Growth and Metabolism in Children Born Small for Gestational Age

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KEYWORDS

• Growth • Small for gestational age • Growth hormone treatment • Metabolic health

KEY POINTS

- Growth hormone (GH) treatment effectively induces catch-up growth and improves adult height in most short children born small for gestational age (SGA).
- During GH treatment, fat mass, insulin sensitivity, and blood pressure decrease, whereas lean body mass increases; favorable changes occur in lipid levels.
- GH-induced lower insulin sensitivity is reversible after GH treatment and 6.5 years thereafter it is similar in GH-treated and untreated short SGA adolescents.
- At 6.5 years after GH treatment, body composition, blood pressure, and lipid levels are similar to untreated short SGA adults, indicating that GH-induced catch-up in height has no unfavorable effects on metabolic health.

INTRODUCTION

Growth and development are important and sensitive parameters of health and disease. The most important measure of growth is body length. Several factors influence postnatal growth, including genetics, hormones, and the physical, emotional, and social environment. The growth hormone (GH) axis (GH-axis) is the main hormonal axis involved in human growth, and is very complex (**Fig. 1**).[1] The anterior pituitary gland produces GH in a pulsatile pattern, and secretion of GH is under control of the hypothalamic hormones GH-releasing hormone (GHRH) and somatostatin. GHRH binds to its receptor in the pituitary and stimulates GH secretion, whereas somatostatin inhibits GH release. Most of the effects of GH are mediated by insulin-like growth factors

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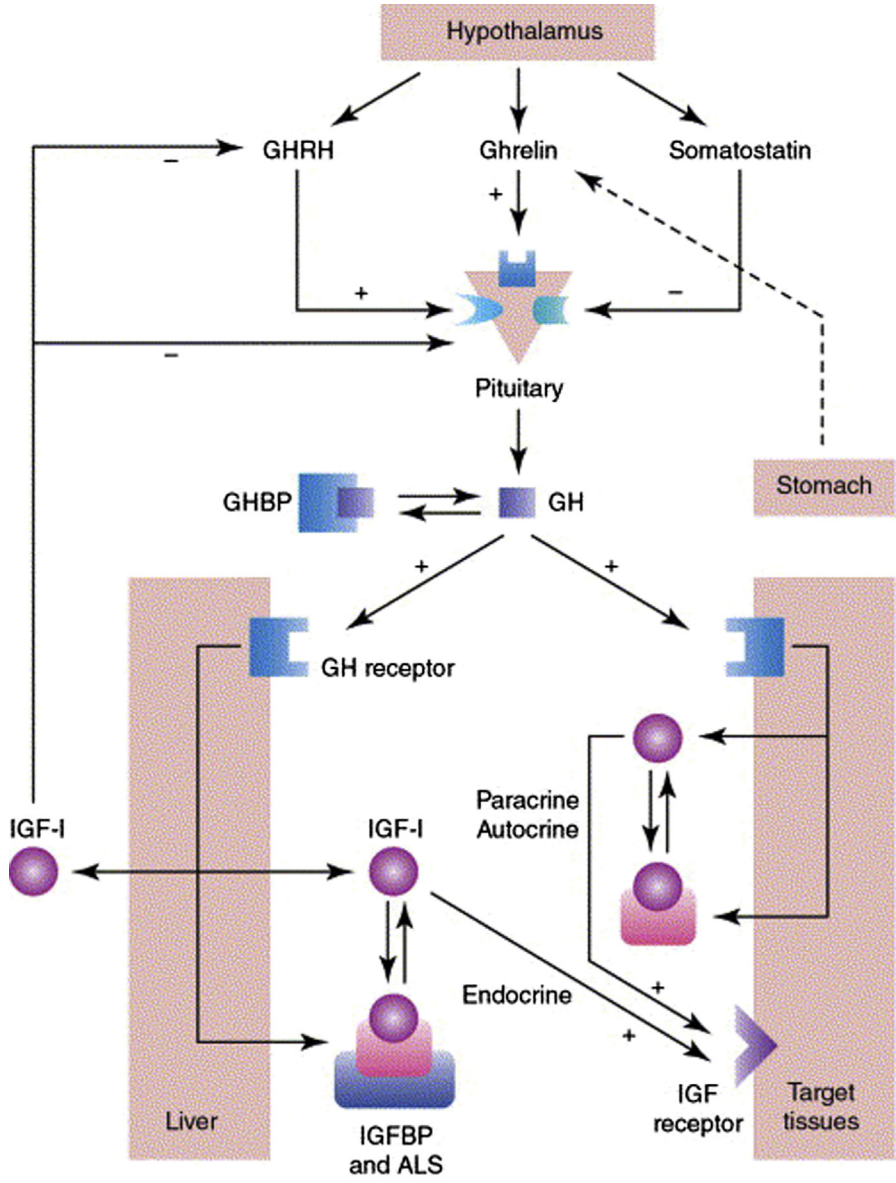

Fig. 1. Physiology of the GH-IGF-IGFBP axis. (*From* Holt RI. Fetal programming of the growth hormone-insulin-like growth factor axis. Trends Endocrinol Metab 2002;13:393; with permission.)

(IGFs). GH has a stimulatory effect on the production of IGF-I, which is synthesized in the liver and secreted into the blood under control of GH, insulin, and nutritional status. Next to growth, IGFs together with insulin and GH, regulate glucose and lipid metabolism and body composition.

Growth assessment requires accurate measurements of height and weight over time, the measurement of parental height, pubertal staging, and the selection of

appropriate growth reference standards. Normal growth patterns have spurts and plateaus and being familiar with normal patterns of growth allows practitioners to recognize and manage abnormal variations. Deviations in growth patterns may be nonspecific or important indicators of serious and chronic medical conditions. Evaluation and management of growth failure is one of the most common reasons for referral to a pediatric endocrinologist. The most common causes of short stature are familial (genetic) short stature and constitutional short stature, which are normal variants of growth. However, several pathologic causes must be considered and ruled out in children presenting with short stature (Table 1).

SMALL FOR GESTATIONAL AGE

Small for gestational age (SGA) accounts for approximately 20% of all cases of short stature.[2] SGA refers to the size of an infant at birth. It is defined as a birth length and/or weight of at least 2 standard deviation scores (SDS) below the mean for gestational age and gender.[3] The etiology of SGA consists of a broad spectrum of maternal, environmental, placental, and fetal factors, but in a significant proportion of cases the reason for being born SGA remains unclear. By definition, 2.3% of all live-born neonates are born SGA. SGA children can be either born full-term or premature. Most children born SGA show spontaneous catch-up growth to a normal weight and height above −2 SDS; however, 10% remain short.[4,5] These children will reach an adult height (AH) below the normal range and/or their target height range. The reason for this insufficient catch-up growth and persistent short stature is poorly understood. It has been hypothesized that disturbances in the GH-axis might underlie this failure.[6–8]

Recombinant GH has been used since 1986 and has replaced GH extracted from human pituitaries. The indications for GH treatment have gradually extended from replacement therapy in children with GH deficiency to conditions in which short stature is not due to GH deficiency. GH treatment for short children born SGA has been licensed for more than 10 years.

This article gives an overview of the effects of GH treatment on growth, body composition, insulin sensitivity, and cardiovascular risk factors in children born SGA.

EFFECTS OF GROWTH HORMONE TREATMENT IN CHILDREN BORN SMALL FOR GESTATIONAL AGE

An overview of the main effects of GH treatment is shown in Table 2.

Effects on Longitudinal Growth

The aim of GH treatment in short SGA children is achieving an AH in the normal range and/or in the target height range of the child. Several clinical studies have shown that GH treatment effectively induces catch-up growth and improves AH in most short children born SGA.[9–13] A systematic review in 2009 identified 4 high-quality trials on AH in short children born SGA treated with GH.[14] Mean height gain was 1.5 SDS in GH-treated versus 0.3 SDS in untreated short children born SGA. GH-induced growth response is, however, highly variable.[12] Several studies have been conducted to determine clinical predictors for growth response to GH treatment. Patient characteristics found to be related to AH SDS were as follows: height SDS at start of GH treatment, target height SDS, GH dose, bone age delay at start, and baseline Insulin-like growth factor binding protein (IGFBP)-3 SDS, explaining approximately 40% of the variability in adult-height SDS.[15]

Short SGA children comprise a heterogeneous group because some are born preterm and others term. Prematurity increases the risk for insufficient postnatal catch-up

Table 1
Causes of short stature

	Characteristics
Idiopathic short stature	
Familial short stature	One or both parents have short stature, often below the 10th percentile. Adult height is short but within the range predicted by parents' height.
Nonfamilial short stature	Short stature with unknown cause, without familial short stature.
Primary growth failure	
Clinical syndromes	
Turner syndrome	Short stature without growth spurts at expected times in childhood. Wide or weblike neck, broad chest with widely spaced nipples, low-set ears, arms that turn outward at the elbows (cubitus valgus), genu valgum, Madelung deformity. Absent pubertal development.
SHOX mutations	Disproportionate short stature, stocky appearance, shorter forearms and lower legs, cubitus valgus, Madelung deformity, high arched palate.
Noonan syndrome	Coarse or elongated facial features, heart disease, short neck, intellectual disability, pectus excavatum and wide-set nipples, cryptorchidism.
Prader-Willi syndrome	Poor muscle tone, almond-shaped eyes, thin upper lip, narrowing of the head at the temples, failure to thrive in infancy, food craving and weight gain in childhood to adulthood, underdeveloped sex organs, intellectual disability, behavioral problems.
Russell-Silver syndrome	Severe intrauterine growth restriction and postnatal growth retardation. Prominent forehead, triangular face, fifth-finger clinodactyl, and body asymmetry.
Other primary growth failures	
Small for gestational age with insufficient catch-up growth	Born SGA with persistent short stature.
Skeletal dysplasias	
Achondroplasia	Disproportionate dwarfism, normal-sized torso and short limbs, prominent forehead, midface hypoplasia.
Hypochondroplasia	Disproportionately short arms and legs similar to but milder than in achondroplasia, shortness of fingers and toes (brachydactyly), broad short hands and feet, lumbar lordosis.
Secondary growth failure	
Undernutrition	Low weight-for-height.
GHD	Progressive growth failure. May also have symptoms of other pituitary hormone deficiencies.
Disorder in an organ system	
Gastrointestinal disease	Celiac disease may mimic GHD. Crohn disease may be present.
Chronic renal disease	Growth impairment may precede the diagnosis of chronic renal disease.
Pulmonary disease	Respiratory symptoms, recurrent infections.

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Table 1
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	Characteristics
Rheumatologic disease	Particularly systemic onset juvenile idiopathic arthritis with fever, arthralgias, rash, lymphadenopathy.
Immunologic disease	Recurrent infections (manifestations vary depending on type of immunodeficiency).
Iatrogenic	
Glucocorticoid therapy	Growth effects are dose-related, greatest with systemic dosing. Mild effects may occur with long-term use of inhaled glucocorticoids.
Endocrine causes of growth failure	
Hypothyroidism	Fatigue, increased sensitivity to cold, constipation, weight gain, hoarseness, thinning hair, slower heart rate, impaired memory, depression.
Cushing syndrome	Weight gain and fatty tissue deposits, particularly around the midsection and upper back, in the face (moon face), and between the shoulders (buffalo hump). Fragile skin, slow healing of cuts, acne, fatigue, muscle weakness, loss of emotional control, cognitive difficulties, glucose intolerance may lead to diabetes, bone loss.

Abbreviations: GHD, growth hormone deficiency; SGA, small for gestational age; SHOX, short stature homeobox.

growth. The growth response to GH treatment is, however, similar in preterm and term short SGA children.[16]

Recently it has been shown that short SGA adolescents can still have impressive catch-up growth, even when they already entered puberty at the start of GH treatment.[11] Height improved from −2.9 SDS at start of treatment to −1.7 SDS at AH. Short SGA children with an expected AH less than −2 SDS at start of puberty benefit from additional gonadotropin-releasing hormone analog (GnRHa) treatment to delay puberty for 2 years to improve AH. From onset of puberty until AH, boys treated with combined GH/GnRHa grew on average 34.5 cm and girls 24.2 cm, which is more than pubertal growth in the reference population.[11]

Effects on Body Composition, Insulin Sensitivity, and Cardiovascular Risk Factors

GH treatment induces catch-up growth and improves AH, but it also reduces several risk factors for cardiovascular disease.

Long-term GH treatment results in an increase in lean body mass due to its anabolic effects on muscle mass, and a decline in fat mass due to the lipolytic effects on fat mass.[17–21] Short SGA children have a reduced insulin sensitivity before receiving GH treatment.[22] GH has well-documented insulin-antagonistic effects and treatment results in a further decline in insulin sensitivity and a compensatory increase in insulin secretion in SGA children.[18,23–26] During long-term GH treatment, blood pressure SDS decreases in GH-treated SGA children and becomes lower than in untreated SGA children.[17,18,27]

Several studies have shown that GH treatment is well tolerated in SGA children and that adverse effects are uncommon.[25,27,28] Nevertheless, all SGA children receiving GH treatment should be monitored regularly for changes in glucose metabolism, blood pressure, and lipid profile to exclude any possible adverse effects of GH.[3,29]

Table 2
Main effects of long-term GH treatment in children born SGA

Author, Year of Publication	Patients	Design	Mean Age at Start GH	Duration	Results	Remarks
Growth						
van Pareren et al,[12] 2003	54	RCT GH dose 1 mg/m^2/d vs 2 mg/m^2/d	8.6 (1.5) 8.3 (1.9)	Until AH (7 y)	Mean height gain was 1.8 and 2.1 SDS 98% reached an AH within the TH range	Similar results in 2 GH dose groups
Carel et al,[9] 2003	168	RCT GH-treated Untreated	12.7 (1.4) 12.8 (1.6)	2.7 y	AH was 0.6 SDS higher in the GH-treated group	—
Dahlgren & Wikland,[10] 2005	77	RCT	10.7 (2.5)	Until AH	Mean height gain was 1.3 SDS 86% of treated children reached an adult height within their target height range	Better catch-up growth in those who started treatment younger
de Kort et al,[16] 2009	392	Longitudinal Preterm vs Term	6.60 (2.3) 7.19 (2.6)	3 y	Response to GH treatment is similar in those born preterm or term	—
Lem et al,[11] 2012	121	RCT GH dose 1 mg/m^2/d vs 2 mg/m^2/d	11.2 (10.0–12.4)	Until AH	GH 2 mg/m^2/d during puberty resulted in better AH. AH was similar in children treated with GH/GnRHa and those with GH only	Children with a poor AH expectation at start of puberty were treated with additional GnRHa for 2 y (combined GH/GnRHa treatment)
Body composition						
Willemsen et al,[21] 2007	25	Longitudinal SGA GH SGA control	6.1 (1.5) 5.9 (1.7)	6 y	• Decrease in fat mass % • Increase in lean body mass	—
de Kort et al,[18] 2009	404	Longitudinal Preterm vs Term	6.7 (2.1) 7.4 (2.6)	4 y	• Decrease in fat mass % and limb fat/total fat ratio • Increase in lean body mass	Increase in lean body mass only in SGA children born term

van der Steen et al,[42] 2015	107	RCT GH dose 1 mg/m^2/d vs 2 mg/m^2/d	11.5 (1.5)	Until AH	At AH, body composition is similar in children treated with GH/GnRHa and those treated with GH only	Children with a poor AH expectation at start of puberty were treated with additional GnRHa for 2 y (combined GH/GnRHa treatment)
Insulin sensitivity						
Sas et al,[25] 2001	78	Longitudinal 1 mg/m^2/d vs 2 mg/m^2/d	7.3 (2.1) 7.2 (2.4)	6 y	Increase in glucose and insulin levels (OGTT)	2 GH dose groups similar
de Zegher et al,[24] 2002	13	Longitudinal GH-treated Untreated	6.3 (4.0–8.0) 4.7 (2.3–6.3)	2 y	• Increase in glucose and insulin levels • Decrease in insulin sensitivity (IVGTT)	After 2 y GH treatment was stopped and changes in glucose homeostasis were reversible
Cutfield et al,[23] 2003	12	Longitudinal	9.3 (1.0)	2 y	Decrease in insulin sensitivity with compensatory increase in acute insulin response (FSIGT)	All children remained prepubertal during treatment, changes were not reversible 3 mo after stop of treatment
de Kort et al,[18] 2009	404	Longitudinal Preterm vs Term	6.7 (2.1) 7.4 (2.6)	4 y	• Decrease in insulin sensitivity (FSIGT) • Increase in insulin secretion and disposition index (FSIGT)	Similar decrease and increase in preterm and term SGA children
Kappelgaard et al,[26] 2014	65	Longitudinal 1 mg/m^2/d vs 2 mg/m^2/d	5.34 (1.46) 5.27 (1.15)	5 y	No change in fasting glucose levels	No difference between 2 GH dose groups
van der Steen et al,[43] 2015	107	RCT GH dose 1 mg/m^2/d vs 2 mg/m^2/d	11.5 (1.5)	Until AH	At AH, insulin sensitivity is similar in children treated with GH/GnRHa and those treated with GH only (FSIGT)	Children with a poor AH expectation at start of puberty were treated with additional GnRHa for 2 y (combined GH/GnRHa treatment)
Blood pressure						
Sas et al,[27] 2000	79	Longitudinal 1 mg/m^2/d vs 2 mg/m^2/d	7.3 (2.1) 7.2 (2.4)	6 y	Decrease in blood pressure SDS	Similar decrease in 2 GH dose groups

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Table 2
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Author, Year of Publication	Patients	Design	Mean Age at Start GH	Duration	Results	Remarks
van Dijk et al,[13] 2007	37	Longitudinal	8.5 (1.7)	6 y	Decrease in systolic and diastolic blood pressure SDS	At 6.5 y after GH, lower than baseline and similar to untreated short SGA adolescents
de Kort et al,[18] 2009	404	Longitudinal Preterm vs Term	6.7 (2.1) 7.4 (2.6)	4 y	Decrease in systolic and diastolic blood pressure SDS	Similar decrease in preterm and term SGA children
van der Steen et al,[42] 2015	107	RCT GH dose 1 mg/m^2/d vs 2 mg/m^2/d	11.5 (1.5)	Until AH	At AH, blood pressure is similar in children treated with GH/GnRHa and those treated with GH only	Children with a poor AH expectation at start of puberty were treated with additional GnRHa for 2 y (combined GH/GnRHa treatment)
Lipids						
Sas et al,[27] 2000	79	Longitudinal 1 mg/m^2/d vs 2 mg/m^2/d	7.3 (2.1) 7.2 (2.4)	6 y	Decrease in TC and LDL No change in HDL	Similar decrease in 2 GH dose groups
van Dijk et al,[13] 2007	37	Longitudinal	8.5 (1.7)	6 y	Decrease in TC, LDLc and HDLc	At 6.5 y after GH, TC and LDLc lower than baseline and TC lower than untreated short SGA adolescents
Kappelgaard et al,[26] 2014	65	Longitudinal 1 mg/m^2/d vs 2 mg/m^2/d	5.34 (1.46) 5.27 (1.15)	5 y	Decrease in TC, LDLc	Different changes in TC, LDLc and HDLc between 2 GH dose groups

Abbreviations: AH, adult height; FSIGT, frequently samples intravenous glucose tolerance test; GH, growth hormone; GnRHa, gonadotropin-releasing hormone analog; HDLc, high-density lipoprotein cholesterol; IVGTT, intravenous glucose tolerance test; LDLc, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; RCT, randomized controlled trial; SDS, standard deviation score; TC, total cholesterol; TH, target height.

METABOLIC AND ENDOCRINE CONSEQUENCES IN ADULTS BORN SMALL FOR GESTATIONAL AGE

Low birth weight is associated with metabolic and cardiovascular adult diseases in late adulthood.[30,31]

Metabolic and Endocrine Consequences in Untreated Adults Born Small for Gestational Age

Short SGA adults have a lower lean body mass than those born appropriate for gestational age (AGA) but a similar fat mass percentage.[32] Fat mass percentage in SGA adults with spontaneous postnatal catch-up growth is, however, higher.[32,33] Insulin sensitivity measured by Frequently Sampled Intravenous Glucose Tolerance (FSIGT) test is similar in SGA and AGA adults, but it is lower in SGA adults with spontaneous catch-up growth.[34] Short adults born SGA have a higher systolic and diastolic blood pressure.[13] Lipid profile in adults born SGA is similar to those born AGA.[35,36] Thus, particularly young adults born SGA with early and spontaneous catch-up in weight show an unfavorable body composition and lower insulin sensitivity as opposed to those who remain short.[37–40]

Metabolic and Endocrine Consequences in Growth Hormone–Treated Adults Born Small for Gestational Age

Concerns had been expressed regarding the long-term effects of GH treatment after discontinuation by increasing the risk for type 2 diabetes and cardiovascular disease in predisposed subjects such as adults born SGA. A longitudinal study showed that discontinuation of GH treatment is associated with a significant increase in percentage body fat and fat mass SDS for 6 months after stop of treatment, whereas lean body mass SDS decreased.[41] At 6.5 years after stop of GH treatment, however, body composition and fat distribution were similar to that of untreated short SGA adults, indicating that GH-induced catch-up growth has no long-term unfavorable effect on fat mass and fat distribution.[32] The GH-induced lower insulin sensitivity during treatment is reversible after stopping GH treatment. At the age of 22 years, 6.5 years after discontinuation of GH-treatment, insulin sensitivity and secretion were similar in GH-treated and untreated short SGA adolescents.[13,41] Systolic blood pressure SDS was significantly lower than at start of treatment and diastolic blood pressure was similar to start at 6.5 years after discontinuation of GH treatment.[13,27,28] Importantly, in previously GH-treated SGA adults, both systolic and diastolic blood pressure SDS at 6.5 years after GH treatment were significantly lower compared with untreated short SGA adults.[13] Cholesterol levels at 6.5 years after GH treatment were similar to levels in untreated short SGA adults.[13]

COMBINING GROWTH HORMONE TREATMENT WITH GONADOTROPIN-RELEASING HORMONE ANALOG TREATMENT

Data have shown that children born SGA with an expected AH less than −2 SDS at start of puberty can benefit from additional GnRHa treatment to delay puberty for 2 years.[11] Recently, it has been shown that combined GH/GnRHa treatment results in a similar body composition, insulin sensitivity, blood pressure, and lipid levels at AH as treatment with GH only.[42,43] Additional GnRHa treatment for 2 years can therefore be considered in pubertal SGA children with a poor AH expectation.

SUMMARY

Short stature is one of the most common conditions presented to pediatric endocrinologists. SGA accounts for approximately 20% of all cases of short stature. Most children born SGA show spontaneous catch-up growth to a normal weight and height above −2 SDS; however, 10% remain short and can be treated with GH to improve AH. GH treatment is effective in inducing catch-up growth and improving AH. It also has positive effects on several risk factors for type 2 diabetes and cardiovascular disease. After discontinuation of GH treatment, the GH-induced reduction in insulin sensitivity is reversible. At 6.5 years after GH treatment, body composition, blood pressure, and lipid levels are similar to untreated short SGA adults, indicating that GH-induced catch-up in height has no unfavorable effects on metabolic health. It remains to be elucidated how metabolic health develops when SGA subjects become older.

Children born SGA with an expected AH less than −2 SDS at start of puberty can benefit from additional GnRHa treatment to delay puberty for 2 years. Combined GH/GnRHa treatment results in a similar body composition, insulin sensitivity, blood pressure, and lipid levels at AH as treatment with GH only. Combined GH/GnRHa can therefore be considered in pubertal SGA children with a poor AH expectation.

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