

## Growth Hormone Treatment in Children Born Small for Gestational Age— Adult Height and Metabolic Consequences

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DOI: 10.17925/USE.2010.06.1.63

### Abstract

Short-term studies of children born small for gestational age (SGA) who do not adequately catch up have shown that growth hormone (GH) treatment over a range of doses is both safe and effective at increasing growth velocity and height standard deviation (SD). Long-term studies have shown an improvement in adult height compared with untreated controls. Predictors of growth response include height and weight at start of GH treatment, pre-treatment growth velocity, target height, and pre-pubertal years treated with GH. Height prediction models are being developed to help maximize GH treatment response. While some short-term studies of GH treatment in SGA children have shown abnormalities in carbohydrate metabolism, long-term studies have demonstrated that these changes were transient. GH treatment has been shown to be safe and effective in increasing adult height of children born SGA. Follow-up is needed for assessment of the long-term effects of GH treatment.

### Keywords

Small for gestational age, growth hormone treatment, adult height, metabolic comorbidities, height prediction

**Disclosure:** Michelle L Klein, MD, has no conflicts of interest to declare. Robert Rapaport, MD, has been a consultant to and served on advisory boards for Novo Nordisk, Pfizer, and Serono, and has performed contracted research for Eli Lilly.

**Received:** October 8, 2010 **Accepted:** November 12, 2010 **Citation:** *US Endocrinology*, 2010;6:63–70

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**Support:** The publication of this article was funded by Novo Nordisk. The views and opinions expressed are those of the authors and not necessarily those of Novo Nordisk.

For decades, small for gestational age (SGA) has been inconsistently defined as a birth weight or length below the 10th, 5th, or 3rd percentile, making uniform assessment of the consequences of being born SGA difficult. In 2007, a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society (GRS) recommended a definition of SGA as a birth weight and/or length  $<-2$  standard deviations (SD) for gestational age.<sup>1</sup> The identification of children born SGA is important because of the effects on growth and development as well as the potential associated comorbidities.

Growth retardation in infancy and short stature in childhood are associated with being born SGA.<sup>2</sup> About 90% of children born SGA catch up to their genetic height potential by about two years of age.<sup>3</sup> Children born premature may take up to four years or more to catch up and are less likely to reach adequate stature than those born at term, especially if they were small for birth length.<sup>4</sup> The reason for growth failure in children born SGA is not completely understood, but theories include intrauterine programming, genetic predisposition, decreased growth hormone (GH) secretion, GH resistance, and reduced sensitivity to insulin-like growth factor (IGF-1).<sup>5–7</sup> Children born SGA who do not catch up have impaired adult heights.<sup>8</sup>

In 2001, the US Food and Drug Administration (FDA) approved human GH for treatment of growth failure in children born SGA who did not catch up by two years of age at a dose of up to 0.48mg/kg/week. In 2003, the European Agency for the Evaluation of Medicinal Products (EMA) approved GH treatment for SGA children who did not catch up by four years of age at a dose of 0.22mg/kg/week. Their criteria for treatment also included a height standard deviation score (SDS) at the start of treatment of  $\leq -2.5$  SD, a growth velocity of  $<0$  SD for age, and a height SDS  $>1$  SD below the mid-parental height. Metabolic abnormalities have been reported in children born SGA regardless of GH treatment and include insulin resistance, cardiovascular disease, type 2 diabetes, and liver disease.<sup>8–12</sup> This article will focus on the effects of GH treatment on short children born SGA, with emphasis on adult height and various metabolic parameters.

### Growth Hormone Treatment During Childhood

The goal of GH therapy in short SGA children is to improve growth velocity during childhood and normalize adult height. Short-term use of GH has been shown to be equally effective in increasing growth velocity and height SD in SGA children regardless of their GH status.<sup>13</sup> GH treatment has also been shown to increase height SDS in children born SGA whether or not they were born SGA for length, length and

weight, or length, weight, and head circumference.<sup>14</sup> Compared with term children born SGA, preterm SGA children had a similar growth response to GH treatment.<sup>15</sup> Initiation of GH therapy over a range of dosages (0.23–0.72mg/kg/week) has been shown to be effective in increasing growth.<sup>16–22</sup>

One study of 101 pre-pubertal SGA (birth weight <10%) children (mean age at start of GH 4.6 years) with heights >3 SD below the mean showed that a dose of 0.48mg/kg/week for a period of three years induced sustained catch-up growth.<sup>18</sup> Growth velocity doubled in the first year and was maintained for the subsequent two years. GH was well tolerated with minimal side effects.

Sas et al. performed a randomized, double-blind, dose–response study in a group of 79 pre-pubertal SGA (birth length SDS <-1.88) children treated for five years with a GH dose of 0.24 or 0.48mg/kg/week.<sup>23</sup> SGA children in both groups had normalization of height and continued to grow along their target height percentile. A dose-dependent response was seen in children who remained pre-pubertal during the entirety of the study with a mean gain in height SDS for bone age significantly more in the higher-dose group. This increase in height SDS was not significantly related to target height SD score, baseline bone age delay, pre-treatment height velocity SDS, baseline IGF-1 SD, or spontaneous GH secretion.

Over a three-year period a multicenter study looked at 48 short pre-pubertal SGA (birth weight and/or length <-2 SDS) children and divided them into three groups: no treatment, GH dose of 0.24mg/kg/week, or GH dose of 0.48mg/kg/week. Compared with the no treatment group, the groups treated with GH showed a dose-dependent increase in growth velocity and had a significant improvement in height SDS.<sup>24</sup> The higher dose of GH did not lead to an increase in GH-related adverse effects (with the exception of increased insulin levels) and was well tolerated.

Rapaport et al. conducted the first open-label, single-arm, multicenter clinical trial in the US looking at 139 short, pre-pubertal children born SGA.<sup>25</sup> These children (<-2 SDS below the mean for birth weight and/or length) received a fixed dose of GH (0.48mg/kg/week) for one year. Over a 12-month period an increase of height SDS of 0.78 ( $p<0.0001$ ) without clinically significant adverse events was observed. Underweight SGA children responded as well to GH treatment as non-underweight SGA children. They concluded that short-term treatment of short pre-pubertal SGA children at a higher fixed dose was safe and effective.

We are aware of only two studies that have challenged the efficacy of GH treatment. One study found no increase in adult height in 29 SGA (birth weight <10%) GH-deficient children (mean age at start of GH 10.9 years) treated with a GH dose of 0.24mg/kg/week for 36–84 months compared with 20 SGA non-GH-deficient children.<sup>26</sup> Another study showed only a modest increase in height in 70 GH-deficient SGA (birth length <-2 SDS) children (mean age at start of GH: 10.7 years) treated with a GH dose of 0.13mg/kg/week for a mean of 4.6 years compared with 40 non-GH-deficient SGA children.<sup>27</sup> Both studies used a lower GH dose than studies that have had success and had participants who were older at the start of the study.

### Growth Hormone Treatment and Adult Height

Without treatment, children born SGA remain short into adulthood and account for 10–20% of adults with heights <2 SD below the mean.<sup>28,8</sup> Meas et al. performed an eight-year follow-up study of 389 SGA (birth weight <10%) children and looked at their adult height at a mean age of 22 and 30 years.<sup>29</sup> The SGA children were compared with 462 children born appropriate for gestational age (AGA). They found that children born SGA were shorter than their AGA counterparts at both 22 and 30 years of age, with a mean difference of 6 and 5cm, respectively. There are several long-term trials that have studied adult height in SGA children treated with GH and these studies have previously been reviewed.<sup>30,31</sup> Many of these studies have limitations, including absence of control groups, inclusion of GH-deficient patients, varying definitions of SGA, small patient populations, and poor adherence and follow-up.

A randomized control study followed 77 short pre-pubertal children born SGA (<-2 SD in birth weight or birth length) over 8.5 years and compared them with 34 untreated short pre-pubertal SGA children. Long-term continuous GH treatment at a dose of 0.23mg/kg/week resulted in an adult height close to height predicted by the parents' stature.<sup>32</sup> The shortest, lightest, and youngest children had the best response to GH. Children receiving GH treatment for more than two years prior to puberty gained 1.7 SD of height (almost 12cm in increased adult height) compared with those treated less than two years prior to puberty, who gained 0.9 SD of height (9cm in increased adult height). Ninety percent of the children in this study treated with GH achieved an adult height within 1 SD of their target height compared with 50% of the untreated children born SGA. No adverse events considered to be drug-related were observed.

Van Pareren et al. carried out a randomized, double-blind, dose–response trial of long-term continuous GH treatment in short pre-pubertal SGA (birth length <-1.88 SD) children using adult height (height velocity <1cm/year or fusion of the growth plates) as the end-point.<sup>12</sup> Fifty-four children were treated with a GH dose of 0.23 or 0.47mg/kg/week for an average of eight years and compared with a control group of short pre-pubertal SGA children not treated with GH. Long-term continuous treatment of short SGA children resulted in normalization of height during childhood and adult height in most children compared with non-treated controls. The difference in adult height SDS was not statistically significant between the GH treatment groups. Eighty-five percent of children treated with GH had adult heights within the normal range and 98% were within the target height range.

Carel et al. performed a randomized controlled trial of GH treatment in 102 SGA (birth length <-2 SD) children who presented with short stature around puberty.<sup>33</sup> The mean age at the start of the study was 12.7 years. The treatment group received a dose of 0.47mg/kg/week and was compared with 47 untreated short peripubertal SGA controls. Mean treatment duration was 2.7 years. GH treatment during puberty significantly increased the adult height of short SGA children compared with untreated short SGA children. The difference between the treatment group and control group was 2.7cm in boys and 4.2cm in girls. Forty-seven percent of the GH-treated children had adult heights

in the normal range compared with 27% of the controls. The height gained in the treated group was directly related to treatment duration.

A recent meta-analysis reviewed long-term studies of short SGA children treated with GH until adult height over the past decade.<sup>34</sup> Inclusion criteria were birth weight and/or length  $<-2$  SDS, initial height  $<-2$  SDS, no previous GH treatment, no growth-impairing comorbid conditions, and a GH treatment range of 0.23–0.47mg/kg/week. Primary outcome measures were adult height SDS and overall height gain SDS. Adult height was attained when growth velocity was  $<2$ cm/year and/or bone age was 15 years in girls and 16 years in boys.

Of the 29 studies reviewed, four randomized controlled trials met inclusion criteria, with 391 children assessed (see *Table 1*).

The mean height gained from the randomized control studies was 1.5 SDS (9.5cm) in the GH-treated children compared with 0.25 SDS (1.6cm) in the untreated children. The mean corrected adult height was -0.46 SDS in GH-treated SGA children compared with -1.26 SDS in untreated SGA children. Maiorana et al. concluded that long-term GH treatment can increase adult height in children born SGA by about 6cm over eight years of treatment. The response to treatment was variable and depended on many factors including age at onset of treatment, pubertal status at onset of treatment, number of pubertal years on treatment, target height, and pre-treatment growth rate. The authors concluded that “There is no convincing evidence to support long-term GH treatment with a GH dose  $>35\mu\text{g}/\text{kg}$  per day.” Additional randomized controlled trials of adult height in short SGA children treated with GH are needed to further evaluate the efficacy, safety, and cost-effectiveness of GH treatment.

### Predictors of Growth Hormone Treatment Response

Clinical trials have shown that major predictors of short-term growth response in children born SGA are the dose of GH (especially during the first year of treatment), shorter height at start of treatment, weight at start of treatment, mid-parental height, younger age, and pre-pubertal years treated with GH.<sup>35,36</sup> The change in height SDS at three and six months of GH treatment was predictive of the growth response at one year in children born SGA.<sup>25</sup> The most important predictor of the second-year response to GH was growth velocity during the first year on treatment. de Zegher et al. showed that in a small group of SGA children treated with GH who had overnight GH profiles measured, greater short-term response was closely associated with a lower baseline peak of overnight GH levels and a lower baseline IGF-1.<sup>37</sup>

For long-term growth response including adult height, a recent randomized double-blind GH dose-response study showed that circulating baseline levels of free IGF-1 and IGF binding protein 3 (IGF-BP3) were better predictors of adult height in children born SGA treated with GH than total IGF-1 or a total IGF-1 to IGF-BP3 ratio.<sup>38</sup> A study by van Pareren et al. concluded that height SDS at the start of GH treatment, target height SDS, and pre-treatment height velocity SDS were positively correlated with adult height, and multiple regression analysis using these variables as well as chronological age compared with bone

age at the start of GH treatment and GH dose accounted for 42% of the variation in adult height SDS.<sup>12</sup> Carel et al. found that bone age retardation at baseline as well as treatment with GH was predictive of an increase in adult height.<sup>33</sup> Maiorana et al. used multiple linear regression analyses of long-term GH studies of adult height in short SGA children to construct a model of prediction of adult height SDS.<sup>34</sup> They found that the major predictors of adult height were height and weight at the start of GH treatment, target height, pre-treatment growth rate, and pre-pubertal years treated with GH; however, future studies are needed to confirm the efficacy of these variables as predictors of adult height.

### Height Prediction Models

The accuracy of height predictions has been questioned since it is dependent on bone age readings, which are inaccurate.<sup>39</sup> However, the objective of growth prediction models is to individualize GH treatment protocol. A small number of studies have used height prediction models to optimize individual GH dosing in short SGA children in the short and long term.

Ranke et al. developed a growth prediction model after analyzing data from 613 short SGA (birth weight  $<-1.28$  SDS) children treated with GH.<sup>35</sup> They correlated annualized growth velocities in these children with potentially significant variables using multiple regression analysis over the first two years of treatment. They used a four-parameter model (age at start of treatment, weight SD score at start of treatment, GH dose, and mid-parental height SD score) and were able to explain 52% of the variability of growth response in the first year of treatment. The dose of GH was the most significant predictor accounting for 35% of variability in GH response. A model for the second year of GH treatment showed that growth velocity during the first year of treatment was the most important predictor of subsequent response. Height outcome may be determined by the first-year response to GH, which is dose dependent.

The OPTIMA study used the Cologne Growth Prediction Model, a mathematical formula comprised of the following variables: bone age delay, pre-treatment IGF-1 levels, urinary deoxypyridinoline (uDPD) measured one month after GH start as a bone marker of early response to GH, and growth velocity annualized over three months.<sup>40,41</sup> The study divided 194 pre-pubertal short SGA (birth weight  $<10\%$  and/or birth length  $<-2$  SDS) children into two groups; a fixed high-dose group (FHD) who received 0.47mg/kg/week of GH for one year and an individually adjusted dose (IAD) group, who received 0.25mg/kg/week for three months and then an adjusted dose based on predicted one-year change in height SDS. If the predicted height SDS change was  $<0.75$ , the dose was increased to 0.47mg/kg/week. Based on these guidelines, at three months, 48% of children in the IAD group were changed to higher dose. They concluded that high fixed doses of GH are not required in 50% of SGA children for at least the first year of GH treatment. Follow-up of this cohort is needed to evaluate the predictive value of the first-year response on subsequent years.

De Ridder et al. developed a model to predict height at pubertal onset and adult height for SGA children treated with GH.<sup>42</sup> Variables used were height SDS at start of GH, target height SDS, chronological age

**Table 1: Trials of Growth Hormone Therapy in Short Children Who Were Born Small for Gestational Age—Study Characteristics, Results, and Grading**

Controls	Random-ization	Controls	n	Age at Start of Therapy	Dose, µg/kg Per Day	Years of Therapy	Height at Start, SDS	Adult Height, SDS	Height Gain, SDS	Δ Adult Height, SDS	Grading
<b>Randomized Controlled Trials</b>											
<b>van Pareren et al., 2003<sup>12</sup></b>											
Treated	Yes	Yes	54 total	8.0	33–67	7.65	-2.95	-1.0	1.95	1.3	Moderate quality, strong recommendation
			28	7.9	33	7.9	-2.9	-1.1	1.8	1.2	Moderate quality, strong recommendation
			26	8.2	67	7.5	-3.0	-0.9	2.1	1.4	Moderate quality, strong recommendation
Untreated			15	7.8	–	–	-2.6	-2.3	0.3	–	
<b>Carel et al., 2003<sup>33</sup></b>											
Treated	Yes	Yes	102	12.7	67	2.7	-3.2	-2.1	1.1	0.6	Moderate quality, weak recommendation
Untreated			47	12.8	–	–	–	-3.2	-2.7	0.5	
<b>Dahlgren and Wikland, 2005<sup>32</sup></b>											
Treated	Yes	Yes	77 total	10.7	33	5.5–8.5	-2.8	-1.4	1.4	0.6	Moderate quality, weak recommendation
			36	8.9	33 (>2y pre-puberty)	8.5	-3.1	-1.2	1.9	0.8	Moderate quality, strong recommendation
			41	12.3	33 (<2y pre-puberty)	5.5	-2.5	-1.6	0.9	0.4	Moderate quality, weak recommendation
Untreated	No		34	8.3	–	–	-2.2	-2.0	2.0	–	
<b>van Dijk et al., 2007<sup>59</sup></b>											
Treated	Yes	Yes	37	8.5	33 and 66	7.3	-2.9	-1.4	1.5	1.2	High quality, strong recommendation
Untreated			25	7.8	–	–	-2.6	-2.6	0	–	
<b>Non-Randomized Controlled Trials</b>											
<b>Ranke and Lindberg, 1996<sup>79</sup></b>											
	No	No	16	12.7	33	4.3	-2.7	-1.7	1.0	–	
<b>Coutant et al., 1998<sup>27</sup></b>											
Treated	No	Yes	70	10.3	19.8	4.6	-2.9	-2.0	0.9	0.2	Low quality, weak recommendation
Untreated			40	–	–	–	-2.8	-2.2	0.6	–	
<b>Zucchini et al., 2001<sup>26</sup></b>											
Treated	No	Yes	29	10.9	33	3–7	-2.3	-1.8	0.5	0.1	Low quality, weak recommendation
Untreated			20	10.7	–	–	-2.0	-1.9	0.1	–	
<b>Rosillo et al., 2005<sup>80</sup></b>											
	No	No	20	9.6	67	2+2 off ± 4	-2.6	-2.0	-2.0	0.6	Low quality, weak recommendation
<b>Bannink et al., 2007<sup>38</sup></b>											
	Yes	No	26	7.5	33	8.5	-3.1	-1.5	1.6	–	Moderate quality, strong recommendation
			20	7.9	67	7.9	-3.1	-1.2	1.9	–	Moderate quality, strong recommendation

Treated groups from the van Pareren et al.<sup>12</sup> and Dahlgren and Wikland<sup>32</sup> studies are displayed as whole groups and subgroups. Δ Cases–controls difference. SDS = standard deviation score; y = years. Source: Maiorana A, Cianfarani S, 2009,<sup>34</sup> reprinted with permission.

compared with bone age at the start of treatment, IGF-BP3 SDS at the start of treatment and GH dose. They studied 150 short SGA (birth length <-2 SDS) children treated with 0.23 or 0.47mg/kg/week of GH for a mean duration of eight years. Seventy-one of those children reached adult height during their study. They found that their model

explained 57% of the variance for height SDS at the onset of puberty and 41% of variance for adult height SDS. IGF-BP3 SDS was superior over IGF-1 SDS as a predictor of adult height. They proposed a protocol in which adult height SDS was first calculated with a dose of 0.23mg/kg/week. If the prediction was 'relatively low' then the

adult height SDS should be calculated with a higher dose of 0.46mg/kg/week. If this prediction was still 'relatively low', the effect of GH treatment was considered uncertain. A formula to calculate a dose in between the above-mentioned doses was provided. They concluded that their prediction model could optimize the GH dose, thereby increasing the adult height attained in short SGA children.

While these height prediction models are still in the early phase of development and require follow-up studies, their potential to decrease the amount of GH prescribed, thereby reducing GH-related adverse effects and lowering overall cost, make them potentially valuable tools for future use in SGA children.

## Growth Hormone Treatment and Metabolic Consequences

### Overall Safety of Growth Hormone Treatment

Overall, GH treatment has been shown to be safe and has been previously reviewed.<sup>43,44</sup> In 2010, Bell et al. published the results of the National Co-operative Growth Study (NCGS) with over 20 years of safety data on almost 55,000 children treated with GH.<sup>45</sup> GH was found to have a good safety profile and the risk of adverse events was low. In addition, there was no evidence of increased malignancy. This is in agreement with the findings of the US SGA Trial.<sup>46</sup> Although the risk of adverse events is low, SGA children being treated with GH should be monitored for potential adverse events with particular focus on papilledema, changes in skin lesions including nevi, worsening of scoliosis, and hip or knee pain suggestive of slipped capital femoral epiphysis.<sup>47</sup>

### Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes

Non-GH-treated children born SGA are at higher risk for cardiovascular disease, insulin resistance, type 2 diabetes, and dyslipidemias.<sup>8,48</sup> Children born SGA have pre-existing insulin resistance, but normal beta-cell function.<sup>49</sup> One study found that SGA children with spontaneous catch-up growth were at increased risk of obesity and insulin resistance compared with short SGA children.<sup>50</sup> The exact causal mechanism of reduced weight at birth and insulin sensitivity in adulthood remains undefined and the proposed theories are beyond the scope of this review. Leger et al. compared 452 SGA young adults at a mean age of 20.6 years with AGA controls looking at adult height reached as well as development of insulin resistance, impaired glucose tolerance with an oral glucose tolerance test, lipids, and high blood pressure as a marker of cardiovascular disease.<sup>8</sup> They found that children born SGA had increased serum insulin and proinsulin concentrations with normal glucose tolerance. There was no significant difference in systolic or diastolic blood pressures, lipids or fibrinogen concentrations as a marker of cardiovascular disease between the two groups. This is in agreement with other studies that have shown children born SGA have decreased insulin sensitivity compared with short AGA controls.<sup>51</sup>

GH treatment has been shown to increase postprandial insulin levels without affecting glycosylated hemoglobin (HbA<sub>1c</sub>), fasting glucose, or glucose tolerance in SGA children.<sup>46,52-54</sup> Mean insulin levels returned to their pre-treatment levels after the discontinuation of GH treatment.<sup>37,55</sup>

A small number of children had glucose tolerance impairment during the course of treatment but this was not sustained. We are unaware of any studies showing a rise in the incidence of type 2 diabetes in SGA children being treated with GH.

Willemssen et al. performed a longitudinal study of 48 children born SGA treated with GH (0.23mg/kg/week) for a mean of 7.5 years and followed them to adult height and for six months off GH.<sup>56</sup> Using an intravenous glucose tolerance test, they looked specifically at insulin sensitivity (Si), capacity of glucose to mediate its own disposal independent of insulin (Sg), acute insulin response (AIR) as a measure of beta-cell function, and the disposal index (DI = AIR x Si), which reflects beta-cell function and insulin sensitivity. Previous studies have suggested that decreased Sg or glucose effectiveness is a risk factor for impaired glucose tolerance and type 2 diabetes in first-degree relatives of patients with type 2 diabetes.<sup>57,58</sup> Si was significantly lower in SGA subjects on GH than in AGA controls but increased significantly after stopping GH. Sg improved significantly after stopping GH treatment and became significantly higher than in AGA controls. Compared with AGA controls, SGA patients had higher insulin secretion both during and after stopping GH treatment, and had a higher DI six months after cessation of GH. Therefore, they concluded that GH treatment in SGA children did not increase the risk of type 2 diabetes since Sg decreased in SGA subjects after stopping GH. It should be noted that this was only measured for a period of six months post GH cessation; longer follow-up is needed to confirm these results.

Van Pareren et al. followed a group of 47 SGA children over six years on two doses of GH (0.21 and 0.49mg/kg/week) and compared them with AGA controls.<sup>55</sup> They saw a significant decrease in systolic and diastolic blood pressure in SGA children treated with GH for six years. No change was observed in blood pressure six months after GH treatment was stopped. Serum triglycerides and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels significantly decreased six years after GH was stopped compared with levels pre-treatment. GH treatment had no effect on the atherogenic index (triglyceride/HDL). The beneficial effects of decreased blood pressure and other risk factors of cardiovascular disease remained six months after GH was stopped. Van Dijk et al. confirmed that 6.5 years after treatment with GH, SGA children had equivalent Si, AIR, and DI compared with SGA subjects not treated. They also demonstrated that 6.5 years after GH, the positive effects of decreased blood pressure, total cholesterol and LDL remained.<sup>59</sup> None of the GH-treated children had increased fasting glucose levels or type 2 diabetes.

These studies confirm the safety and potential positive effects of long-term GH use. Further long-term studies are needed to exclude any negative effects of GH on type 2 diabetes risk in short children born SGA and to formulate specific surveillance recommendations.

### Adiponectin and Leptin

Adipocytokines, such as adiponectin and leptin, are bioactive proteins that behave in autocrine, paracrine, and endocrine ways, and have been associated with various metabolic processes in the body including insulin metabolism.<sup>60,61</sup> Therefore, they have been targeted as potential players in insulin response to GH in SGA children.

Adiponectin acts as an insulin sensitizer, and its serum level has been shown to be inversely related to body mass index (BMI) and measures of insulin resistance.<sup>62</sup> A study of non-SGA children showed that adiponectin concentrations were decreased in boys and pubertal children.<sup>63</sup> No association was observed between fasting insulin, homeostasis model assessment of insulin resistance (HOMA), and adiponectin concentration. Studies of adiponectin levels in SGA children have revealed adiponectin levels can be lower, higher, or the same as AGA controls, even when adjusted for sex, age, BMI, and insulin resistance.<sup>64-67</sup>

Another study showed that after four months of GH treatment at a dose of 0.28mg/kg/week SGA children had a significant decrease in high molecular weight (HMW) adiponectin levels and no change in leptin.<sup>68</sup> There was a significant increase in the HOMA seen over the four-month treatment period in the GH-treated group. Willemssen et al. showed no change in adiponectin levels after 24 months of GH treatment in pre-pubertal SGA children compared with untreated SGA controls.<sup>69</sup>

A long-term study of short SGA children receiving either 0.23 or 0.46mg/kg/week of GH followed adiponectin levels over a seven-year period and then six months after cessation of GH. The GH-treated groups showed decrease in adiponectin levels from baseline; however, there was no difference when compared with age-matched controls.<sup>70</sup> An 18.2% drop in adiponectin levels was associated with puberty although this was not statistically significant. After accounting for GH dose, girls at near adult height were found to have significantly higher adiponectin levels than boys. No associations were seen between changes in adiponectin levels and GH-mediated changes in insulin sensitivity. In light of these studies, much remains to be identified about the role of adiponectin and insulin sensitivity in SGA children treated with GH.

Leptin is released by adipocytes in direct proportion to adipocyte tissue mass and acts by binding to the leptin receptor. It is thought to act as an afferent satiety signal, modulating appetite and energy expenditure. Studies involving leptin-deficient mice have shown that replacement of leptin reverses hyperphagia, obesity, hyperinsulinemia, and diabetes.<sup>71</sup> Although the exact mechanism is unknown, leptin is thought to act as a signal in the regulation of insulin sensitivity.

Yu et al. suggested leptin acts as a signaling hormone that triggers the onset of puberty via stimulation of luteinizing-hormone-releasing hormone (LHRH).<sup>72</sup>

Rapaport et al. reported no change in leptin levels in 139 short pre-pubertal children born SGA treated with GH for 12 months.<sup>25</sup> Boguszewski et al. measured the serum leptin levels in pre-pubertal children before and after GH treatment and found that girls in the SGA and AGA groups had statistically higher leptin levels than boys.<sup>73</sup> Younger children born SGA (<5.5 years of age) had significantly higher levels of leptin than older SGA children, even after adjustment for chronological age and sex. Short SGA children had decreased serum leptin concentrations compared with AGA children. They found that the higher the leptin levels pre treatment, the better the growth response to GH treatment. Leptin levels decreased with GH treatment,

but the difference was not significant. It was postulated that leptin could be used as a potential marker of response to GH in short SGA children.

A follow-up multicenter study looked at leptin levels in SGA children treated with GH at various doses and over a longer period of time.<sup>74</sup> Leptin levels were reduced in SGA children during GH treatment in a dose-dependent manner with the most significant changes in serum leptin occurring within the first year of starting GH. They hypothesized that the decrease in serum leptin levels that occurred in response to GH treatment was due to a reduction in adipose tissue mass. After two years of GH treatment, the changes seen in leptin levels reversed.

Boonstra et al. used a seven-day standardized food questionnaire to assess caloric, fat, carbohydrate, and protein intake in short pre-pubertal SGA children before and after GH.<sup>75</sup> At baseline, overall food intake was reduced compared with the recommended daily intake for age-matched AGA children. After one year, a significant increase in intake of calories, fat, carbohydrates, and protein was observed in SGA children treated with GH compared with non-treated SGA controls. A significant decrease in leptin levels was also observed in the GH-treated group. Leptin may play an important role in growth, pubertal development, and glucose metabolism, but follow-up studies are needed to better understand that role and how it is affected by GH.

### Body Composition, Fat Mass, and Bone Mineral Density

Data on GH and body composition in SGA children are limited. Rapaport et al. showed an improved body composition in 139 short pre-pubertal children treated with GH over a 12-month period.<sup>25</sup> Using bioelectric impedance analysis, they found that lean body weight increased significantly and body fat percentage decreased significantly from baseline to 12 months.

Willemssen et al. examined the effect of GH on body composition in a longitudinal six-year randomized controlled study using dual-energy X-ray absorptiometry scan (DXA).<sup>76</sup> Short pre-pubertal SGA children were divided into a GH-treated group (0.24mg/kg/week) and a control group for three years. After three years, the control group was also treated with the same GH dose. They found that GH-treated children had a significant increase in lean body mass SDS, bone mineral density (BMD) SDS, and a larger decrease in fat percentage SDS compared with untreated controls. These findings remained after six years of treatment.

A follow-up study showed that six months after GH treatment was stopped, percent fat SDS and fat mass increased significantly while lean body mass decreased.<sup>56</sup> Similar results were seen in another study that used magnetic resonance imaging (MRI) to assess muscle and adipose tissue.<sup>77</sup> Three years after GH treatment, the SGA group had significantly greater muscle tissue cross-sectional area compared with the control group. Adipose tissue decreased in the SGA groups after one year of GH treatment, and then increased to a similar level as controls.

A three-year study of GH treatment in 28 short pre-pubertal SGA children showed that BMD of the total body, BMD of the lumbar spine,

and BMD adjusted for bone size were all significantly increased from baseline.<sup>78</sup> This increase was not seen in untreated SGA controls. Further studies are needed to confirm the positive effects of GH on body composition.

## Conclusion

GH has been shown to be both safe and effective in improving height velocity and adult height in children born SGA who do not adequately catch up. To date, no persistent adverse metabolic consequences have been reported, although transient effects including increased insulin resistance have been seen. Long-term surveillance needs to be established for potential adverse metabolic effects with GH treatment.

The consensus statement by the International Societies of Pediatric Endocrinology and the GRS in 2007 recommended that "Long-term surveillance of all those who receive GH is essential."<sup>1</sup> Further studies are required to validate potential associations of GH treatment in children born SGA and metabolic comorbidities. ■



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- Clayton P, Cianfarani S, Czernichow G, et al., Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society, *J Clin Endocrinol Metab*, 2007;92(3):804–10.
- Karlberg J, Wikland A, Growth in full-term small-for-gestational-age infants: from birth to final height, *Pediatr Res*, 1995;38:733–9.
- Albertsson-Wikland K, Karlberg J, Postnatal growth of children born small for gestational age, *Acta Paediatr Suppl*, 1997;423:193–5.
- Albertsson-Wikland K, Boguszewski M, Karlberg J, Children born small-for-gestational age: postnatal growth and hormonal status, *Horm Res*, 1998;49:7–13.
- De Zegher F, Francois I, van Helvoirt M, et al., Small as fetus and short as child: from endogenous to exogenous growth hormone, *J Clin Endocrinol Metab*, 1997;82:2021–6.
- Hales CN, Barker DJP, The thrifty phenotype hypothesis, *British Medical Bulletin*, 2001;60:5–20.
- Hofman PL, Cutfield WS, Robinson EW, et al., Insulin resistance in short children with intrauterine growth retardation, *J Clin Endocrinol Metab*, 1997;402–6.
- Leger J, Levy-Marchal C, Bloch J, et al., Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study, *BMJ*, 1997;315:341–7.
- Barker DJ, Hales CN, Fall CH, et al., Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth, *Diabetologia*, 1993;36:62–7.
- Andersen A-MN, Osler M, Birth dimensions, parental mortality, and mortality in early adult age: a cohort study of Danish men born in 1953, *Int J Epidemiol*, 2004;33:92–9.
- Jaquet D, Deghmoun S, Chevenne D, et al., Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth, *Diabetologia*, 2005;48:849–55.
- Van Paerelen Y, Mulder P, Houdijk M, et al., Adult height alter long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial, *J Clin Endocrinol Metab*, 2003;88:3584–90.
- Azcona C, Albanese A, Bareille P, et al., Growth hormone treatment in growth hormone-sufficient and -insufficient children with intrauterine growth retardation/Russell-Silver syndrome, *Horm Res*, 1998;50:20–7.
- Ester W, Bannink E, van Dijk M, et al., Subclassification of small for gestational age children with persistent short stature growth patterns and response to GH treatment, *Horm Res*, 2008;69:89–98.
- De Kort SWK, Willemsen RH, van der Kaay DCM, et al., Does preterm birth influence the response to growth hormone in short, small for gestational age children?, *Clin Endocrinol*, 2009;70:582–7.
- Job JC, Chaussan JL, Job B, et al., Follow-up of three years of treatment with growth hormone and of one post treatment year, in children with severe growth retardation of intrauterine onset, *Ped Res*, 1996;39:354–9.
- Chernausk SD, Breen TJ, Frank GR, Linear growth in response to growth hormone treatment in children with short stature associated with intrauterine growth retardation: the National Cooperative Growth Study experience, *J Pediatr*, 1996;128:S22–7.
- Fjellestad-Paulsen A, Czernichow P, Brauner R, et al., Three-year data from a comparative study with recombinant human growth hormone in the treatment of short stature in young children with intrauterine growth retardation, *Acta Paediatr*, 1998;87:511–7.
- De Zegher F, Maes M, Gargosky SE, et al., High-dose growth hormone treatment of short children born small for gestational age, *J Clin Endocrinol Metab*, 1996;81:1887–92.
- Rapaport R, Growth and growth hormone in children born small for gestational age, *Growth Horm IGF Res*, 2004;14:S3–6.
- Lanes R, Growth hormone treatment in patients with intrauterine growth retardation, *J Clin Endocrinol Metab*, 2000;85:1345–6.
- Rapaport R, Tuvemo T, Growth and growth hormone in children born small for gestational age, *Acta Paediatr*, 2005;94:1348–55.
- Sas T, de Waal W, Mulder P, et al., Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial, *J Clin Endocrinol Metab*, 1999;84:3064–70.
- Boguszewski M, Albertsson-Wikland K, Aronsson S, et al., Growth hormone treatment of short children born small-for-gestational-age: the Nordic Multicentre Trial, *Acta Paediatr*, 1998;87:257–63.
- Rapaport R, Saenger P, Wajnrach MP, Predictors of first-year growth response to a fixed-dose growth hormone treatment in children born small for gestational age: results of an open-label, multicenter trial in the United States, *J Ped Endo Metab*, 2008;21:411–22.
- Zucchini S, Cacciari E, Balsamo A, et al., Final height of short subjects of low birth weight with and without growth hormone treatment, *Arch Dis Child*, 2001;84:340–3.
- Coutant R, Carel JC, Leitrai M, et al., Short stature associated with intrauterine growth retardation: final height of untreated and growth hormone-treated children, *J Clin Endocrinol Metab*, 1998;83:1070–4.
- Davies PSW, Valley R, Preece MA, Adolescent growth and pubertal progression in the Silver-Russell syndrome, *Arc Dis Childhood*, 1988;63:130–5.
- Meas T, Deghmoun S, Armoogum P, et al., Consequences of being born small for gestational age on body composition: an 8-year follow-up study, *J Clin Endocrinol Metab*, 2008;93:3804–9.
- Simon D, Leger J, Carel JC, Optimal use of growth hormone therapy for maximizing adult height in children born small for gestational age, *Best Pract Res Clin Endocrinol Metab*, 2008;22:525–37.
- Jung H, Rosilio M, Blum W, et al., Growth hormone treatment for short stature in children born small for gestational age, *Adv Ther*, 2008;25:951–78.
- Dahlgren J, Albertsson Wikland K, Final height in short children born small for gestational age treated with growth hormone, *Pediatr Res*, 2005;57:216–22.
- Carel JC, Chatelain P, Rochiccioli P, et al., Improvement in adult height after growth hormone treatment in adolescents with short stature born small for gestational age: results of a randomized controlled study, *J Clin Endocrinol Metab*, 2003;88:1587–93.
- Maiorana A, Cianfarani S, Impact of growth hormone therapy on adult height of children born small for gestational age, *Pediatrics*, 2009;124:e519–31.
- Ranke MB, Lindberg A, Cowell CT, et al., Prediction of response to growth hormone treatment in short children born small for gestational age: analysis of data from KIGS (Pharmacia International Growth Database), *J Clin Endocrinol Metab*, 2003;88:125–31.
- De Zegher F, Albertsson-Wikland K, Wollmann HA, et al., Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years, *J Clin Endocrinol Metab*, 2000;85:2816–21.
- De Zegher F, Ong K, Van Helvoirt M, et al., High-dose growth hormone (GH) treatment in non-GH-deficient children born small for gestational age induces growth responses related to pre-treatment GH secretions and associated with a reversible decrease in insulin sensitivity, *J Clin Endocrinol Metab*, 2002;87:148–51.

38. Bannink EMN, van Doorn J, Mulder PGH, et al., Free/dissociable insulin-like growth factor (IGF)-I, not total IGF-1, correlates with growth response during growth hormone treatment in children born small for gestational age, *J Clin Endocrinol Metab*, 2007;92:2992–3000.
39. Rapaport R, Adult height predictions for constitutional growth delay, growth hormone treatment for idiopathic short stature and the FDA: are they related?, *Horm Res*, 2006;65:197–9.
40. Jung H, Land C, Nicolay C, et al., Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study, *Eur J Endocrinol*, 2009;160:149–56.
41. Schonau E, Westermann F, Rauch R, et al., A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency, *Eur J Endocrinol*, 2001;144:13–20.
42. De Ridder MAJ, Stijnen T, Hokken-Koelega ACS, Prediction model for adult height of small for gestational age children at the start of growth hormone treatment, *J Clin Endocrinol Metab*, 2008;93:477–83.
43. Saenger P, Czernichow P, Hughes I, et al., Small for gestational age: short stature and beyond, *Endocrine Reviews*, 2007;28:219–51.
44. Poduval A, Saenger P, Safety and efficacy of growth hormone treatment in small for gestational age children, *Curr Opin Endocrinol Diabetes Obes*, 2008;15:375–82.
45. Bell J, Parker KL, Swinford RD, et al., Long-term safety of recombinant human growth hormone in children, *J Clin Endocrinol Metab*, 2010;95:167–77.
46. Cutfield WS, Lindberg A, Rapaport R, et al., Safety of growth hormone treatment in children born small for gestational age: the US trial and KIGS analysis, *Horm Res*, 2006;65(Suppl. 3):153–9.
47. Lee PA, Chernausk SD, Hokken-Koelega ACS, et al., International Small for Gestational Age Advisory Board Consensus Development Conference Statement: Management of Short Children Born Small for Gestational Age, April 24–October 1, 2001, *Pediatrics*, 2003;111:1253–61.
48. Osmond C, Barker DJP, Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women, *Environ Health Perspect*, 2000;108(Suppl. 3):545–53.
49. Veening MA, van Weissenbruch MM, Heine R, et al., B-cell capacity and insulin sensitivity in pre-pubertal children born small for gestational age, *Diabetes*, 2003;52:1756–60.
50. Ong KKL, Ahmed ML, Emmett PM, et al., Association between postnatal catch-up growth and obesity in childhood: prospective cohort study, *BMJ*, 2000;320:967–71.
51. Arends NJT, Boonstra VH, Duivenvoordt HJ, et al., Reduced insulin sensitivity and the presence of cardiovascular risk factors in short pre-pubertal children born small for gestational age (SGA), *Clin Endo*, 2005;62:44–50.
52. Davidson MB, Effect of growth hormone on carbohydrate and lipid metabolism, *Endocr Rev*, 1987;8:115–31.
53. Bachmann S, Bechtold S, Bonfig W, et al., Insulin sensitivity decreases in short children born small for gestational age treated with growth hormone, *J Pediatr*, 2009;154:509–13.
54. Sas T, Mulder P, Aanstoot HJ, et al., Carbohydrate metabolism during long-term growth hormone treatment in children with short stature born small for gestational age, *Clin Endocrinol*, 2001;54:243–51.
55. Van Pareren Y, Mulder P, Houdijk M, et al., Effect of discontinuation of growth hormone treatment on risk factors for cardiovascular disease in adolescents born small for gestational age, *J Clin Endocrinol Metab*, 2003;88:347–53.
56. Willemsen RH, Willemsen S, Hokken-Koelega ACS, Longitudinal changes in insulin sensitivity and body composition of small-for-gestational-age adolescents after cessation of growth hormone treatment, *J Clin Endocrinol Metab*, 2008;93:3449–54.
57. Cnop M, Vidal J, Hull RL, et al., Progressive loss of B-cell function leads to worsening glucose tolerance in first-degree relatives of subjects with type 2 diabetes, *Diabetes Care*, 2007;67:77–82.
58. Martin BC, Warram JH, Kroleski AS, et al., Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study, *Lancet*, 1992;340:925–9.
59. Van Dijk M, Bannink EMN, van Pareren YK, et al., Risk factors for diabetes mellitus type 2 and metabolic syndrome are comparable for previously growth hormone-treated young adults born small for gestational age (SGA) and untreated short SGA controls, *J Clin Endocrinol Metab*, 2007;92:160–5.
60. Bozzola E, Meazza C, Arvigo M, et al., Role of adiponectin and leptin on body development in infants during the first year of life, *Ital J Pediatrics*, 2010;36:1–8.
61. Pittas AG, Joseph NA, Greenberg A, Adipocytokines and insulin resistance, *J Clin Endocrinol Metab*, 2004;89:447–52.
62. Kadowaki T, Yamauchi T, Kubota N, et al., Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome, *J Clin Invest*, 2006;116:1784–92.
63. Punthakee Z, Delvin EE, O'Loughlin J, et al., Adiponectin, adiposity, and insulin resistance in children and adolescents, *J Clin Endocrinol Metab*, 2006;91:2119–25.
64. Cianfarani S, Martinez C, Maiorana A, et al., Adiponectin levels are reduced in children born small for gestational age and are inversely related to postnatal catch-up growth, *J Clin Endocrinol Metab*, 2004;89:1346–51.
65. Lopez-Bermejo A, Casano-Sancho P, Fernandez-Real JM, et al., Both intrauterine growth restriction and postnatal growth influence childhood serum concentrations of adiponectin, *Clin Endocrinol*, 2004;61:339–46.
66. Evagelidou EE, Giapros VI, Challa A, et al., FERUM adiponectin levels, insulin resistance, and lipid profile in children born small for gestational age are affected by the severity of growth retardation at birth, *Eur J Endocrinol*, 2007;156:271–7.
67. Miras M, Ochetti M, Martin S, et al., Serum levels of adiponectin and leptin in children born small for gestational age: relation to insulin sensitivity parameter, *J Ped Endocrinol Metab*, 2010;23:463–71.
68. Ibanez L, Lopez-Bermejo A, Diaz M, et al., Growth hormone therapy in short children born small for gestational age: effects on abdominal fat partitioning and circulating follistatin and high-molecular-weight adiponectin, *J Clin Endocrinol Metab*, 2010;95:1–6.
69. Willemsen RH, van Dijk M, de Rijke YB, et al., Effect of growth hormone therapy on serum adiponectin and resistance levels in short, small-for-gestational-age children and associations with cardiovascular risk parameters, *J Clin Endocrinol Metab*, 2007;92:117–23.
70. Willemsen RH, Mulder PGH, van Toorenbergen AW, et al., Long-term GH treatment is not associated with disadvantageous changes of inflammatory markers and adipocytokines in children born small for gestational age, *Clin Endocrinol*, 2008;68:198–205.
71. Pelleymounter MA, Cullen MJ, Baker MB, et al., Effects of the obese gene product on body weight regulation in ob/ob mice, *Science*, 1995;269:540–3.
72. Yu WH, Kimura M, Walczewska A, et al., Role of leptin in hypothalamic-pituitary function, *Proc Natl Acad Sci*, 1997;94:1023–8.
73. Boguszewski M, Dahlgren J, Bjarnason R, et al., Serum leptin in short children born small for gestational age: relationship with the growth response to growth hormone treatment, *Eur J Endocrinol*, 1997;137:387–95.
74. Boguszewski MCS, de Zegher F, Albertsson-Wikland K, et al., Serum leptin in short children born small for gestational age: dose-dependent effect of growth hormone treatment, *Horm Res*, 2000;54:120–5.
75. Boonstra VH, Arends NJT, Stijnen T, et al., Food intake of children with short stature born small for gestational age before and during randomized GH trial, *Horm Res*, 2006;65:23–30.
76. Willemsen RH, Arends NJT, Bakker-van Waarde WM, et al., Long-term effects of growth hormone (GH) treatment on body composition and bone mineral density in short children born small for gestational age: six-year follow-up of a randomized controlled GH trial, *Clin Endocrinol*, 2007;67:485–92.
77. Leger J, Garel C, Fjellestad-Paulsen A, et al., Human growth hormone treatment of short-stature children born small for gestational age: effect on muscle and adipose tissue mass during a 3-year treatment period and after 1 year's withdrawal, *J Clin Endocrinol Metab*, 1998;83:3512–6.
78. Arends NJT, Boonstra VH, Mulder PGH, et al., GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of randomized controlled GH trial, *Clin Endocrinol*, 2003;59:779–87.
79. Ranke MB, Lindberg A, Growth hormone treatment of short children born small for gestational age or with Silver-Russell syndrome: results from KIGS (Kabi International Growth Study), including the first report on final height, *Acta Paediatr*, 1996;417(Suppl.):18–26.
80. Rosilio M, Carel JC, Ecosse E, Chaussainon JL, Adult height of pre-pubertal short children born small for gestational age treated with GH, *Eur J Endocrinol*, 2005;152(6):835–43.