Growth Hormone Treatment of Short Children Born Small for Gestational Age

Francis de Zegher, Inge Francois, Monique van Helvoirt, Dominique Beckers, Lourdes Ibáñez and Pierre Chatelain

Short children born small-for-gestational-age (SGA) appear to be at an increased risk of having a poly-endocrinopathy, including a degree of growth hormone (GH) deficiency and/or insulin-like growth factor 1 (IGF-1) resistance. Among GH-deficient children, those born SGA present a lower growth response to GH therapy than those not born SGA. The growth response of short SGA children to GH treatment does not appear to depend significantly on the secretory status of GH (as judged by provocative testing), indicating that the SGA condition (IGF-1 resistance) predominates over the availability of endogenous GH in determining the short stature of the majority of these children. When a higher than replacement dose of GH is administered, the growth response of short SGA children matches that of GH-deficient non-SGA children, indicating that the IGF-1 resistance towards growth can be overcome, and that a normal stature can be obtained, at least throughout childhood. It is anticipated that, increasingly, the indications and the doses for GH therapy in children will become interlinked with the emerging principles of endocrine programming in early life.

By definition, nearly three percent of human infants are born small-for-gestational-age [SGA; low standard deviation score (SDS) for weight and/or length at pre-term or term birth]. The majority of SGA infants present sufficient postnatal catch-up growth to normalize their stature by two years of age, independently of whether they were born prematurely or at term (Hokken-Koelega *et al*. 1995). Approximately ten percent of children born SGA remain short – they maintain a height below –2 SDS throughout childhood (Karlberg and Albertsson-Wikland 1995). Although small body size of prenatal origin was among the very first conditions treated with growth hormone (GH) (Ducharme and Grumbach 1961), paradoxically, it was one of the last forms of proportionate short stature to be explored with exogenous GH in a randomized, controlled fashion (de Zegher *et al*. 1996a). In the meantime, the pathophysiological rationale for GH treatment in short SGA children has been consolidated [reviewed in de Zegher *et al*. (1997b)].

Here, we summarize the results obtained with GH treatment in short SGA children, as classified into three subgroups. For the first two subgroups (short SGA children with GH deficiency or Turner syndrome), GH treatment is a recognized therapy and, accordingly, analysis for these subgroups is based on clinical experience, details of which are available from KIGS, an international database containing growth results and adverse events documented in children receiving GH treatment (de Zegher *et al*. 1998). For the third subgroup (short SGA children without GH deficiency or Turner syndrome), GH treatment has been explored in clinical trials, and results from these studies are reviewed and compared with clinical experience. In all three subgroups, attention is focused on prepubertal children who were aged between two and eight years at the start of GH treatment and who were followed for at least two years.

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- **SGA and GH Treatment**

The KIGS database contains information on a large cohort of children receiving GH treatment (n = 23 333 by May 1997), with data on birthweight and gestational age being available for 93% of these. The prevalence of the SGA condition was examined within KIGS. Here, only birthweight SDS for gestational age was taken into account, the SGA condition being defined as a birthweight below –2 SD for gestational age and the prevalence being adjusted for the ethnic diversity of birthweight. The appropriate-for-gestational-age (AGA) condition was defined as any non-SGA condition. The overall prevalence of GH treatment was found to be approximately twice as high in SGA as in AGA children.

- **SGA and GH Deficiency**

Idiopathic GH deficiency is the largest diagnostic category within KIGS (n >10 000). The prevalence of GH treatment for idiopathic GH deficiency was found to be at least 50% higher in the SGA than in the AGA children, presumably because SGA children are at higher risk of developing 'idiopathic' GH deficiency [reviewed in de Zegher *et al*. (1997b)].

Table 1 summarizes some characteristics of prepubescent AGA and SGA children treated with GH over two years for idiopathic GH deficiency. Although the AGA and SGA groups were similar for age, height SDS (adjusted for parental height) and GH dose, the height gain over two years of conventional GH treatment was nearly 20% higher in AGA than in SGA children, while the safety profile was similar (de Zegher *et al*. 1998). These findings corroborate

Table 1. Characteristics (mean and SD) of prepubertal AGA and SGA children treated with GH over two years (age range at start 2–8 years) because of idiopathic GH deficiency, as registered by KIGS [de Zegher *et al.* (1998)]

GH Deficiency 0–2 y	*AGA*	*SGA*	p
n	1329	238	
Birthweight SDS	–0.5 ± 0.9	–2.8 ± 0.8	<0.0001
Age at start (y)	5.5 ± 1.5	5.5 ± 1.5	NS
Parental-adjusted height SDS	–2.2 ± 1.3	–2.2 ± 1.3	NS
GH dose (IU kg^{-1} wk^{-1})	0.54 ± 0.17	0.55 ± 0.20	NS
Δ height SDS 0–2 y	1.09 ± 0.65	0.89 ± 0.58	<0.0001
			mean ± SD

The AGA and SGA groups were similar for age and parental-adjusted height SDS at start of treatment, and for GH dose. The increase in height SDS was approximately 20% higher in AGA than in SGA children. NS = not significant ($p > 0.01$).

the notion that the somatotropic axis of SGA children might be altered at multiple sites (Balsamo *et al*. 1995, Chatelain *et al*. 1996, de Zegher *et al*. 1996b). Specifically, the growth responses of GH-deficient SGA children to conventional GH treatment indicate that, as a group, short SGA children have a dysfunctional component in the peripheral part of their somatotropic axis (Rosenfeld 1996) at a level beyond the availability of GH and even beyond the generation of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) (Boguszewski *et al*. 1996, de Zegher *et al*. 1996b). The ensuing question is whether the latter hyporesponsiveness can be overcome by administering a higher dose of GH (see below).

- **SGA and Turner Syndrome**

Turner syndrome is the largest diagnostic category in KIGS for which GH therapy is provided consistently in higher than substitutive doses (n ~3000). The prevalence of GH treatment for Turner syndrome was found to be nearly three times higher in SGA than in AGA girls, presumably because girls with Turner syndrome are at higher risk of being born SGA. Table 2 summarizes some characteristics of young AGA and SGA children treated with GH for Turner syndrome. GH treatment with a higher dose over two years resulted in a similar height gain and safety profile for AGA and SGA girls with Turner syndrome (de Zegher *et al*. 1998). These findings indicate either that the SGA condition does not detectably affect the growth response to exogenous GH in Turner syndrome, or that the impact of the SGA status on the growth response is overcome by the use of a higher GH dose. Current evidence cannot differentiate between these two possibilities. Independently of the underlying pathophysiology, at present there is no basis to recommend the use of a higher GH dose in SGA as compared with AGA girls with Turner syndrome.

Table 2. Characteristics (mean and SD) of prepubertal AGA and SGA girls with Turner syndrome treated with GH over two years (age range at start 2–8 years), as registered by KIGS [de Zegher *et al.* (1998)]

Turner Σ 0–2 y	*AGA*	*SGA*	p
n	136	44	
Birthweight SDS	–0.62 ± 0.87	–2.75 ± 0.69	<0.0001
Age at start (y)	5.5 ± 1.5	5.7 ± 1.6	NS
Parental-adjusted height SDS	–2.2 ± 1.3	–2.1 ± 0.7	NS
GH dose (IU kg^{-1} wk^{-1})	0.83 ± 0.24	0.82 ± 0.29	NS
Δ height SDS 0–2 y	0.76 ± 0.39	0.75 ± 0.49	NS
			mean ± SD

The AGA and SGA groups were similar for age and parental-adjusted height SDS at start of treatment. The GH dose was relatively high in both groups. The increase of height SDS in SGA girls was similar to that in AGA girls. NS = not significant ($p > 0.01$).

- **SGA without GH Deficiency or Turner Syndrome**

Randomized, controlled, multicenter trials established the ability of GH treatment to normalize the height of short, prepubertal SGA children without GH deficiency or Turner syndrome, apparently without increasing the incidence of precocious puberty, glucose intolerance, hypertension or other adverse effects (de Zegher *et al*. 1996a and 1997a). The GH dose, the child's age and – to a lesser extent – the parental-adjusted height SDS at the start of treatment were found to be crucial determinants of the growth response (Chatelain *et al*. 1994, de Zegher *et al*. 1996 a and b, Albanese and Stanhope 1997); placebo injections induced no consistent growth acceleration (Chatelain *et al*. 1994). Dose-dependent increases in height and weight gain were observed over two years (Fig. 1). GH treatment was well tolerated in all study groups.

The importance of the child's age has long been underscored as a determinant of the growth responses to GH, of bone maturation and, consequently, of the effect on final height prognosis. For a quarter of a century, GH treatment has been explored without parallel controls, and this approach has led to a prolonged underestimation of the efficacy of GH treatment in short SGA children [reviewed in de Zegher *et al*. (1997a)]. The capacity of GH treatment to increase final height prognosis – despite an acceleration of bone maturation (de Zegher *et al*. 1996a, b and 1997b) – is evident when studies include randomized controls and when both the GH dose and the children's ages are taken into account (Fig. 2).

- **SGA with GH Deficiency versus SGA without GH Deficiency**

GH stimulation tests have long been used to categorize children as either GH deficient or not. In many countries, GH-deficient SGA children receive GH treatment as a recognized therapy (registered by KIGS), whereas non-GH-deficient children might only be treated within the framework of clinical trials (see above). This setting provided an opportunity to delineate the relative impacts of GH deficiency and the SGA condition on the response to exogenous GH: growth results of GH-deficient SGA children were compared with those of non-GH-deficient SGA children. As shown in Table 3, GH-deficient and non-GH-deficient SGA children presented similar growth responses to matched doses of GH. These findings indicate that the SGA condition predominates over the GH secretory status (judged by provocative testing) in determining the growth response to exogenous GH (de Zegher *et al*. 1998).

- **Efficacy of GH Treatment: SGA versus GH Deficiency**

As stated above, an important question is whether the ~20% deficit in the growth response to GH, observed in SGA as compared with AGA children, can be compensated for over a prolonged period by administering a dose of GH that is ~20% higher. This issue was addressed by comparing the four-year growth responses of GH-deficient AGA children with those of SGA children (pooled results of GH-deficient and non-GH-deficient children, see above), the latter receiving a 20% higher dose of GH. As shown in Table 4, the growth response of SGA children was similar to that of the reference population, indicating that the GH-induced height gain in SGA children can be normalized over at least four years by administering a GH dose that is slightly higher than the conventional GH dose (de Zegher *et al*. 1998).

- **Conclusions and Future Directions**

This overview of epidemiological and experimental data on GH treatment of short children born SGA summarizes

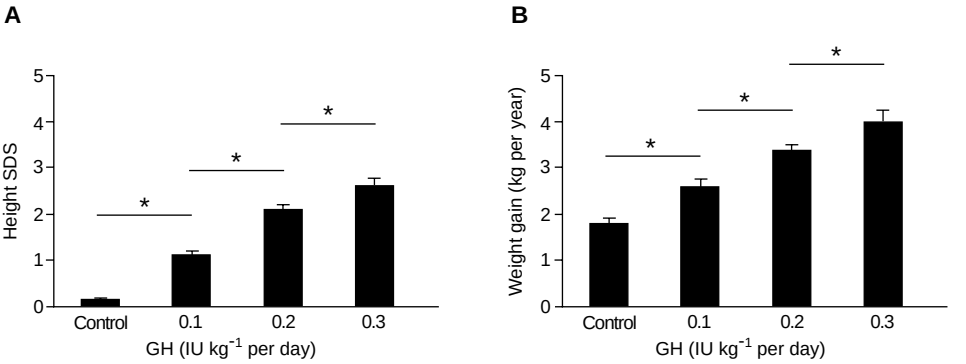

Figure 1. Epi-analysis results of (**A**) height and (**B**) weight gain (mean and SEM) from three independent, randomized, controlled, multicenter studies in short, prepubertal, non-growth hormone (GH)-deficient SGA children treated with three doses of GH over two years (0.1–0.3 IU kg^{-1} daily, corresponding to 0.70–2.10 IU kg^{-1} per week). The study population (n = 146) had a mean standard deviation score (SDS) of –2.9, birthlength SDS of –3.6, chronological age of 4.9 years (range, 2–8 years), actual height SDS of –3.6 and weight SDS of –6.3. Adapted from de Zegher *et al*. (1996a). *, p <0.01.

novel insights, namely: (1) According to clinical experience, SGA children are over-represented in the global population of children receiving GH treatment. Hence, prenatal growth restrictions and postnatal GH treatment are more closely related than has been recognized previously. (2) The prevalence of idiopathic GH deficiency appears to be higher in SGA than in AGA children, and the growth response to conventional GH treatment appears to be ~20% lower in SGA children than in GH-deficient AGA children. (3) In Turner syndrome, there appears to be no need to increase (further) the GH dose for SGA as compared with AGA girls. (4) Controlled studies have provided evidence that supports the administration of GH in early childhood as an effective and well-tolerated treatment to normalize, in a dose-dependent fashion, the short stature of those SGA children without GH deficiency or Turner syndrome. Currently, different regimens of GH treatment (continuous vs intermittent higher dose) are being explored over a longer term. (5) The magnitude of the growth response to exogenous GH in short SGA children appears to be determined by the SGA condition rather than by the secretory status of GH. (6) The 20% deficit in GH-induced height gain of SGA children, as compared with GH-deficient AGA children, can be overcome for

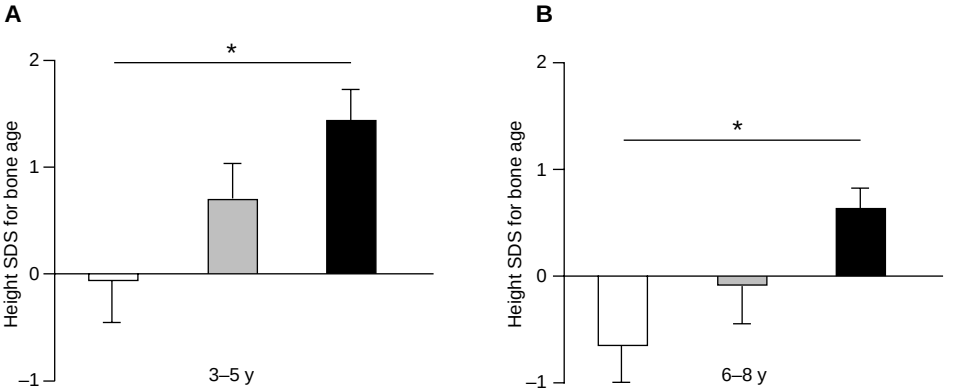

Figure 2. Change in height standard deviation score (SDS) for bone age (mean and SEM) in (**A**) younger and (**B**) older short, prepubertal SGA children over two years. Children were randomized to be either untreated (control; open bar) or to receive growth hormone (GH) treatment at a low dose (0.1 IU kg^{-1} daily; shaded bar) or a high dose (0.2 or 0.3 IU kg^{-1} daily; closed bar). The indicated ages are mean ages during the two-year study period (age range at start, 2–8 years). The study population was the same as for Fig. 1. Adapted from de Zegher *et al*. (1996a and 1997a). *, p <0.01.

Table 3. Baseline characteristics and growth responses (mean and SD) over two years of GH treatment in dose-matched groups of prepubertal SGA children (age range at start 2–8 years) with idiopathic GH deficiency (from KIGS) and without GH deficiency (from clinical trials) [de Zegher *et al.* (1998)]

SGA 0–2 y	*GHD KIGS*	*non-GHD trials*	p
n	55	82	
Age at start (y)	5.4 ± 1.5	5.1 ± 1.5	NS
Parental-adjusted height SDS	–2.2 ± 1.2	–2.1 ± 1.3	NS
GH dose (IU kg^{-1} wk^{-1})	0.68 ± 0.05	0.69 ± 0.05	NS
Δ height SDS 0–2 y	0.98 ± 0.51	1.05 ± 0.45	NS
			mean ± SD

The GH-deficient and non-GH-deficient groups were comparable in age and parental-adjusted height SDS at start of treatment. The increase in height was similar in GH-deficient and non-GH-deficient SGA children.

several years by administering an average GH dose that is ~20% higher than the conventional GH dose.

Thus, GH treatment is established as a promising therapy that tends to normalize the stature of short, prepubertal children born SGA. This treatment deserves further exploration. A few avenues for potentially fruitful further research are outlined below.

(1) Although progress has been made in our understanding of the somatotropic axis of short SGA children, more insight is needed at the cellular and molecular levels, not only into the pathophysiology of diminished growth in short SGA children, but also into the prenatal pathogenesis of the postnatal growth failure in these children. The elucidation of the mechanism underlying the IGF-1 resistance of short SGA children is a challenge which is of particular interest (Rosenfeld 1996).

(2) There is increasing evidence that the endocrinopathy of short SGA children might not be restricted to the somatotropic axis. Endocrine topics that are being studied include: insulin sensitivity (Hofman *et al*. 1997, Ibañez *et al*. 1998), adreno-cortical function (Clark *et al*. 1996, Francois and de Zegher 1997, Ibáñez *et al*. 1998) and gonadal function (Francois *et al*. 1997, Ibáñez *et al*. 1998). The potential impact of GH treatment on these endocrine aspects of short SGA children remains to be delineated.

(3) The spectrum of GH doses and administration schedules that has been explored in SGA children is more extensive than in any other condition of prepubertal short stature. It is plausible that this experience, once consolidated, will facilitate the individualization of GH treatment schedules through the use of validated growth prediction models.

(4) To our knowledge there are at present no controlled data on the pubertal growth component of short SGA children treated with GH before and/or during puberty. It remains to be established to what extent the attenuated pubertal growth spurt of short SGA children (Preece 1997) can be modulated by prepubertal and/or pubertal GH treatment.

(5) Hitherto, the effects of GH treatment on the growth of short SGA children have been judged mainly by changes in total body height and weight. However, skeletal growth in these children might be affected differentially by both prenatal growth restriction and GH treatment, as exemplified by the craniofacial complex (Van Erum *et al*. 1997). A similar phenomenon might occur among and even within non-skeletal organs and systems. The relative amounts of muscle- and fat-mass, the lymphoid system, the heart, the eyes, the liver and the kidneys of SGA children are all likely to receive attention in future studies.

(6) Until now, a basic idea about the growth of short SGA children was that adverse environmental factors during early life had definitively 'reprogrammed' the (genetic) growth trajectory of these children towards a lower level (Widdowson and McCance 1963 and 1975, Barker 1994, Gluckman *et al*. 1996). However, the majority of SGA children, who received high-dose GH treatment for two years in early life (de Zegher *et al*. 1996b), now appears to be capable of maintaining (for up to

Table 4. Characteristics and growth responses (mean and SD) over four years of GH treatment (age range at start 2–8 years) in prepubertal AGA children with idiopathic GH deficiency (from KIGS), as compared to prepubertal SGA children with or without idiopathic GH deficiency (selected for mean GH dose from KIGS and from clinical trials, respectively) [de Zegher *et al.* (1998)]

0–4 y	*AGA + GHD*	*SGA*	p
n	707	81	
Birthweight SDS	–0.42 ± 1.0	–2.7 ± 0.9	<0.0001
Age at start (y)	5.4 ± 1.5	4.9 ± 1.5	NS
Parental-adjusted height SDS	–2.5 ± 1.3	–2.6 ± 1.4	NS
GH dose (IU kg^{-1} wk^{-1})	0.57 ± 0.15	0.70 ± 0.05	<0.0001
Δ height SDS 0–4 y	1.55 ± 0.87	1.49 ± 0.71	NS
			mean ± SD

SGA children received either a dose of 0.7 IU kg^{-1} per week over 4 years (n = 67) or 1.4 IU kg^{-1} per week over two years followed by two years without GH administration (n = 14); these treatment regimens are known to result in a similar increase in height SDS over four years [de Zegher *et al.* (1997b)]. The GH-deficient AGA children and the SGA children had a similar age and parental-adjusted height SDS at the start of treatment. Note the GH dose difference between groups. The increase in height SDS in SGA children was similar to that of GH-deficient AGA children. The results indicate that the nearly 20% lower increment of height SDS in SGA children (Table 1) can be overcome by administering a nearly 20% higher dose. NS = not significant (p >0.01).

four years after GH withdrawal) a growth trajectory close to the genetic target level, and do so without advanced bone maturation. These observations indicate that early, short-term, high-dose GH administration holds potential as a 're-programming' treatment and could be a curative rather than symptomatic therapy for short SGA children. This fascinating possibility is becoming a focus of active research.

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