^{5–8}

Children with idiopathic short stature (ISS) are treated with growth hormone (GH) under the assumption that there is no interference of GH treatment and timing of puberty. However, some recent studies suggest that GH treatment may alter the timing of puberty.^{9–14} It is well established that an early onset of puberty may lead to short adult stature, as can be observed, for example, in children with precocious puberty. By contrast, hypogonadal boys with late induction of puberty become relatively tall.^{15,16} There is only one randomised controlled study in a small number of girls with ISS. This study reported no influence of GH treatment on bone maturation or on the timing of puberty.⁷

GH treatment in ISS is usually started before the onset of puberty and continued until final height is attained. Long term GH treatment with continuation during puberty is very expensive, and it is unknown whether GH treatment during puberty adds to final height gain. There are two observations indicating that GH treatment is most effective before puberty, including a

dose dependent increment in height SDS before puberty,^{4,17} and a strong correlation between height at onset of puberty and final height.^{18,19} Furthermore, we have previously shown that pubertal height gain on GH treatment was not different between GH treated children and untreated historical controls.⁹

We sought to improve the cost–benefit ratio of GH treatment in ISS by starting treatment at a young age, in a relatively high dose, in the context of a randomised controlled study in which treatment was discontinued once the individual had entered puberty. In this paper we present the results of the first five years of our study, with the unexpected finding that GH induces a more rapid rate of bone maturation before puberty and an earlier onset of puberty than in controls. These findings may have important clinical implications for the treatment with GH of children with ISS.

SUBJECTS AND METHODS

Study subjects

Forty prepubertal children with short stature who did not meet the classical criteria for the diagnosis of GH deficiency

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; GH, growth hormone; IGF, insulin like growth factor; ISS, idiopathic short stature

Table 1 Mean (SD) baseline characteristics in 35 children with idiopathic short stature

	Controls (n=18)	GH treatment (n=17)
Age at start (y)	7.4 (1.8)	8.4 (1.7)
GH peak at provocation test ($\mu\text{g/l}$)	25.2 (13)	27.9 (22)
Birth weight (kg)	3.1 (0.5)	3.3 (0.4)
Birth length (cm)	49.0 (2.4)	49.8 (1.4)
Height SDS	-2.7 (0.3)	-2.9 (0.60)
BMI SDS	-0.8 (0.6)	-0.3 (0.9)
Bone age at start (y)	5.0 (1.9)	5.4 (1.5)
Bone age delay at start (y)	2.4 (1.1)	3.0 (1.1)
Height SDS for bone age	0.5 (1.9)	0.5 (1.2)
Target height SDS	-0.9 (0.7)	-1.0 (0.6)

were enrolled in a multicentre study and were randomly assigned to a GH treatment group (n = 20) and a control group (n = 20). After randomisation, one child in the GH treatment group was found to have neurofibromatosis, while two children refused GH treatment, leaving 17 children (13 boys, four girls) in this group. Two children in the control group refused follow up and/or assessment, leaving 18 children (13 boys, five girls). Inclusion started in December 1993 and ended in December 1996. At present, 12 GH treated children and nine controls have completed four years of study; eight GH treated children and seven controls have completed five years of study.

The protocol was reviewed and approved by the medical ethics committees at the three participating centres (Catharina Hospital, Eindhoven (n = 18), Sophia's Children's Hospital, Rotterdam (n = 12), Free University Hospital Amsterdam (n = 5)), and the parents of all children gave written consent for the study. When appropriate, the consent of the children was also obtained.

Inclusion criteria at enrolment were: age 4–8 years for girls and 4–10 years for boys; height less than -2.0 SDS²⁰ with no evidence of malnutrition, hormonal, or systemic disease; birth length greater than -2.0 SDS²¹; sitting height/subischial leg length ratio between 3rd and 97th centile were established.²² In all cases the peak stimulated GH concentration was greater

than 10 $\mu\text{g/l}$ (1 $\mu\text{g} = 2$ IU, The First International Reference Preparation of hGH, MRC London, code 66/217 was used as standard) after provocation (exercise, arginine, clonidine, L-dopa, or glucagon).

Study protocol

Auxology

All children were evaluated at baseline. Children in the GH treatment group were followed every three months during treatment and at least once a year thereafter. Children in the control group were followed on a yearly basis. Evaluations included measurements of height (mean of four measurements performed by the same observer (LV) at the same hour of day on a Harpenden stadiometer), sitting height (mean of two measurements (LV)), and weight (LV). Pubertal staging was assessed by one investigator in all children at all visits (GAK), according to the method of Tanner. The Prader orchidometer was used to determine testicular size in boys. The onset of puberty was defined as B2 in girls, and a testicular volume ≥ 4 ml (G2) in boys.²³ Pubertal data at full year visits were used for comparisons between GH treated children and controls.

Bone age radiographs were measured yearly in all children and were determined according to the method of Greulich and Pyle by one independent investigator. Height was expressed as

Table 2 Number of controls and GH treated children in relation to auxological measurements during five years of study

	Group	Start	After 1 y	After 2 y	After 3 y	After 4 y	After 5 y
Number of children	Controls	18	18	18	17	9	7
	GH Rx	17	17	17	8	1	0
	on off				9	11	8
Age	Controls	7.4 (1.8)	8.4 (1.8)	9.4 (1.8)	10.5 (1.8)	11.5 (2.1)	12.5 (2.1)
	GH Rx	8.4 (1.7)	9.4 (1.7)	10.4 (1.7)	11.3 (1.7)	13.1 (1.0)	14.4 (0.8)
Height SDS	Controls	-2.7 (0.3)	-2.6 (0.4)	-2.6 (0.5)	-2.5 (0.6)	-2.3 (0.8)	-2.2 (1.2)
	GH Rx	-2.9 (0.6)	-2.6 (0.5)	-1.8 (0.5)	-1.3 (0.5)	-1.3 (0.6)	-1.4 (0.8)
BMI SDS	Controls	-0.8 (0.6)	-0.9 (0.6)	-0.8 (0.7)	-1.0 (0.8)	-0.9 (0.9)	-1.3 (0.9)
	GH Rx	-0.3 (0.9)	-0.4 (0.9)	-0.1 (0.8)	-0.0 (0.9)	0.0 (1.0)	-0.2 (1.3)
Bone age	Controls	5.0 (1.9)	6.1 (2.0)	7.1 (2.0)	8.1 (1.9)	9.3 (2.3)	11.0 (2.6)
	GH Rx	5.4 (1.5)	6.5 (1.7)	8.5 (1.7)	10.1 (1.7)	12.0 (1.1)	13.3 (1.4)
Height SDS for BA	Controls	0.5 (1.9)	0.1 (1.6)	-0.2 (1.4)	-0.5 (1.0)	-0.5 (1.3)	-0.8 (0.8)
	GH Rx	0.5 (1.2)	0.4 (1.3)	-0.1 (1.1)	-0.2 (0.7)	-0.4 (0.6)	-0.5 (0.8)
Sitting height SDS	Controls	-2.6 (0.7)	-2.4 (0.7)	-2.4 (0.9)	-2.3 (0.8)	-2.2 (1.0)	-2.2 (1.1)
	GH Rx	-2.4 (1.4)	-1.9 (1.1)	-1.2 (0.9)	-0.9 (0.8)	-1.0 (0.8)	-1.0 (0.9)
Sitting height/height SDS	Controls	-0.6 (1.2)	-0.4 (1.1)	-0.5 (1.5)	-0.4 (1.2)	-0.6 (1.1)	-0.8 (0.6)
	GH Rx	-0.0 (2.0)	0.4 (1.6)	0.4 (1.2)	0.2 (0.9)	0.1 (0.9)	0.2 (0.8)

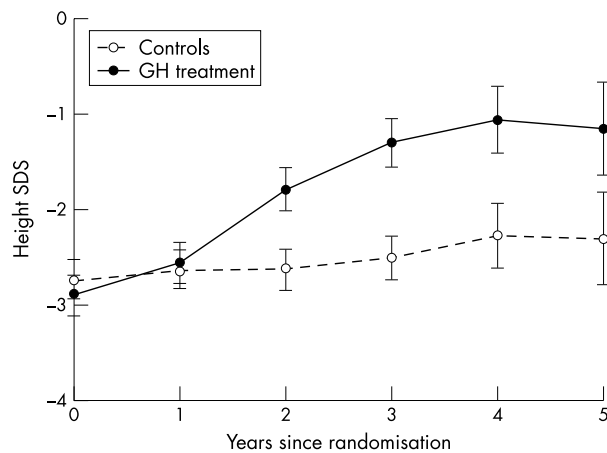


Figure 1 Height SDS for chronological age during five years of study in GH treated children compared to controls. Bars represent the 95% confidence intervals of the means.

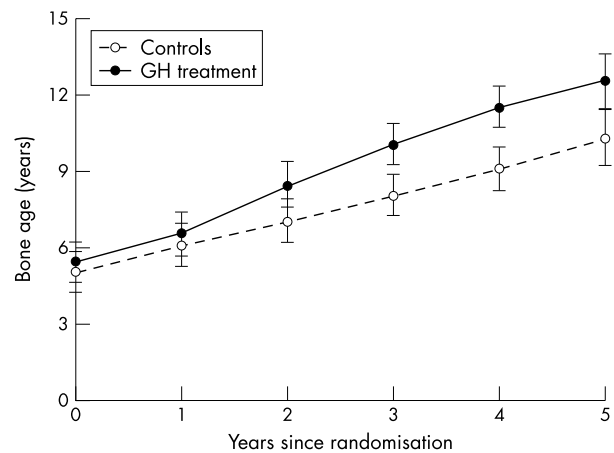


Figure 2 Bone age during five years of study in GH treated children compared to controls. Bars represent the 95% confidence intervals of the means.

SDS for chronological age (CA) and for bone age (BA) according to Dutch references.²⁰ Body mass index (BMI) was calculated (weight/height²) and expressed as SDS.²⁴ Sitting height and sitting height/height ratio were also expressed as SDS.²² Target height was calculated (father's height + mother's height + or - 12 cm for boys and girls, respectively)/2 + 3 cm (for secular trend) and expressed as SDS.²⁰

GH protocol

GH was administered seven days per week subcutaneously, between 1800 and 2000 hours. Biosynthetic hGH (Genotropin) was kindly provided by Pharmacia & Upjohn AB (Stockholm, Sweden). To assess GH responsiveness, children assigned to the GH treatment group were treated according to the protocol of the "GH dose response study" during the first year of study. GH treatment was administered during two periods of three months with either 1.5 or 3.0 IU/m², separated by two washout periods of three months without GH treatment. Results of this part of the study are described elsewhere.^{24a} After one year of study, high dose GH treatment with 6.0 IU (= 2 mg) per m² per day was started. In children with a body surface area close to 1 m², this dose is equivalent to 0.21 IU (0.07 mg) per kg body weight per day (0.5 mg/kg/week). GH treatment was discontinued after the onset of puberty had occurred. However, all children received at least two full years of treatment. When puberty occurred after these two years, GH treatment was discontinued at the end of a complete year's treatment (for example, three or four years of GH treatment).

Statistics

Results are expressed as mean (SD). Baseline characteristics of controls and GH treated children were compared using an unpaired *t* test. Differences in auxological characteristics between controls and treated children were analysed using mixed model analysis of variance. The cumulative proportion of children in puberty was illustrated with Kaplan–Meier curves and tested for differences between controls and treated children using the log rank test. Correction for confounding effects of age and sex was done using the Cox regression model.

RESULTS

Auxology

Baseline characteristics were not different between controls and GH treated children (table 1). Table 2 shows the number of non-treated and treated children during five years of follow up in relation to the auxological data. Height SDS for chronological age (CA) showed a small but not significant increment

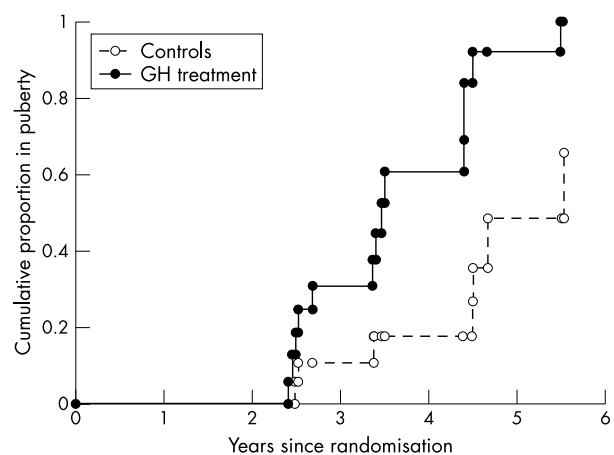


Figure 3 Cumulative proportion of GH treated and control children in puberty since start of study, adjusted for age at randomisation and sex.

of 0.3 SDS during the first year of low dose treatment. However, in the second and subsequent years of high dose GH treatment, height SDS for CA increased significantly ($p < 0.001$) in treated children compared to controls (fig 1). BMI SDS was not significantly influenced by GH treatment. Bone age advancement was not different between non-treated and treated children during the first year of low dose treatment. However, there was a statistically significant ($p = 0.001$) difference in bone age advancement in the second and subsequent years after high dose GH treatment compared to controls (fig 2). Height SDS for bone age (BA) decreased in both groups, and was not different ($p = 0.96$) between GH treated children and controls during five years of follow up. Sitting height SDS increased significantly in GH treated children compared to controls ($p = 0.012$). Body proportions, however, expressed as the ratio of sitting height/height SDS, were not altered by GH treatment ($p = 0.96$).

Puberty

In boys, 11 of 13 GH treated children entered puberty during the study period compared to seven of 13 controls, with a median age of 12.2 and 13.9 years respectively. In girls, two of four treated girls, with a median age of 10.2 years, entered puberty, whereas one control of five entered puberty at the age 9.9 years.

Figure 3 shows the cumulative proportion of children in puberty for both GH treated children and controls. The number of GH treated children in puberty exceeded the

number of control children in puberty after three, four, and five years of study. The relative risk for an earlier puberty of GH treatment was 6.9 (2.1–22.3, $p = 0.0002$). There was a statistically non-significant difference in age at randomisation between controls and GH treated children. Therefore, we calculated the relative risk for an earlier puberty of GH treatment adjusted for age and sex; the adjusted relative risk was 4.7 (1.4–15.8, $p = 0.012$). Fifty per cent of GH treated children were in puberty after 3.5 years since randomisation compared to 50% of controls after 4.7 years since randomisation. When analysing only the children of 8 years or older at randomisation (seven controls and eight GH treated children, mean ages 9.8 years and 9.8 years respectively, $p = 0.68$), the relative risk for an earlier puberty of GH treatment was 4.2 ($p = 0.06$).

DISCUSSION

We report five year results of a randomised controlled study of 26 boys and nine girls with ISS. Our study design was based on several current concepts regarding GH treatment in ISS. First, our children were randomised around the age of 8. Previous studies indicate that young children with ISS may benefit most from GH treatment.^{25–27} In particular, we sought to maximise the duration of prepubertal GH treatment, as an association between the height at onset of puberty and final height was reported.^{18–19} Second, we used a relatively high GH dose of 6.0 IU/m². Evidence suggests a GH dose dependent relation in the first year growth response, expressed as change in height velocity or change in height SDS.^{4 6 17 26 28 29} Similarly, a comparison of various studies of GH treatment^{7 8 13 30} revealed a GH dose dependent relation for final height.¹⁷ Third, we discontinued GH treatment as soon as the first signs of puberty occurred. Rekers-Mombarg and colleagues reported a substantial height gain before puberty, but no change in height SDS during puberty⁹ despite continuation of GH treatment. Thus, our study was designed to maximise final height with an optimal cost–benefit ratio, using short term high dose GH treatment restricted to the prepubertal period.

Height SDS for chronological age improved significantly in GH treated children compared to controls. The magnitude of the increment in height SDS after GH treatment with 6.0 IU/m² was comparable to the findings of Lesage and colleagues⁴ after 9.0 IU/m². However, bone age advanced 3.6 years/2 years on high dose GH treatment compared to 2 years/2 years in untreated controls. As a result of this rapid rate of bone maturation, height SDS for bone age (BA), a predictor of final height,⁵ did not improve in GH treated children or controls. These results suggest that short term benefits on height SDS for chronological age may not be followed by a gain in final height.

There are two studies with data on bone maturation before puberty in relation to GH treatment.^{7 10} In these studies GH treatment was started around 8 years, similarly to our study design. Kawai and colleagues¹⁰ also showed that height SDS for BA did not improve during prepuberty, at a much lower GH dose (approximately 2 IU/m²) than utilised in our study. In contrast, McCaughey and coworkers⁷ found no accelerating effect on bone maturation, employing a randomised controlled study design with an intermediate GH dose of approximately 4 IU/m²/day. We showed a rapid rate of bone maturation on a GH dose of 6.0 IU/m²/day, which was not mediated by sex steroids, as all children were still prepubertal during the second year of study. It is difficult to compare our results with studies that started GH treatment at a later age. Some authors reported a rapid rate of bone maturation after GH treatment,^{10 12 29} but others did not.^{4 25} Inclusion of children in puberty has probably biased results because sex steroids advance bone maturation. Moreover, none of these studies included randomised controls. Thus, our results support the concept that high dose GH treatment during prepuberty has undesirable effects on bone maturation.

Our study is the first to show an earlier puberty as a result of GH treatment in children with ISS compared to randomised controls. Pubertal staging was performed in a prospective manner in both GH treated children and controls at all visits by one single investigator. We closely searched for early signs of puberty because our protocol included a stop of GH treatment in the year after the onset of puberty. Intervals between visits to the clinic did not influence the accuracy of the estimated onset of puberty because comparisons of full year data of both GH treated children and controls were made. Age at start of randomisation as a confounding factor could not have influenced the results of our study. There was a non-significant difference in age between GH treated children and controls, and adjustment for age did not alter the effects of GH on the earlier onset of puberty. Moreover, analysing a small group of children older than 8 years at the start of the study showed the same result.

The absence of a relation between GH treatment and an earlier onset of puberty in most previous studies may be explained by differences in age, reference data for pubertal onset, and GH dose. First, if GH treatment is started just before the normal age of puberty, no early onset of puberty is to be expected.^{11 14 31} Second, some studies used the pubertal data of reference populations for comparison.^{11 12 31} This introduces a bias about the effect of GH treatment on puberty in ISS, because the age at onset of puberty in non-treated ISS children is later than in normal children.^{14 32} A third explanation for the failure to find a relation between prepubertal GH treatment and an earlier onset of puberty is that lower GH doses were used in these studies.^{7 11 13 14 31} Two studies^{9 10} did also show an earlier onset of puberty in GH treated girls and boys, while being treated with lower GH doses than our 6.0 IU/m². The early onset of puberty in these studies is probably related to selection procedures of the controls, and not to GH treatment. Kawai *et al* used GHD individuals as controls.¹⁰ This may have resulted in an increase in pubertal onset difference between groups, since GHD children have delayed puberty.⁵ In the study of Rekers-Mombarg and colleagues,⁹ the intervals between visits to the clinic in historical ISS controls were much longer compared to GH treated children, probably introducing a false late assessment of puberty in controls. Thus, in view of previous investigations, it is the combination of young age at GH treatment, use of randomised controls, and treatment with a relatively high GH dose that lead to our finding of an earlier onset of puberty in GH treated children. Again, this factor may compromise the potential effect of GH treatment on final height.

The advanced rate of prepubertal bone maturation in our GH treated children may be the result of GH induced oestradiol secretion by the gonads,³³ or a result of direct stimulation of GH and insulin like growth factor (IGF-I) receptors in the growth plate.³⁴ The effect of GH on the onset of puberty may be ascribed to a direct effect of GH and/or IGF-I on the hypothalamus. However, to date, no GH or IGF-I receptors have been identified in the hypothalamus or pituitary, but it is known that IGF-I can influence hypothalamic function; IGF-I can exert a negative feedback on GH secretion. Wilson *et al* have shown that GH may facilitate ovarian maturation by synergistic action with gonadotropins.³³ In their study in female rhesus monkeys they showed that GH treated intact animals have an earlier initial rise in serum LH concentrations and secrete significantly higher amounts of estradiol compared to non-treated intact animals. Thus, an earlier onset of puberty in our GH treated children may be caused by this direct effect of GH on the gonads. Alternatively, an IGF-I effect on gonadal sex steroids secretion is hypothesised, as IGF-I receptors are also present on the gonads.³⁵

We conclude that short term, high dose GH treatment during prepuberty results in a significant improvement of height SDS, but an unexpected high rate of bone maturation and an

earlier onset of puberty were observed. At present we have no indication that young children with ISS benefit from high dose GH treatment in the prepubertal period.

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COMMENTARY

Many children with short stature of ill defined aetiology, so called idiopathic short stature (ISS), have received growth hormone (GH) treatment over the past 10–15 years with the aim of improving their final height. These children are short when compared to parental height, have normal GH reserve during standard GH provocation tests, absence of other endocrine or chronic disease or bone dysplasia, and normal intrauterine growth. Many such children may have constitutional delay in growth, in itself a poorly understood abnormality in the tempo of growth and physical maturation. Despite normal GH reserve, these children may have ill defined dysfunction in the GH-IGF-I axis.

Many of these children have now reached final height, and we are beginning to be able to define how much height has actually been gained.¹ This analysis is by no means easy, as few of the studies in ISS have had matched contemporaneous control groups. Nevertheless a few firm conclusions may be drawn:

- Response to GH in the short, mid, and long term is markedly variable. This is likely to reflect the diverse causes for the short stature gathered under the umbrella of ISS.
- Overall gains in final height reported in a range of studies performed in different populations are 3–9 cm. However on

an individual basis, there are children in these studies who have not gained in height at all, while others have shown a considerable increase.

- Improvements in growth velocity and increments in height SDS on GH in the prepubertal years are dose dependent.

Kamp and colleagues now report a different strategy for treating ISS children. They have reasoned that a possible way to optimise the cost–benefit of GH treatment is to use high dose GH (6 IU/m²/day = 2 mg/m²/day ≅ 70 µg/kg/day) up to the peripubertal period but not thereafter. This tactic is further supported by data indicating that GH treatment over the pubertal years does not lead to further height gain above that achieved during the prepubertal years. Unfortunately this strategy is not without disadvantage as Kamp *et al* have found. Pubertal onset was brought forward significantly compared to untreated controls, while bone age advanced 3.6 years over two years in the treated group and an expected 2 years in the controls. Height SDS for bone age (as a marker of possible final height) after five years was not different between the groups. This is an important and timely observation. The dose dependent growth response in this condition has been a temptation to use ever larger doses of GH to buy height gain early in the hope that this gain will persist through to final height. A disturbance to the timing of puberty, with the onset being brought forward, could wipe out this gain.

There are a number of observations that link the GH and hypothalamic–pituitary–gonadal axes. Boys with congenital GH deficiency (GHD) can have poor phallic development and undescended testes. Children with isolated idiopathic GHD enter puberty later than normal children. In addition there is both *in vivo* and *in vitro* evidence that GH acts as a gonadotrophin, enhancing the effect of FSH/LH on the gonad.² Other animal data implicate GH and/or IGF-I in the reactivation of the gonadotrophin releasing hormone (GnRH) pulse generator that is the hallmark of the initiation of the pubertal process. It is perhaps not surprising therefore that high dose GH in the prepubertal years can increase bone maturation and bring forward the onset of puberty.

Other studies in ISS, although not all, have reported positive effects of GH on the onset of puberty and the excess accrual of bone age over chronological age during the prepubertal years. In some of these studies, there has been concern about the control group used for comparison of the timing of pubertal events. Kamp and colleagues' study circumvents this problem by having contemporaneous randomly assigned controls. The latter were one year younger than the treated group at enrolment, but only had 0.6 years less bone age delay. Nonetheless the number of treated children entering puberty before the controls was very significant, and could still be seen when only the older children (>8 years at start) were assessed.

Why is this study a timely observation? This relates to another group of children, whose long term response to GH has been extensively studied over the past decade. Children who are born small/short for gestational age (SGA) and fail to catch up in their early postnatal years have been treated with a range of GH doses in either continuous or intermittent regimens. Within this group, there are diverse aetiologies, often poorly defined as seen in ISS, for the growth disorder: the group may encompass those with Russell–Silver syndrome, those with ill defined dysmorphic syndromes, and/or those with dysfunction in the GH–IGF-I axis. In the natural course of their growth and development, some of these children will develop premature adrenarche and/or early puberty.

Studies of GH use over 5–6 years in children with SGA have been reported,^{3,4} which include treatment groups receiving comparable GH doses to those used by Kamp *et al* in ISS (namely 2 mg/m²/day). Patients showed a significant increase in height SDS, but bone age did advance significantly more than chronological age. Nevertheless Sas and colleagues³ have shown that the increase in height SDS for bone age remained significant, implying height gain despite bone age advance. In studies assessed by de Zegher and colleagues,⁴ bone age advanced 1.6 years more than chronological age over six years treatment with high dose GH (67 or 100 µg/kg/day). These children were 4–5 years of age at the start of treatment, and therefore further follow up will be required to assess timing and duration of puberty in the whole group.

Final height data on GH treatment have been reported in SGA.¹ Similar to ISS, the early and mid-term responses to GH are variable, and overall height gain is of a similar magnitude to that seen in ISS. Extrapolating from Kamp and colleagues' study, any strategy that aims to maximise prepubertal growth with high dose GH in SGA may be at risk of bringing forward puberty in a condition where this is already an underlying risk. It is possible to ameliorate this problem by use of GnRH analogues to halt pubertal progression, but this requires polypharmacy and more injections.

Wider use of GH in ISS and SGA children will require careful surveillance, and judicious use of GH dosing. Kamp and colleagues' study illustrates a number of important points about GH studies:

- Matched contemporaneous controls followed long term are essential in new indications or new strategies for using GH.
- GH has potent growth promoting, anabolic, and metabolic actions, but it also affects other hormonal systems, such as the gonadal axis.
- The dose response for the different actions of GH in the range of conditions where GH is already used has not been rigorously defined.

Growth hormone has been used therapeutically in a very wide range of conditions, not only in children but also in adults. It is right that we should explore potential indications for this important biological drug. We should not however forget that we must also continue to explore the basic molecular mechanisms that create these varied actions and try to understand how such actions affect individual patients. It is this sort of approach that might lead to a modification to GH regimens that achieve height gain, but reduce the influence on upregulation of the tempo of maturation.

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