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What is the evidence for beneficial effects of growth hormone treatment beyond height in short children born small for gestational age? A review of published literature

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Keywords: growth hormone treatment; short stature; small for gestational age.

Abstract

Background: An increasing body of evidence supports the view that both an adverse intrauterine milieu and rapid postnatal weight gain in children born small for gestational age (SGA) contribute towards the risk for the development of chronic diseases in adult life.

Content: The aim of this review was to identify and summarize the published evidence on metabolic and cardiovascular risk, as well as risk of impaired cardiac function, intellectual capacity, quality of life, pubertal development and bone strength among children born SGA. The review will then address whether growth hormone (GH) therapy, commonly prescribed to reduce the height deficit in children born SGA who do not catch up in height, increases or decreases these risks over time.

Summary: Overall, there are limited data in support of a modest beneficial effect of GH therapy on the adverse metabolic and cardiovascular risk observed in short children born SGA. Evidence to support a positive effect of GH on bone strength and psychosocial outcomes is less convincing.

Outlook: Further evaluation into the clinical relevance of any potential long-term benefits of GH therapy on metabolic and cardiovascular endpoints is warranted.

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Introduction

An increasing body of evidence supports that both the intrauterine milieu and rates of weight gain during early childhood may contribute toward the risk of developing chronic diseases in adulthood [1]. The mechanisms by which an event in childhood or fetal life can have a permanent effect on adult health remain relatively poorly understood. However, several candidate mechanisms are implicated, including permanent changes in an organ structure, programmed changes in gene expression through epigenetic modifications and persistent effects on regulation of cellular aging [2]. Associations have been observed between low birthweight and the occurrence in adult life of a group of chronic diseases, including coronary heart disease, stroke, type 2 diabetes (T2D) and hypertension [3, 4], with an apparently increased risk in those who gain weight rapidly during infancy leading to obesity [5]. Evidence accumulated over the past two decades has improved the understanding of the link between early life and long-term health [6], as well as showing links with cognitive [7] and psychosocial endpoints.

Naturally, these associations with adult disease have raised concerns about children born small for gestational age (SGA) with persistent short stature who may end up receiving growth hormone (GH) therapy. SGA is commonly defined as birthweight and/or birth length that is at least two standard deviation scores (SDS) below the mean for gestational age [8]. Children born SGA are a heterogenous group and etiology varies between subgroups. Infants can be full term or preterm and may or may not have experienced severe intrauterine growth retardation. Although the majority (>86%) of children born SGA achieve catch-up growth in height during the first 6–12 months of life, approximately half of the remaining infants will remain short into adult life [9]. Most of these children do not have classical GH-deficiency, but have varying degrees of resistance in the GH–insulin-like growth factor I (IGF-I)

axis [10]. This small subgroup of children born SGA who do not show catch-up growth will be eligible for GH therapy.

The consequence in adult life in terms of metabolic outcomes of children who are eligible for GH therapy remains relatively unknown. The impact of GH treatment is likely to be complex and may vary according to the underlying etiology of their growth failure. As GH does not induce the rapid catch-up in weight, which is suggested to be a key factor in the adverse metabolic risk [1], but increases lean mass more than fat mass, it may have a beneficial effect on body composition. However, GH is an important modulator of insulin sensitivity [11] and may potentially worsen metabolic risk. Alternatively, as the phenotypic outcomes in subjects born SGA closely resemble those of individuals with untreated GH deficiency (GHD), including increased adiposity and reduced lean mass, data from animal models suggest that GH might potentially reverse the adverse effects of prenatal programming [12].

The aim of this review was to identify and summarize the published evidence on metabolic and cardiovascular risk, as well as intellectual capacity, quality of life and bone strength among children born SGA. The review then addresses the impact of GH therapy, commonly prescribed to reduce the height deficit in children born SGA with persistent short stature, on these early markers of future disease risk. The overall potential for GH to increase or decrease the risk of long-term disease will be reviewed with respect to currently available evidence. As data from long-term longitudinal follow-up studies on the effects of GH therapy on metabolic risk in short children born SGA are scarce, we are heavily reliant on data showing short-term changes in potential surrogate markers, until more long-term data become available.

Materials and methods

A search of the PubMed database was performed to identify studies that reported associations between GH treatment and health outcomes of interest and were published between January 1996 and September 2017. Inclusion criteria were: studies in human patients born SGA, treated with GH as monotherapy; and peer-reviewed original papers published in English. Studies that reported outcomes following the cessation of GH therapy as well as those that reported outcomes during GH therapy were included. Interventional and observational studies were accepted. Studies focused on the effects of GH therapy on height that reported only baseline characteristics of patients, or that did not define the identifying characteristics of children born SGA, were not included. No limit was applied regarding the subjects' age at the time of the outcome assessment.

Search terms representing the following categories were combined (1) the population: SGA; (2) outcomes related to cardiovascular structure and function (aortic dilation, aortic distensibility, intima–media thickness, blood pressure [BP]); or to metabolic diseases (overweight, adiposity, insulin resistance, glucose tolerance, beta-cell function) and cardiovascular risk including blood lipid profile (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides); or to pubertal development; or to bone strength (bone mineral density, bone mineral content and fracture rates); or to neurocognitive development (neurodevelopment, cognition, intelligence quotient, motor function, behavior) or to health-related quality of life (HRQoL). Titles and abstracts of retrieved publications were screened to identify relevant studies. Full-text publications of potentially eligible studies were then screened for inclusion if they met the inclusion criteria. An additional manual search of the reference lists of relevant review articles was made to ensure a complete collection. Around 440 full-text publications were reviewed.

From the initial 440 publications identified in our search based on their titles, 115 were found to be of potential interest after screening the abstracts. Of these, 46 publications met all the inclusion and none of the exclusion criteria when the full text of each reference was screened, and these formed the basis of the review.

Results

The results are divided into two sections, with the first describing the clinical characteristics of patients without GH therapy and the second the characteristics of these patients after GH therapy.

Patients born SGA who did not receive GH therapy

Metabolic risk

Insulin sensitivity

Insulin resistance has been shown in young adults and children born SGA [13, 14]. In the Hagenau study, metabolic syndrome was found at 22 years of age in 2.3% of individuals born SGA compared with 0.3% born appropriate for gestational age (AGA) [15].

Compared with counterparts born AGA, prepubertal children born SGA had significantly lower insulin sensitivity [16], although the first phase of insulin response was similar at 48 h after birth [17]. Although some data suggest that insulin sensitivity is mainly determined by body mass index (BMI) or catch-up weight in prepubertal SGA children [14, 18], other studies show no relationship with catch-up weight [19, 20]. However, published research has found that children born SGA have a seemingly intrinsic insulin resistance, and that a rapid catch-up in weight gain can significantly increase their short- and long-term risk of developing metabolic-related health issues [21]. In

young adults, a significantly greater progression of BMI, higher percentage body fat and higher proportion of obese individuals born SGA was reported compared with individuals born AGA [22]. These data suggest that the consequences of fetal growth restriction on body composition and associated risks for metabolic disease may evolve beyond the completion of early postnatal catch-up.

Among adolescents and young adults born SGA, significantly increased insulin levels [23] and a greater insulin response to a glucose load [24] are reported, reflecting a compensated insulin resistance [25]. This pattern was especially prevalent in those with early rapid weight gain [18]. Both the tempo of fetal and early postnatal growth may be critical for the development of insulin resistance into adult life. Among older men (64–72 years old) with low birth weight (<3.18 kg) percentage body fat and fat mass were significantly higher and fat-free soft tissue, muscle mass and muscle-to-fat ratio were all significantly lower compared with those with high birth weight (>3.86 kg) [26]. Furthermore, children with catch-up weight gain between birth and 2 years of age were heavier, taller and fatter (more central fat distribution) at 5 years of age than other children from a normal birth cohort [27]. The mechanisms that signal and regulate early postnatal catch-up growth may influence associations between small size at birth and risks for disease in adulthood.

Serum levels of IGF-I at delivery were significantly lower in infants born SGA than in those born AGA, but by 3 years of age, after completion of catch-up growth, IGF-I levels were higher, especially in those born SGA with catch-up weight gain, and were associated with insulin resistance, weight and BMI [28]. The rapid increase in postnatal IGF-I levels observed in SGA but not AGA infants during their first year was positively associated with insulin secretion and longitudinal growth [28]. Indeed, in one study involving 29 children born SGA, catch-up growth and high BMI (>17 kg/m^2) during infancy and early childhood were intricately associated with the development of insulin resistance [14]. However, in general, serum levels of IGF-I are lower in children born SGA who remain short during childhood compared with those born AGA [29].

A variety of hormonal changes have been described in infants born SGA. Adiponectin acts as an insulin sensitizer and serum levels are inversely related to BMI as well as insulin resistance. In children born SGA, adiponectin levels lower, higher, or the same as in AGA or short AGA controls even following adjustment for sex, age, BMI and insulin resistance, have been described [30–32]. The apparent discrepancies may be due to methodological aspects and varying selection criteria for controls. An important role of leptin in determining long-term energy homeostasis has been proposed and data from animal models suggest that leptin's effects are modulated by both pre- and postnatal nutrition status [33]. Animal model data suggest that hypoleptinemia during a critical phase of development may be important in metabolic programming [34]. Young adults born SGA exhibit increased adiposity compared with AGA controls and lower serum levels of leptin, even after correction for gender, BMI and hyperinsulinemia [15].

Body composition

Children born SGA with catch up weight gain after birth have higher central adiposity than those born AGA [35] and potentially elevated hepatic fat [36]. It is not clear whether this predisposition is due to low birth weight itself or rapid postnatal catch-up growth, but evidence from animal models suggests that intrauterine growth restriction is associated with a decreased capacity to store fat subcutaneously, thereby promoting deposition of fat in ectopic sites [37]. These changes in metabolism and body composition during infancy were associated with reduced levels of adiponectin [38], fibroblast growth factor 19 [39] and vascular markers of atherogenesis [40]; however, these findings should be interpreted with caution due to the small numbers of patients (n = 22–29). Increased appetite may lie behind the catch-up phenomenon. Although nutrient intake may be lower in very young children born SGA than AGA peers, intake increased with age during childhood [41]. An increased production of ghrelin and IGF-I and the development of insulin resistance could be an adaptive mechanism to achieve normal growth in SGA children [42].

Individuals born SGA may have an abnormal ratio of white and brown adipocytes; white adipose tissue stores energy in the form of triacylglycerol, while brown adipose tissue dissipates energy as heat, using fatty acids to maintain body temperature. An overexpression of acyl coenzyme A synthetase long-chain family member 1 (ACSL1) in mature adipocytes in infants born SGA was associated with increased cellular lipid content [43]; although this may promote rapid catch-up growth it may also increase the release of esterified fatty acids and eventually lead to insulin resistance. Together, elevated ACSL1 levels and a high-calorie diet may interact to induce obesity and related comorbidities in individuals born SGA. Adult fatty liver, an indicator of insulin resistance and metabolic disease, was shown to be associated with both low birthweight and with preterm birth [44] in

the Bogalusa Heart and the Cardiovascular Risk in Young Finns studies.

Cardiovascular risk

A negative effect of intrauterine growth retardation on the structure and function of the cardiovascular system has been reported [45]. As many of these alterations are subclinical and may not be evident in very young children [46], the long-term effect of these changes in adult life remain to be determined. Compared with their AGA peers, infants born SGA (n = 18–22) may display significantly impaired central aortic compliance (aortic strain, aortic distensibility, p = 0.05) [47], while older children may have significantly impaired endothelial function [48]. Significantly raised levels of interleukin-6 [49], triglycerides and apolipoprotein-B/apolipoprotein-A1 ratio have also been identified in neonates born SGA compared with those born AGA [50]. In adults born SGA, some statistically significant but subtle changes in cardiac structure and function have been identified compared with adults born AGA, including increased left ventricular (LV) end systolic and end diastolic diameters and lower LV stroke volume, although these differences were not significant when indexed for either body surface area or height [51]. These are less marked than the changes described in childhood and are unlikely to play a pathogenic role in elevated cardiovascular risk [51].

There is mixed evidence supporting an association between being born small and BP, with one study showing higher systolic BP [52] and another showing no difference between children born SGA and those born AGA [53]. In adults born SGA, a small inverse but not statistically significant relationship between birth weight for gestational age with BP was shown with each quintile increment in body weight/gestational age percentile associated with a 1.04-mmHg decrement in adult systolic BP and a 0.63-mmHg decrement in diastolic BP, controlling for sex, age, site, smoking, and race/ethnicity. The relationship was strongest among those in the lowest decile of body weight/gestational age [54]. Impaired functioning of the autonomic nervous system has been described in children born SGA, with over-activity of the sympathetic nervous system, evidenced by higher heart rate and lower heart rate variability (HRV) [55]. A correlation between height and HRV has been described [55] and the finding that the sympathetic component of the control of HRV was higher in infants born SGA (n = 27) than in infants born AGA (n = 23) may link with findings in adulthood of an association between being born SGA and increased risk for cardiovascular disease [56].

Beta-cell function and impaired glucose tolerance

Numerous studies have shown an association between low birthweight and risk of developing T2D. Development of T2D reflects the inability of the beta-cell to increase insulin secretion in response to insulin resistance. Children born SGA with rapid catch-up growth in weight during the first year of life have higher fasting insulin levels than those without catch-up growth or AGA infants, suggesting that they may be insulin resistant [57]. At 4 years of age, children born SGA (n = 27) with compensatory catch-up in weight during the first year of life had mild disturbances of glucose tolerance and lower insulinogenic index consistent with impaired beta-cell function compared with age-matched healthy peers born AGA (n = 62) [58]. A similar increase in risk for T2D was found in infants with normal birthweight with rapid weight gain, especially in the first 3 months after birth [59]. Children born SGA tend to gain more central and intra-abdominal fat than those born AGA tending to become viscerally obese between 6 and 8 years of age [60]. Obese children born SGA exhibit deficits in early insulin response and reduced disposition index (DI) that result in higher area under the plasma glucose concentration-time curve ($AUC_{glucose}$), compared with obese children born AGA or large for gestational age [61]. Both reduced compensatory beta-cell secretion [17] and similar beta-cell capacity to AGA peers [62] have been reported. In young adult males with low birthweight, a combination of abnormalities suggestive of T2D including increased abdominal obesity, decreased insulin secretion, and reduced forearm glucose uptake was observed compared with healthy peers [63]. Moreover, an increased risk of T2D was found in middle aged adults born SGA [64]. The association between birthweight and risk of T2D appears to be mediated via combined effects on beta-cell function and insulin sensitivity. However, it is worth noting that short stature *per se* is associated with increased risk for T2D [65, 66]. Lower insulin secretion was independently related to shorter stature at 8 years of age relative to parental height [67].

Lipid profile

An adverse lipid profile has been reported in some studies of children born SGA. In one study nearly half of full-term children born SGA had their serum cholesterol and LDL-cholesterol in the highest quartile of that of the control group [68]. In one study involving 24 children born SGA, an adverse cardiometabolic profile was observed in children born SGA compared with AGA peers, with a worsening of

this profile during adolescence [69], although adjustment for individual characteristics including BMI lessens the difference between SGA and AGA individuals [70].

Puberty

Children born SGA are more likely to start puberty early than those born AGA with early menarche or faster progression through puberty [71]. Furthermore, although the onset of puberty in many short SGA children starts at an appropriate age [72, 73] this may be relatively late for their bone age [71]. A more rapid bone maturation during puberty compared with AGA children and an earlier and shorter peak height velocity during adolescence has been reported in short girls born SGA compared with children born AGA [71], which may result in lower pubertal height gain as a result of an earlier fusion of growth plates.

At the start of puberty, compared with girls born AGA, girls born SGA may have significantly increased baseline and stimulated estradiol and 17-hydroxyprogesterone [74]. However, serum anti-Müllerian hormone (AMH) levels appear to be unaffected by SGA birth [75, 76] suggesting that girls born SGA are unlikely to have a reduced follicle pool. Conflicting data have been reported regarding levels of dehydroepiandrosterone sulfate (DHEAS) in prepubertal children born SGA. In one study, serum DHEAS levels in prepubertal children (3 – 9 years) were reported to be similar between age-matched AGA children and short children born SGA [77]. Another study reported that the serum DHEAS level was higher in short children born SGA ($n = 29$) than in age-matched children born AGA ($n = 24$) [78]. Among pubertal children, the DHEAS levels tended to be higher in those born SGA than AGA ($p = 0.06$) [78]. Other reports suggest that young women born SGA ($n = 20$) are characterized by hypergonadotrophinemia (elevated follicle-stimulating hormone and luteinizing hormone levels) and by a reduced uterine and ovarian size compared with healthy peers born AGA [79]. Of interest, links between early puberty and T2D risk have been proposed [80].

Bone strength

In children born SGA with short stature, low muscle mass may be associated with changes in bone geometry; as assessed by peripheral quantitated computed tomography (pQCT), total bone area, cortical area, cortical thickness, strength-strain index and muscle area were significantly lower than normal references, suggesting impaired bone strength [81]. Impaired bone mineralization has been reported in one study ($n = 18$) [82] and higher bone strength in another study ($n = 31$) [83] of SGA infants, in particular those born preterm. Lower bone accretion in preterm infants born SGA than in infants born AGA, independent of body size, suggest that prenatal conditions for bone accretion may not be replicated postnatally [84]. Lower body weight in infants born SGA was suggested as a potential risk factor for fracture [85] and an increased predisposition for fracture as a result of lower peak bone mass and higher risk of osteopenia was reported in young adults born SGA [86]. A study involving 15 preterm infants born SGA suggested that they may be at increased risk of low bone mass in adult life [87], with some data supporting that early life weight gain, especially peak weight velocity may be related to bone health, as assessed by vertebral cross sectional area, in adult life [88]. However, as bone mineral content is related to bone size, it should also be considered that low bone-mineral content may simply reflect smaller bone size in subjects born SGA.

Cognition, self-esteem, psychosocial issues

There is conflicting evidence regarding the effect of being born SGA on neurodevelopmental and behavioral problems. Variable degrees of developmental delay and behavioral problems have been reported in short children born SGA and being born SGA was reported to have a clinically significant impact on academic performance in 10-year old children [89, 90]. However, recent evidence suggests that high-quality parenting in early childhood may positively impact on deficits in long-term reading, math and fine motor skills related to SGA birth [91]. Data in adults are conflicting. Some reports suggest that SGA and intrauterine growth retardation may not be harmful for adult cognitive ability, at least not in individuals born at near-term. Other data suggest that there is a higher prevalence of psychiatric disorders (longitudinal development), as well as less likelihood of academic achievement, and more likelihood of unemployment in adults born SGA than in AGA-matched counterparts [92].

Quality of life

Data on the effect of short stature on HRQoL in otherwise healthy children is not conclusive. Although some evidence suggests that height has only a negligible impact on psychosocial adaptation [93], challenging the traditional association between short stature and poor HRQoL [94],

data from some studies support that short stature in SGA or at least being born SGA may impact on HRQoL [95].

Heterogeneity of results within and between studies – evidence for genetic and epigenetic effects

Children born SGA who do not show catch-up growth may share many of the adverse metabolic features most evident in those who gain weight rapidly during infancy, and there is considerable research interest in possible epigenetic modulation of gene expression and how this could mediate early-life programming of increased risk of adult-onset disease [96].

However, in the small infants who fail to catch up, genetic factors may also be important. Limited evidence supports a role for IGF-I receptor mutations in children born SGA [97], although there is some evidence that insulin-receptor polymorphism, previously associated with adult vascular and metabolic diseases and T2D, may also be associated with pregnancies complicated by SGA births [98]. Polymorphic variation in IGF binding protein-I and -3 axes may also play a role in the complex interaction between spontaneous growth, glucose homeostasis and lipid metabolism in short children born SGA [99, 100]. Short SGA children carrying the d3-growth hormone receptor polymorphism had increased spontaneous growth, lower insulin sensitivity and a compensatory increase in glucose, C-peptide and insulin before GH therapy compared with children homozygous for the full-length allele [101].

Effects of GH therapy in children born SGA

As space constraints did not permit inclusion in the tables of all studies that showed the effects of GH treatment, we selected those considered as key studies (with a robust study design and focused on the relevant endpoint rather than reporting it as an incidental outcome) and which reported data on responses during rather than after GH therapy.

Metabolic risk

Effects of GH therapy on insulin resistance and T2D

Findings on the effects of GH therapy on metabolic risk in included studies are summarized in Table 1. Accumulated data show that treatment with GH results in a reduction in insulin sensitivity [103] and a compensatory increase in acute insulin response (AIR) during the first year of treatment [105]. However, the compensatory increase in AIR was found to be insufficient, resulting in a reduction in the DI, although not leading to T2D [105]. Increases in glucose and insulin levels during GH treatment were reported in studies of up to 3 years' duration [102, 104, 106]. Fasting insulin and glucose levels increased significantly during 6 years' GH treatment but were not significantly different from baseline, 6 months after stopping GH; at 6.5 years after stopping GH, they were higher than baseline, but similar to untreated SGA controls [107]. In another study, 5 years after stopping GH after the attainment of adult height, insulin sensitivity, beta-cell function and body composition of previously treated children were similar to untreated adults born SGA, suggesting that long-term GH treatment had no unfavorable metabolic effects in early adulthood [108]. Taken together, these data suggest that GH treatment in SGA children may not increase the risk of T2D or metabolic syndrome [107] and that changes in carbohydrate metabolism observed during GH treatment are reversible. However, caution should be exercised in those subjects with a family history of T2D. Very long-term follow-up studies will be required to determine whether GH treatment increases or decreases long-term risk for T2D in subjects born SGA.

Effects of GH therapy on body composition

Findings on the effects of GH therapy on body composition in included studies are summarized in Table 2. Treatment with GH is associated with a substantial reduction in adipose tissue mass and an increase in lean body mass (LBM) [109–114]. This leads to a normalization of BMI [109]. In 14 prepubertal children born SGA, 3 years of GH treatment was associated with increased muscle cross-sectional area and increased adipose tissue cross-sectional area [115]. At third year end, muscle tissue cross-sectional area change was significantly greater in GH-treated children born SGA than in age-matched controls, but adipose tissue cross-sectional area change was similar between the two groups [115]. In 11 GH-treated short children born SGA, GH-induced catch-up growth was accompanied by a less adipose tissue but with a more central fat distribution [116], thus some baseline anomalies were amplified (more deficit of subcutaneous fat, both at total body level and in the abdominal region), thereby amplifying the deficit in subcutaneous fat [117]. In the 14 prepubertal children who had received GH for 3 years, maintenance of muscle and adipose tissue mass was observed during a 1-year withdrawal period [115]. In adolescents born SGA, discontinuation of GH therapy was associated with a marked change

Table 1: Summary of included studies on metabolic risk, including glucose homeostasis, during GH therapy in patients born SGA.

Outcome	Study design	No. of subjects	Demographics[a]	Summary of findings[a]
Fasting glucose, insulin, HOMA IR (Chatelain et al. [102])	Retrospective analysis of data from open, multicenter, randomized trial	100	Age:[b] Group 1; 4.7 (1.7) years; Group 2; 5.6 (1.9) years Duration of GH treatment: 3 years	During 3 years of GH treatment, fasting glucose (mmol/L) increased from 4.4 (0.7) to 4.8 (0.5) ($p < 0.01$ vs. baseline). Insulin $AUC_{180\ min}$ (μU/mL/180 min) increased from 3363 (2570) to 5365 (2678) ($p < 0.001$ vs. baseline); HOMA IR increased from 1.3 (1.2) to 2.1 (1.1) ($p < 0.01$ vs. baseline). A_{1C} not reported
Glucose, insulin and A_{1C} (Sas et al. [103])	Prospective, randomized, double-blind dose-response	78	Age: 7.3 (2.2) years Duration of GH treatment: 6 years	Mean fasting glucose increased by 0.5 mmol/L after 1 year of GH treatment and were stable thereafter. 2-h $AUC_{glucose}$ and AUC_{A1C} were below baseline after 6 years GH. A_{1C} within normal range throughout treatment. Fasting insulin and glucose-stimulated insulin levels increased during GH treatment
Diabetes and glucose homeostasis (Schwartz et al. [104])	Prospective, open label, non-comparative Phase IV	278	Age 7.4 (2.7) years Duration of GH therapy: 2 years	No child developed diabetes; fasting glucose and OGTT values were all below normal limits (126 and 200 mg/dL, respectively); A_{1C} was within normal limits at all times; fasting insulin was 35.7 (34.7) pmol/L at baseline and 60.3 (49.9) at 2 years ($p < 0.0001$); HOMA increased from 1.01 (1.03) at baseline to 1.74 (1.39) at 2 years ($p < 0.0001$)
Insulin secretion as assessed by AIR, IS, HOMA and DI (Jensen et al. [105])	Randomized, parallel group, multicenter study	110	Age: 6.28 (1.69) years Duration of GH therapy: 1 year	After 1 year there was a significant increase in fasting insulin ($p < 0.0001$) and C-peptide ($p < 0.0001$) that resulted in a decrease in insulin sensitivity ($p < 0.0001$) and a reduction in DI ($p = 0.032$). Fasting blood glucose ($p < 0.0001$) and A_{1C} ($p = 0.008$) were increased from baseline but remained within normal levels
Glucose, insulin; C-peptide, insulin sensitivity (HOMA) (log), AIR (log), DI (log) (Thankamony et al. [106])	Multicenter, open-label	89	Age: 6.2 (1.6) years Duration of GH therapy: 1 year	(Baseline vs. 1 year); glucose (mmol/L), 4.32 (0.66) vs. 4.70 (0.55), $p < 0.0001$; insulin (pmol/L [log]), 1.19 (0.28) vs. 1.59 (0.22), $p < 0.0001$; C-peptide (pmol/L [log]), 2.30 (0.24) vs. 2.61 (0.17), $p < 0.0001$; insulin sensitivity (HOMA) (log); 2.38 (0.25) vs. 2.06 (0.17), $p < 0.0001$; AIR (log), 3.13 (0.24) vs. 3.39 (0.26), $p < 0.0001$; DI (log), 5.51 (0.24) vs. 5.46 (0.23), $p = 0.11$

[a]Data are presented as mean (standard deviation). [b]Group 1: 3 years' GH treatment and 5-year follow-up; Group 2: 1 year untreated, 3 years' GH then 5-year follow-up. Data are geometric mean (95% confidence interval). A_{1C}, glycated hemoglobin; AIR, acute insulin response; $AUC_{180\ min}$, area under the plasma concentration–time curve from 0 to 180 min; AUC_{A1C}, area under the plasma glycated hemoglobin concentration–time curve; $AUC_{glucose}$, area under the glucose plasma concentration–time curve; DI, disposition index: beta-cell functions assessed from AIR (area under the plasma insulin concentration–time curve from 0 to 10 min corrected for baseline insulin levels) x Si; GH, growth hormone; HOMA, homeostasis model assessment; HOMA IR, homeostasis model assessment-estimated insulin resistance; (log), log-transformed to normality; IS, insulin sensitivity (calculated from fasting C-peptide); OGTT, oral glucose tolerance test.

in body composition after 6 months; fat mass SDS and body fat increased, and LBM SDS decreased (but remained within the normal range) [118]. At 5 and 6.8 years after GH treatment, both adipose tissue and LBM were similar between GH-treated and untreated adults born SGA, suggesting that there may not be any long-term benefits, but also no unfavorable effects, of long-term GH therapy in terms of body composition [108, 119]. In addition, adults born SGA (previously GH-treated and untreated) still had a lower LBM and higher fat mass than adults born AGA [119].

Table 2: Summary of included studies related to body composition during GH therapy in patients born SGA.

Outcome	Study design	Number of subjects	Demographics	Summary of findings
BMI (Sas et al. [109])	Randomized, double-blind, multicenter, dose-response trial	79	0.033 mg/kg/day (n = 41): 7.3 (2.1) years; 0.067 mg/kg/day (n = 38): 7.2 (2.4) years Duration of GH treatment: 6 years	Pre-treatment the BMI SDS was below 0. After 6 years of GH treatment the BMI SDS increased significantly ($p < 0.001$) to values not different from 0
BMI, LBM, total body fat, trunk fat mass, limb fat mass, total body fat (%), trunk fat (%), limb fat (%), trunk-limb fat ratio (body composition assessed by DXA) (Thankamony et al. [106])	Open-label, multicenter	89	Age: 6.2 (1.6) years Duration of GH therapy, 1 year Control group included 26 untreated	(Baseline vs. 1 year) BMI, kg/m^2, 14.16 (1.49) vs. 14.68 (1.62), $p < 0.0001$; lean mass (kg) 11.5 (2.66) vs. 15.6 (3.55), $p < 0.0001$; total body fat mass (kg), 2.26 (1.06) vs. 2.06 (1.12), $p < 0.007$; trunk fat mass (kg), 0.68 (0.37) vs. 0.72 (0.41), $p = 0.13$; limb fat mass (kg), 1.10 (0.68) vs. 1.00 (0.67), $p = 0.0002$; total body fat, %, 15.80 (5.80) vs. 11.2 (4.7), $p < 0.0001$; trunk fat, %, 10.6 (4.66) vs. 8.63 (4.03), $p < 0.0001$; limb fat %, 23.1 (9.70) vs. 14.6 (7.70), $p < 0.0001$; trunk-limb fat ratio, 0.61 (0.20) vs. 0.84 (0.32), $p < 0.0001$
Body composition (DXA) (Boonstra et al. [110])	Open-label multicenter	62 GH-treated	Age, GH-treated: 5.9 (1.6) years Duration of GH therapy: 1 year	Fat SDS: baseline, −1.4 (0.5), after 1 year, GH-treated, −1.6 (0.5); untreated, −1.1 (0.6) (GH-treated vs. untreated, $p = 0.03$); LBM SDS: baseline, −2.7 (0.5), after 1 year, GH-treated, −1.8 (0.5), untreated −2.6 (0.4 (GH-treated vs. untreated, $p < 0.001$); skinfold SDS: baseline, −1.2 (0.8); after 1 year, GH-treated, −1.9 (0.6), untreated, −1.0 (1.0) (GH-treated vs. untreated, $p < 0.001$); BMI SDS, baseline, −1.3 (0.9); after 1 year, GH-treated, −1.2 (0.9), untreated, −1.0 (0.9) (GH-treated vs. untreated, n.s.)
Body composition (LBM SDS, fat percentage SDS) assessed using DXA (Willemsen et al. [111])	Open-label with randomized control group	16 GH-treated	Age: 6.1 (1.5) years Duration of GH therapy: 6 years	LBM SDS_{age}, baseline −2.0 (0.3); 6 years GH, −0.9 (0.7), $p < 0.001$ vs. baseline; % body fat SDS_{age}: baseline, −1.0 (0.8); 6 years GH, −1.6 (0.7), $p < 0.05$ vs. baseline
Percentage body fat; lean body weight (assessed with BIA) (Rapaport et al. [112])	Open-label, multicenter	139	Mean age: 6.5 (2.4) years Duration of GH therapy: 1 year	Percentage body fat decreased from baseline to 12 months (median −2.6%, $p < 0.0001$); lean body weight increased from baseline to 12 months (median 3.4 kg, $p < 0.0001$)
Fat area; muscle area (Schweizer et al. [113])	Open-label, prospective	34	Age: 7.3 (2.7) years Duration of GH therapy: 2 years	Fat area SDS_{height}, baseline −0.6 (1.9). 2 years' GH, −1.5 (1.5), $p < 0.001$; muscle area SDS_{height}: baseline, −1.8 (1.01); 2 years' GH therapy, −0.78 (1.37), $p < 0.001$
Fat area; muscle area (Martin et al. [114])	Open-label, prospective	37	Age: 6.81 (2.33) years Duration of GH therapy: 1 year	Fat area SDS, baseline, −1.45 (1.08); 6 months GH, −0.91 (1.72), n.s.; muscle area $SDS_{height;}$ baseline, −1.65 (1.16); 6 months' GH, 0.79 (0.78), $p < 0.001$ vs. baseline

BIA, bioelectric impedance analysis; BMI, body mass index; DXA, dual-energy X-ray absorptiometry, Fat area SDS_{height}, Fat area (= total cross-sectional area – muscle area and –total bone area) SDS adjusted for height; GH, growth hormone; LBM, lean body mass; LBM SDS_{age}, lean body mass SDS adjusted for age; n.s., not significant; % body fat SDS_{age}, % body fat SDS adjusted for age; SDS, standard deviation score; SGA, short for gestational age.

Taken together, these findings suggest a greater deficit in subcutaneous fat, both in the abdominal region as well as at total body level, with GH treatment. Putative benefits in body composition during GH treatment do not appear to be sustained after cessation of treatment.

Cardiovascular risk: structure and function

Findings on the effects of GH therapy in children born SGA on cardiovascular structure and function in included studies are summarized in Table 3.

Carotid intima–media thickness was similar between GH-treated children born SGA and healthy controls, but was lower than in children born SGA with spontaneous catch-up growth [120], suggesting that the pharmacological catch-up may be less detrimental from a cardiovascular viewpoint than spontaneous catch-up growth. In another study, carotid intima–media thickness was not different between patients who received GH treatment at physiological doses (patients with GHD), patients who received GH at supraphysiological doses (a mixed population born SGA, Turner syndrome

Table 3: Summary of included studies on cardiovascular risk, including BP, during GH therapy in patients born SGA.

Outcome	Study design	Number of subjects	Characteristics	Summary of findings
BP, carotid ultrasound measurements (de Arriba et al. [120])	Cross-sectional, observational	Prepubertal, 99 (GH-treated, n = 54; untreated, n = 55; Pubertal, 72 (GH-treated, n = 41; untreated, n = 31)	Age: Prepubertal, GH-treated, 7.4 (2.0) years Prepubertal, untreated, 5.8 (2.0) years Pubertal, GH-treated, 13.0 (1.4), Pubertal, untreated, 13.0 (1.5) years	Prepubertal, systolic and diastolic BP was higher in patients with natural catch-up than in GH-treated patients (systolic, 101.0 [10.4] vs. 93.5 [9.0]; diastolic 59.7 [8.7] vs. 54.5 [7.2] mmHg). In pubertal children, systolic BP was higher in untreated vs. GH-treated children (112.5 [9.2] vs. 106.4 [11.0], p = 0.00), but diastolic BP was similar between untreated and GH-treated SGA groups (62.1 [8.3] vs. 61.8 [7.1]). IMT was lower in patients receiving GH than those with spontaneous catch-up growth or controls in both the prepubertal group (0.34 vs. 0.41 vs. 0.32, p = 0.00) or pubertal group (0.34 vs. 0.42 vs. 0.34, p = 0.000)
cIMT (Knop et al. [121])	Prospective, open-label	31 SGA	Mean age: 10.9 years Duration of GH treatment: 4.4 years	Mean cIMT was similar between GH-treated and untreated children. A_{1C} and BMI SDS were significantly correlated with mean cIMT for all children
BP (Sas et al. [109])	Randomized, double-blind, dose-response	79	Age: GH, 0.1 IU kg/day, 7.3 (2.1) years, 0.2 IU kg/day, 7.2 (2.4) years Duration of GH therapy: 6 years	Systolic BP_{age} decreased to values close to 0 (0.4 [1.1] to 0.0 [1.1]); diastolic BP_{age} decreased to values below 0 (–0.4 [1.0]) to –0.9 [0.8])
BP (Willemsen et al. [122])	Randomized, prospective, case-control	38 GH-treated	Age: 6.4 (1.1) years Duration of GH therapy: 3 years	Systolic BP SDS increased during the first 6 months of GH therapy (1.2 [0.9] to 1.6 [1.1]) but at 3 years was similar to that in untreated SGA controls (0.5 [1.0] vs. 0.5 [1.0] SDS). After 3 years, diastolic BP SDS decreased from 0.3 (1.2) to 0.0 (0.8) in the GH-treated patients and from 0.4 (0.9) to –0.4 (0.8) SDS in the untreated SGA controls
BP (de Kort et al. [123])	Prospective, open-label	404	Age: 6.7 (2.1) years (n = 143) preterm 7.4 (2.6) years; (n = 261) term Duration of GH therapy: 4 years	At baseline, BP was significantly higher in SGA vs. healthy peers (p < 0.001) and was significantly higher in preterm vs. term SGA (p = 0.008 [systolic]; p < 0.001 [diastolic]). After 4 years, systolic BP SDS decreased significantly in both preterm SGA (1.1 [1.0; 1.3][a] to 0.9 [0.6–1.1]; p < 0.05) and term SGA (0.8 [0.7; 0.9] to 0.7 [0.5; 0.9] p < 0.05) and diastolic BP SDS decreased from 0.5 [0.3; 0.6] to 0.0 [–0.2; 0.1] (p < 0.001) in preterm SGA and from 0.2 [0.1; 0.3] to –0.1 [–0.2; 0] (p < 0.05) in term SGA

[a]Data are model estimate (95% confidence interval). Data are mean (SD) unless otherwise stated. A_{1C}, glycated hemoglobin; BP, blood pressure; BP_{age}, BP adjusted for age; cIMT, carotid intima–media thickness; GH, growth hormone; SGA, small for gestational age.

and idiopathic short stature) and untreated healthy controls [121].

BP

GH therapy appears to have a favorable effect on BP in short children born SGA during up to 6 years of GH therapy [109, 120, 122, 123]. After 3 years of GH treatment, systolic BP SDS significantly decreased from baseline in GH-treated patients, but remained similar to baseline in untreated SGA controls [122]. In another study, systolic BP was higher in prepubertal patients born SGA with spontaneous catch-up growth and in healthy controls than in GH-treated short patients born SGA. In pubertal children, systolic BP was similar between GH-treated children born SGA and healthy controls, but was lower than in children born SGA with spontaneous catch-up growth [120]. In the same study, in the prepubertal group, diastolic BP was higher in those with spontaneous catch-up growth and in healthy controls than in GH-treated patients born SGA, while in pubertal children, diastolic BP was not different between the three groups [120]. In adolescents treated with GH to adult height, no change was observed in BP after GH was stopped, with systolic BP SDS remaining close to zero and diastolic BP SDS below zero [124].

There are some data to suggest that GH treatment in childhood for short stature due to idiopathic GHD, idiopathic short stature, or being born SGA may be associated with increased risk of intravascular hemorrhage in adult life relative to a healthy population [125]. However, the number of subjects was small and risk of such an event in an untreated population is unknown. Nevertheless, further monitoring of stroke in this population is warranted and there are no data to support increased BP risk from GH treatment.

Lipid profile

Findings on the effects of GH therapy on lipids in included studies are summarized in Table 4. In three studies, GH treatment was associated with a decrease in total cholesterol and LDL-cholesterol, and either no change or an increase in HDL-cholesterol and triglycerides (n = 22–79) [109, 126, 127]. However, in another study after short-term GH therapy (1 year) no change in total cholesterol, LDL- or HDL-cholesterol, but a significant increase in triglycerides was observed (n = 89) [106]. Decrease in LDL-cholesterol and increase in HDL-cholesterol and triglycerides reported by Krebs and co-workers [126] were accompanied by positive changes, possibly associated with a reduction in cardiovascular risk, in potentially atherogenic parameters, including inflammatory markers and growth factor-related parameters, for example, lipoprotein-associated phospholipase A2 and high-sensitivity C-reactive protein [126]. Shortly after stopping GH in adolescents born SGA who had achieved adult height, triglycerides increased and HDL-cholesterol decreased significantly [128]; however, these findings were based on a small group of 21 patients born SGA. Several years after stopping GH, total cholesterol was similar to levels among untreated short adults born SGA [107].

Accumulated data are thus inconclusive regarding the effect, if any, of GH treatment on the lipid profile in short children born SGA and further long-term studies are required to evaluate implications of GH therapy on this parameter.

Puberty

Reports suggest GH therapy does not impact age at onset or progression through puberty [129, 130]. No effect on serum AMH [75, 131] or DHEAS [77] has been reported. Short-term GH treatment may be associated with an increase in uterine size, ovarian volume and number of follicles [131] equating to a near normalization of these parameters, which were lower than normal in a group of 18 Danish girls born SGA at GH start, compared with a healthy Danish population. However, the absence of a matched control group means that it cannot be determined if these changes might be attributed to normal growth. Although reassuring, these preliminary data support that monitoring of puberty and ovarian function during GH therapy in girls born SGA is prudent.

Bone strength

Bone strength may be improved during long-term GH treatment in short SGA children [81, 111, 132] (Table 5). However, differences in the techniques used to assess structure and mass of bone and muscle in these studies, dual-energy X-ray absorptiometry (DXA) and pQCT, may impact on results, with DXA allowing measurement of total or regional body fat, muscle mass and bone mass in a two-dimensional manner, and pQCT, a three-dimensional visualization of these parameters.

A biphasic change in bone geometry during GH treatment was demonstrated in one study, with a significant increase in total bone area, marrow area and muscle area, but lowering of bone mineral content during the first year

Table 4: Summary of included studies related to lipid profile during GH therapy in patients born SGA.

Outcome	Study design	Number of subjects	Demographics	Summary of findings
Total cholesterol, LDL-cholesterol, HDL-cholesterol (Sas et al. [109])	Randomized, double-blind, dose-response, multicenter	79	Mean ages in GH treatment groups were 7.2 and 7.3 years. Duration of GH therapy: 6 years	Total cholesterol (baseline vs. 4 years); 4.7 (0.8) vs. 4.3 (0.7) (ref value: 3.2–6.0) mmol/L); LDL-cholesterol, 2.9 (0.7) vs. 2.5 (0.6) (ref: 1.3–3.7) mmol/L; HDL-cholesterol, 1.3 (0.3) vs. 1.3 (0.3) mmol/L (ref: 0.9–1.6)
Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides (Thankamony et al. [106])	Prospective, open-label	89	Age: 6.2 (1.6) years Duration of GH therapy: 1 year	(Baseline vs. 1 year GH therapy) total cholesterol (mmol/L), 3.94 (0.72) vs. 3.88 (0.70), $p = 0.38$; LDL-cholesterol (mmol/L), 2.23 (0.63) vs. 2.15 (0.58), $p = 0.11$; HDL-cholesterol (mmol/L), 1.47 (0.35) vs. 1.42 (0.33), $p = 0.070$; triglycerides (mmol/L) 0.64 (0.33) vs. 0.83 (0.40), $p = 0.001$
LDL-cholesterol, small dense LDL-cholesterol, HDL-cholesterol, triglycerides (Krebs et al. [126])	Prospective, non-interventional	33 SGA	Median age: 6.5 years Duration of GH therapy: 1 year	Significant reduction in small dense LDL-cholesterol (baseline vs. 1 year), 20.7 vs. 17.3 mg/dL, $p = 0.020$; increase in HDL-2a; 16.4 vs. 17.8 mg/dL, $p = 0.004$; increase in triglycerides, 56.5 vs. 66.0 mg/dL, $p = 0.025$
LDL-cholesterol, HDL-cholesterol, Serum 7α-hydroxycholesterol, 24S-hydroxycholesterol (Hirayama et al. [127])	Case-control study	22	Mean age: 4.7 (1.1); 11 received GH Duration of GH therapy: 1 year	In the GH-treated group, compared with baseline, LDL-cholesterol decreased by 6.6% at 6 months and by 8.8% at 12 months ($p < 0.01$), HDL-cholesterol increased by 1.7% ($p = 0.07$) and 3.3% ($p < 0.01$). Serum 7α-hydroxycholesterol (marker for hepatic cholesterol elimination) concentration increased by 34% at 6 months and by 35% at 12 months ($p < 0.01$). In addition, 24S-hydroxycholesterol increased by 25% and 26% ($p < 0.001$). No changes from baseline were observed in the untreated group

GH, growth hormone; HDL-2a, HDL-cholesterol with density 1.100–1.150 kg/L [126]; HDL, high-density lipoprotein; LDL, low-density lipoprotein; small dense LDL-cholesterol, atherogenic LDL-5 and LDL-6 [126].

Table 5: Summary of selected studies related to bone metabolism during GH therapy in patients born SGA.

Outcome	Study design	n	Demographics	Summary of findings
Bone mineral density (DXA) (Arends et al. [132])	Multicenter randomized/ open-label	12	Age: GH-treated, 6.0 (1.6) years; controls, 5.9 (1.5) years Duration of GH therapy: 3 years	BMD_{LS} SDS (baseline vs. 3 years) –1.7 (1.0) vs. 0.1 (0.6); $p < 0.005$ vs. controls [–1.3 (0.6)]; BMD_{TB} SDS –0.9 (1.1) vs. 0.2 (0.7); $p < 0.005$ vs. controls (–1.0 [0.8])
BMC (pQCT) (Schweizer et al. [81])	Open-label, longitudinal	47	Age: 7.1 (2.5) years Duration of GH therapy: 2 years.	BMC (baseline vs. 2 years). 24 (11) vs. 33 (12) mg/mm, BMC SDS, –0.89 (1.39) vs. –1.16 (1.21)
BMD_{LS}, $BMAD_{LS}$ (DXA) (Willemsen et al. [111])	Open-label, longitudinal	25 (16 were GH-treated); Duration of GH therapy, 6 years	Age: GH-treated, 6.1 (1.5) years; controls, 5.9 (1.7) years Duration of GH therapy: 6 years	BMD_{LS}, baseline vs. 6 years, –1.5 (1.0) vs. –0.3 (0.7), ($p < 0.001$); $BMAD_{LS}$, –0.7 (1.3) vs. –0.2 (1.0), ($p < 0.05$)

BMC, bone mineral content; $BMAD_{LS}$, bone mineral apparent density of lumbar spine corrected for bone size; BMD_{LS}, bone mineral density of lumbar spine, BMD_{TB}, bone mineral density of the total body; DXA, dual energy X-ray absorptiometry; GH, growth hormone; pQCT, peripheral quantitative computed tomography; SGA, small for gestational age; SDS, standard deviation score.

of GH treatment [81]. Another study showed that while GH treatment significantly improved bone mineral density in patients born SGA, a gradual decrease occurred after stopping GH (starting at 18 months for males and 2–5 years in females) [133]. Five years after stopping GH, the bone mineral density was similar between previously treated individuals born SGA compared with untreated individuals born SGA or born AGA [133].

Exogenous GH may indirectly improve bone structure and strength as a consequence of improving muscle mass. Clinical relevance of these increases in bone strength in GH-treated children is not immediately apparent, as bone fractures are uncommon; however, the greater the cortical area, the higher the strength–strain index, and the consequent enhancement of bone strength may potentially reduce risk for fracture in later life.

Cognition, quality of life, self-esteem and psychosocial issues

Data on the effect of GH therapy on cognition are inconsistent. In a Dutch study, a positive effect of GH on attention was shown after 2 years of GH therapy [134], while long-term treatment was associated with improvement in intelligence quotient (IQ), behavior, and self-perception from scores below average to scores comparable to Dutch peers [135]. In contrast, in a randomized, controlled, Belgian study, no beneficial effect of GH treatment on IQ, cognition, or behavior was observed [89, 136], and a retrospective review of 64 cases in Spain similarly confirmed no clinical effect of GH therapy on IQ [137]. Differences in methodological aspects of these studies, including test instruments, length of follow-up, and stringency of criteria for definition of SGA, may explain part of the differences in these findings. Furthermore, while being born SGA is recognized to place a child at risk for impaired intelligence and cognition, the overall outcome for each individual is dependent on the balance of factors including socioeconomic status, parental intelligence and severity of growth restriction [138]. In summary, there is no conclusive evidence that GH affects IQ.

A positive impact of GH therapy on quality of life (QoL) in short children born SGA has been reported in a number of studies [139, 140], including behavior, depression, psychosocial [141] and physical functioning [95, 142]. In one study, improvement was noted as little as 3 months after initiation of GH [141]. However, despite improvement in QoL, this sometimes remained below that of AGA peers [95, 142] perhaps related to the questionnaire used for QoL assessment [139]. In another study, an improvement in wellbeing of the child was reported in half of parents of both treated and untreated children after 2 years, suggesting an adaptation to short stature over time [136]. However, a high risk of bias identified in the majority of the literature on the effects of GH treatment effects on psychological outcomes (in particular, lack of blinding) substantially weakens confidence in their results. This may serve to explain variability of findings for these outcomes across studies [143].

Conclusions

In this review, we have attempted to summarize available evidence on how being born SGA affects outcomes other than height, including cardiovascular and metabolic risk, bone strength and QoL. We also addressed the effects of GH therapy on these parameters. Unsurprisingly, the impact of GH on outcomes in short children born SGA is extremely complex and outcome data are limited.

We have concentrated on the potential impact of treatment with GH in the minority of SGA infants who do not catch up in height and remain small during early childhood. It is unclear whether they represent extremes of adverse intrauterine exposures, unrecognized genetic defects, or reprogramming of metabolism through functional changes or epigenetic adaptations. Although SGA children recommended for GH therapy may only represent less than 10% of those born SGA, the potential positive impacts of GH therapy on metabolic, bone, cognition and psychological impact require further assessment.

Overall, potential impact of GH on metabolic and T2D risk is encouraging, in that short-term effects of GH treatment on fasting glucose and insulin resistance did not result in increased risk for T2D. However, family history may be a more important risk factor and long-term follow-up studies will be required to evaluate fully the effects of SGA and treatment with GH. Critical to the risk for T2D is the effect of GH replacement on insulin sensitivity/insulin secretion: the DI, and the data are conflicting with regard to young people born SGA and treated with GH therapy; however, on balance, the data are reassuring.

Follow-up of GH-treated subjects after stopping GH therapy clearly demonstrates that on cessation of GH therapy, body composition, notably fat mass, insulin sensitivity and beta-cell function were comparable between previously GH-treated subjects and untreated subjects born SGA. These data suggest that any favorable effects of GH on these endpoints were not sustained. Spontaneous

catch-up growth appears to be the main factor associated with increased risk of long-term health problems. This is an important area for further research. Studying the differentiation of visceral adipose tissue in individuals born SGA, and the effect of GH on this process, may throw light on whether adipogenesis, programmed in fetal life, might be responsible for the high risk of metabolic syndrome in adult life and whether GH treatment has potential to improve this risk.

A possible indirect effect of GH therapy on muscle mass in improving bone strength has been described in some studies, which if sustained into adult life may impact on the likelihood of developing osteoporosis or risk of fracture.

There is inconclusive evidence to support a favorable effect of GH therapy on QoL and psychosocial endpoints in short children born SGA; however, further research is clearly needed in this area.

Overall, these data suggest that in addition to catch-up growth, there are limited data in support of a modest beneficial effect of GH therapy on metabolic and cardiovascular risk and bone strength; however, further evaluation into the clinical relevance of potential long-term favorable effects on these endpoints is warranted. Evidence to support a beneficial effect of GH on psychosocial outcomes is less convincing.

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