Received: 18 March 2022 | Revised: 12 May 2022 | Accepted: 15 May 2022

DOI: 10.1111/cen.14782

ORIGINAL ARTICLE

WILEY

Improved growth with growth hormone treatment in children after hematopoietic stem cell transplantation

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Abstract

Objective: Hematopoietic stem cell transplantation (HSCT) can be a curative treatment for malignant and nonmalignant diseases in children but is associated with significant late effects including growth failure. Growth hormone treatment (GHRx) is offered to improve growth, but limited data are available on its effect on adult height (AH). We aim to evaluate the effectiveness of GHRx.

Design: Single-center retrospective study.

Patients: Thirty-four patients who had received GHRx for ≥1 year were matched with two controls each, without GHRx, based on sex, indication for HSCT (malignancy, benign haematological disease or immunodeficiency), age at HSCT and conditioning with/without total body irradiation (TBI). All had reached AH.

Measurements: The primary outcome measure was the difference between AH and predicted AH (PAH) at start of GHRx or the equivalent age in controls (AH−PAH), calculated according to Bailey and Pinneau.

Results: GHRx was started at age 12.0 ± 2.6 years; median treatment duration was 3.8 years (range 1.7–9.2). AH−PAH standard deviation score (SDS) was significantly higher in growth hormone (GH) treated boys (−0.5 ± 0.7 SDS) than in controls (−1.5 ± 1.0 SDS, $p < .001$). Girls also had a higher AH−PAH after GHRx (+0.5 ± 0.6 SDS) compared to controls (−0.2 SDS ±0.7, $p < .01$). AH remained approximately 2 SDS below target height (TH) in treated and untreated individuals. Among GH-treated children, AH−PAH was higher in those who had received busulfan-based compared to TBI-based conditioning.

Conclusion: GHRx had a significant positive effect on AH compared to PAH, although AH remained far below TH. Higher AH−PAH was observed in girls and in those conditioned without TBI.

KEYWORDS

adolescent, body height, child, growth hormone, hematopoietic stem cell transplantation, total body irradiation, transplantation conditioning

1 | INTRODUCTION

Allogenic hematopoietic stem cell transplantation (HSCT) can be a curative treatment for children with malignant and nonmalignant diseases, but can come with long term side effects. These include endocrinological problems, such as growth retardation and infertility.[1]

Several studies show that adult height (AH) standard deviation score (SDS) is lower than pre-HSCT height SDS, especially after total body irradiation (TBI).[2–7] HSCT has been associated with neurosecretory dysfunction and growth hormone (GH) deficiency.[6] However, gonadal dysfunction, hypothyroidism, damage to the epiphyseal growth plates and graft-versus-host disease and its treatment have also been implicated in growth impairment.[2–5,8–11]

Positive short-term effects of GH treatment on growth velocity have been reported in children after HSCT but few studies have assessed AH and most had small study populations.[1] Whereas some reported improved AH with GH treatment[9,10] others found no significant difference between treated and untreated individuals.[4,12] Variations in underlying disease, conditioning regimen and age at start of GH treatment may account for some of the differences in findings.

Because of the limited and conflicting evidence currently available, it is difficult to counsel children and their families on the expected height gain from GH treatment and to decide who would benefit most from the treatment.[1] Therefore, we aimed to investigate the effect of GH treatment on AH in a cohort of individuals who have undergone HSCT, comparing their growth to that in matched controls who had undergone HSCT, but did not receive GH treatment. In addition, we assessed which factors influenced the effect of GH treatment.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We selected children treated with GH after HSCT at the Willem-Alexander Children's Hospital, Leiden University Medical Centre between 1980 and 2011. Children were included if (1) they had received ≥1 year of GH therapy, (2) they had reached AH (defined as a growth velocity <2 cm/year) before December 2017, (3) their AH could be retrieved from medical files and (4) parental height was available. We excluded children who had received GH treatment before HSCT.

2.2 | Control patients

Each patient was matched with two control patients who (1) were ≥2 years after HSCT, (2) had never received GH treatment, (3) whose AH could be retrieved from medical files, (4] had reached AH after HSCT and before December 2017. Children with known genetic causes of impaired growth were excluded. The following matching criteria were applied in the stated order: (1) indication for HSCT, (2) sex, (3) conditioning with or without TBI and (4) closest age match at the time of HSCT. Indications for HSCT were grouped into three categories: malignant disease (acute lymphocytic leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia), immunodeficiencies (hemophagocytic lymphohistiocystosis, severe combined immunodeficiency) and benign haematological disease (Diamond-Blackfan anaemia, beta-thalassemia, severe aplastic anaemia, sickle cell disease) (see Supporting Information: Table 1 for overview of diagnoses per group). Conditioning regimens were grouped into three categories: TBI-based, busulfan-based and other (mostly cyclophosphamide).

2.3 | Growth hormone treatment (GHRx) protocol

GH treatment was offered from 1997 onwards as routine clinical care to children who fulfilled all of the following criteria: (1) ≥2 years after HSCT, (2) current height < −1.3 SDS, (3) growth deflection >0.25 SDS in 1 year or >1 SDS in several years and/or growth below target height (TH) range, (4) absence of other causes of impaired growth, (5) no contraindication for GH treatment (such as genetic predisposition for tumours, e. g., Fanconi anaemia) and (6) bone age (BA) < 13 years for girls and <15 years for boys. The standard dose of GH treatment was 1.3 mg/m^2/day (equals approximately 0.04 mg/kg/day), in a single daily dose subcutaneously. Follow-up consisted of visits every 3–4 months for GH treated patients, and once a year for those without GH treatment. GH treatment was continued until AH unless the patient wished to stop before AH was reached.

2.4 | Collection of data

Data on HSCT, growth from before HSCT until AH, and on puberty were collected from medical files. Height SDS for sex and age was calculated using Dutch references.[13] TH was calculated using the formula[13]: (height father + height mother + 13)/2 + 4.5 for boys and (height father + height mother -13)/2 + 4.5 for girls. Onset of puberty was defined as first recording of Tanner breast stage B2 or genital stage G2,[14] or as the start of sex hormone treatment for pubertal induction. BA was assessed according to Greulich and Pyle.[15]

Because GH treatment was offered to shorter children, we did not choose AH as primary outcome parameter, but rather compared how close AH was to the predicted adult height (PAH) at the start of GH treatment (or at the equivalent age in controls) between the groups. PAH was calculated according to Bayley and Pinneau (B&P)[16] using height and BA at start of GH treatment, or at the equivalent age for matched controls. Because the prediction of AH also has its limitations, we included distance to TH as a second outcome measure.

2.5 | Statistical analyses

IBM SPSS Statistics, version 25.0 was used for statistical analyses with significance defined as $p < .05$. Data are presented as mean ± SD

TABLE 1 Baseline characteristics of children with and without GH treatment

	GH treated patients			Non-GH treated patients		
	Boys (*N* = 23)	Girls (*N* = 11)	Total (*N* = 34)	Boys (*N* = 46)	Girls (*N* = 22)	Total (*N* = 68)
Indication HSCT						
Haematological malignancy	19 (83%)	9 (82%)	28 (82%)	38 (83%)	18 (82%)	56 (82%)
Paediatric immunodeficiency	2 (9%)	-	2 (6%)	4 (9%)	-	4 (6%)
Haematological	2 (9%)	2 (18%)	4 (12%)	4 (9%)	4 (18%)	8 (12%)
Decade of transplantation						
1980–1990	1 (4%)	1 (9%)	2 (6%)	7 (15%)	5 (23%)	12 (18%)
1991–2000	17 (74%)	7 (64%)	24 (71%)	18 (39%)	12 (55%)	30 (44%)
2001–2010	5 (22%)	3 (27%)	8 (24%)	21 (46%)	5 (23%)	26 (38%)
Conditioning regimen						
TBI-based	19 (83%)	6 (55%)	25 (74%)	35 (76%)	12 (55%)	47 (70%)
Busulfan-based	4 (17%)	5 (46%)	9 (27%)	9 (20%)	7 (32%)	16 (24%)
Other	-	-	-	2 (4%)	3 (14%)	5 (7%)
Age at HSCT (years)	7.3 ± 4.1	5.6 ± 3.8	6.8 ± 4.0	9.2 ± 3.5	6.1 ± 3.5	8.2 ± 3.7
Height at HSCT (cm; range)	121.6 (67.0–160.3)**	93.5 (77.5–148.5)	111.1 (67.0–160.3)*	137.7 (63.5–167.5)	122.7 (67.0–160.5)	133.3 (63.5–167.5)
Height SDS at HSCT (range)	−1.4 (−4.2 to 1.2)**	−1.5 (−2.4 to −0.2)**	−1.4 (−4.2 to 1.2)***	−0.5 (−4.4 to 1.9)	−0.2 (−1.7 to 2.4)	−0.5 (−4.4 to 2.4)
BA at HSCT (years)	6.5 (1.5–11.5)*	4.0 (1.3–13.0)	4.9 (1.3–13.0)	9.0 (3.6–14.8)	5.0 (1.5–10.0)	8.6 (1.5–14.8)
Age at start GHRx[a] (years)	12.6 ± 2.5	10.7 ± 2.2	12.0 ± 2.6	12.7 ± 2.5	10.6 ± 2.3	12.0 ± 2.6
Height at start GHRx[a] (cm)	145.9 (121.3–174.2)*	129.7 (115.5–153.0)	141.3 (115.5–174.2)**	155.2 (123.3–178.6)	144.4 (114.9–162.8)	151.2 (114.9–178.6)
Height SDS at start GHRx[a]	−1.8 ± 1.1**	−2.2 ± 1.1***	−1.9 ± 1.1***	−0.8 ± 1.4	−0.6 ± 1.1	−0.7 ± 1.3
BA at start GHRx[a] (years)	12.6 (7.0–15.0)	10.6 (6.8–13.0)	11.5 (6.8–15.0)	11.9 (4.0–15.0)	10.3 (6.3–14.0)	11.5 (4.0–15.0)
Tanner stage B/G at start GHRx[a]						
1	10 (44%)	8 (73%)	18 (53%)	22 (48%)	13 (59%)	35 (52%)
2	10 (44%)	1 (9%)	11 (32%)	9 (20%)	3 (14%)	12 (18%)
3	1 (4%)	2 (18%)	3 (9%)	7 (15%)	4 (18%)	11 (16%)
4	1 (4%)	-	1 (3%)	5 (11%)	1 (5%)	6 (9%)
5	1 (4%)	-	1 (3%)	3 (7%)	1 (5%)	4 (6%)
PAH at start GHRx[a] (cm)	171.4 ± 8.4**	154.1 ± 7.9***	165.8 ± 11.5***	180.1 ± 10.5	164.8 ± 6.7	175.2 ± 11.9
PAH SDS at start GHRx[a]	−1.8 ± 1.2**	−2.5 ± 1.2***	−2.0 ± 1.2***	−0.5 ± 1.5	−0.9 ± 1.0	−0.7 ± 1.4
TH (cm)	182.6 ± 7.9	168.9 ± 6.0	178.2 ± 9.8	184.8 ± 6.8	171.2 ± 5.7	180.4 ± 9.1
TH SDS	−0.2 ± 1.1	−0.3 ± 0.9	−0.2 ± 1.0	0.1 ± 1.0	0.1 ± 0.9	0.1 ± 0.9
Duration of GHRx (years)	3.7 (1.7–9.2)	4.9 (2.4–8.6)	3.8 (1.7–9.2)	-	-	-
Height SDS at start puberty	−1.4 ± 1.4*	−1.7 ± 1.4**	−1.5 ± 1.4**	−0.8 ± 1.5	−0.6 ± 1.0	−0.8 ± 1.3

Note: Data in absolute numbers (percentage) or mean ± SD, or median (range).

Abbreviations: BA, bone age; GH, growth hormone; GHRx, growth hormone treatment; HSCT, hematopoietic stem cell transplantation; PAH, predicted adult height; SDS, standard deviation score; TBI, total body irradiation; TH, target height.

[a]Or at equivalent age in controls.

*$p < .05$; **$p < .01$; ***$p < .001$ for comparison to non-GH treated group.

unless stated otherwise. The difference between AH and PAH at the start of GH treatment, and between AH and TH was compared between GH treated patients and controls using an independent *t*-test. For analysing the effect of sex and of age at start GH treatment on AH−PAH, the difference in AH−PAH between groups transplanted in different decades and the correlation between first-year GH response and AH−PAH, linear regression was used, with AH −PAH as dependent variable.

2.6 | Ethics

The Ethical Committee of Leiden University Medical Centre approved the study. The need for informed consent was waived because of the retrospective nature of the study.

3 | RESULTS

3.1 | Background characteristics

Thirty-four GH treated patients were included (Figure 1). Seventeen were previously included in the study by Bakker et al. who reported on AH in seven of them.[9] Patient characteristics at HSCT are shown in Table 1. GH treated patients were younger than control patients at time of HSCT (mean age 6.8 ± 4.0 vs. 8.2 ± 3.7 years), and most were treated for malignant haematologic disorders (n = 28). Conditioning regimens were similar in GH treated patients and controls. Twenty-five GH treated patients received TBI (median dose 7.5 Gy, range 6–12, fractionated in n = 6) as did 47 controls (median dose 7.5 Gy, range 4–14, fractionated in n = 15). One control was not conditioned with TBI but had previously received craniospinal irradiation (24 Gy on the brain; 15 Gy on the spine). Of the children who were treated with GH, 29 had undergone GH stimulation tests (clonidine, arginine or exercise stimulation tests) or overnight GH sampling. Seven met the criteria for (partial) GH deficiency, three for neurosecretory dysfunction (defined as sufficient GH response in a GH stimulation test but IGF-1 < −2 SDS or reduced spontaneous GH secretion) and 19 had normal results. In the control group 15 children had been tested and 1 met the criteria for GH deficiency but parents declined GH treatment. Pubertal induction was required in 4 (17%) GH treated boys and 6 (13%) control boys and in 6 (55%) GH treated girls and 11 (50%) control girls. Three GH treated children received GnRH analogue treatment to delay puberty.

3.2 | Growth in boys

GH treated boys started GH treatment at 12.6 ± 2.5 years when mean height was −1.8 ± 1.1 SDS versus −0.8 ± 1.4 in controls (Table 1). At the start of treatment, their PAH was lower than that of controls (−1.8 ± 1.2 SDS vs. −0.5 ± 1.5 SDS). After a median GH treatment duration of 3.7 years (range 1.7–9.2), they reached a mean AH of −2.3 ± 1.2 SDS versus −2.0 ± 1.2 SDS in controls (Table 2). Height SDS decreased by −0.5 ± 0.9 between the start of GH treatment and AH in GH treated boys versus −1.2 ± 0.9 SDS in controls (difference −0.7, 95% confidence interval (CI) [−1.2 to −0.3], p = .002). AH SDS was significantly closer to PAH SDS in the GH treated group (AH−PAH −0.5 ± 0.7) than in controls (−1.5 ± 1.0, difference between groups 1.0, 95% CI [0.5–1.5], p < .001). However, AH was −2.1 SDS below TH for both GH treated patients and controls.

3.3 | Growth in girls

Girls started GH treatment at 10.7 ± 2.2 years when mean height was −2.2 ± 1.1 SDS versus −0.6 ± 1.1 SDS in controls (Table 1). Their PAH at the start of treatment was lower than PAH of controls (−2.5 ± 1.2 SDS vs. −0.9 ± 1.0 SDS). After a median GH treatment duration of 4.9 years (range 2.4–8.6), the GH treated group reached a mean AH of −2.1 ± 1.4 SDS versus −1.1 ± 0.8 SDS in controls (Table 2). In GH

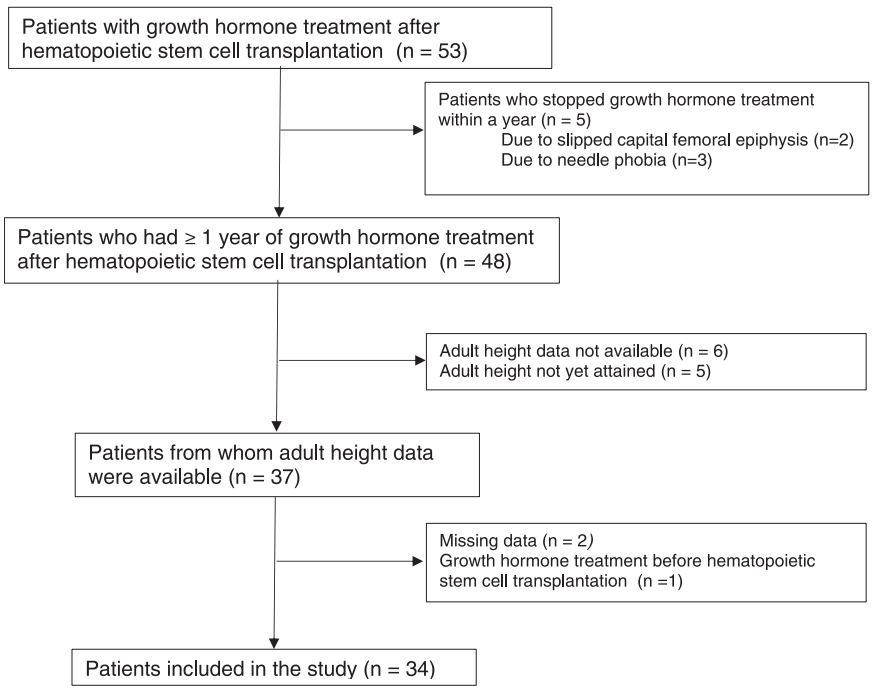

FIGURE 1 Flow diagram of the selection of patients

TABLE 2 Growth outcomes in children with and without GH treatment

	GH treated			Non-GH treated patients		
	Boys (*N* = 23)	Girls (*N* = 11)	Total (*N* = 34)	Boys (*N* = 46)	Girls (*N* = 22)	Total (*N* = 68)
AH (cm)	167.9 (8.8)	157.3 (8.9)*	164.5 (10.1)	169.6 (8.4)	163.6 (5.4)	167.7 (8.1)
AH (SDS)	−2.3 (1.2)	−2.1 (1.4)*	−2.2 (1.3)	−2.0 (1.2)	−1.1 (0.8)	−1.7 (1.2)
AH–PAH (cm)	−3.5 (5.0)***	3.2 (4.0)*	−1.3 (5.6)***	−10.5 (6.9)	−1.3 (4.7)	−7.5 (7.6)
AH–PAH (SDS)	−0.5 (0.7)***	0.5 (0.6)*	−0.2 (0.8)***	−1.5 (1.0)	−0.2 (0.7)	−1.1 (1.1)
AH–TH (cm)	−14.7 (6.5)	−11.6 (6.8)	−13.7 (6.7)	−15.2 (6.5)	−7.6 (5.7)	−12.8 (7.2)
AH–TH (SDS)	−2.1 (0.9)	−1.8 (1.1)	−2.0 (1.0)	−2.1 (0.9)	−1.2 (0.9)	−1.8 (1.0)
AH–Height at start GHRx[a] (SDS)	−0.5 (0.9)**	0.2 (0.7)*	−0.3 (0.9)***	−1.2 (0.9)	−0.5 (0.6)	−1.0 (0.9)

Note: Data are shown as mean (SD).

Abbreviations: AH, adult height; GH, growth hormone; GHRx, growth hormone treatment; PAH, predicted adult height; SD, standard deviation; SDS, standard deviation score; TH, target height.

[a]Or at equivalent age in controls.

*$p < .05$; **$p < .01$; ***$p < .001$ for comparison to non-GH treated group.

treated girls, height SDS increased between the start of treatment and AH by +0.2 SDS (±0.7), whereas it decreased in controls by −0.5 SDS (±0.6) (difference between groups 0.6, 95% CI [0.2–1.1], $p = .01$). GH treated females reached an AH that was 0.5 SDS ±0.6 above PAH at start GH treatment, whereas in controls AH was 0.2, SDS ±0.7 below PAH (difference between groups 0.7, 95% CI [0.2–1.2], $p = .01$). AH was below TH in both GH treated patients and controls, without a significant difference between the groups (−1.8 vs. −1.2 SDS).

3.4 | Factors associated with growth outcomes

3.4.1 | First year growth response

As GH treatment is an expensive treatment, the first-year growth response is often analysed as a predictor of the effect of GH treatment. Linear regression showed a significant correlation between change in height SDS in the first year of GH treatment and the difference between AH and PAH ($p = .007$, $R^2 = 0.207$).

3.4.2 | Sex, age at start of GH treatment and decade of transplantation

Univariate analysis showed that for males AH was on average 0.98 SDS further below PAH than for females 95% CI [−1.49 to −0.48], $p < .001$. An inverse relation was found between age at start of GH treatment and AH–PAH SDS, with a decrease of $B = -0.14$ SDS per year older at start, 95% CI [−0.24 to −0.04], $p = .009$. However, in multivariate analysis including both sex and age at start of GH treatment, only male sex was significantly negatively associated with AH–PAH SDS, $B = -0.82$ ($p = .003$). AH–PAH SDS was not significantly different between the three groups transplanted in different decades $B = -0.219$, 95% CI [−0.78 to 0.33] ($p = .43$).

3.4.3 | Conditioning regimen

Among GH treated individuals, those who had received a busulfan-based conditioning regimen on average reached an AH above PAH whereas AH in those with TBI conditioning was, on average, below PAH (Figure 2A). The difference was 0.88 SDS, 95% CI [0.30–1.45], ($p = .004$). AH was further above PAH in GH treated children compared to controls, both in those with busulfan-based conditioning (mean difference 1.28 SDS, 95% CI [0.32–2.2], $p = .01$) and in those conditioned with TBI (0.88 SDS, 95% CI [0.44–1.32], $p < .001$). AH was below TH in all groups (Figure 2B).

3.4.4 | GH deficiency and pubertal induction

Within the GH treated cohort, the difference between AH and PAH was similar in those with GH deficiency ($n = 7$) and those with a normal GH status ($n = 19$) (mean difference −0.47 SDS, 95% CI [−1.15 to 0.22]) and in those who did not ($n = 21$) and did ($n = 10$) need pubertal induction (mean difference −0.47 SDS, 95% CI [−1.12 to 0.18]) (three individuals who received puberty suppression were not included in the latter analysis).

In a multivariate analysis of the entire cohort including sex, GH treatment and conditioning regimen, the need for pubertal induction was not associated with the difference between AH and PAH either ($p = .87$).

4 | DISCUSSION

Our study shows a beneficial effect of GH treatment in children with impaired growth after HSCT. Our primary outcome measure, AH minus PAH at the start of GH treatment (or equivalent age in controls), indicated a mean gain of 7.1 cm or 1.0 SDS in boys and of

4.5 cm or 0.7 SDS in girls. The positive effect of GH was also reflected by the fact that height SDS did not decrease as much in GH treated children as it did in untreated children between the time GH treatment was started and the time AH was reached. Within the GH treated group, AH was further above PAH in those conditioned with busulfan compared to TBI. Females reached a higher AH compared to PAH than males, both with and without GH treatment. However, in all groups AH remained 1-2 SDS below TH.

A limited number of studies have previously reported on AH after GH treatment in children after HSCT. First, Bakker et al.[9] reported that AH was 1.1 SDS for males and 1.3 SDS for females above PAH in GH-treated patients after HSCT with TBI-based conditioning, whereas non-GH treated controls, reached an AH close to PAH (−0.02 SDS for both genders). This positive effect of GH treatment on PAH−AH is similar to that in our study for males (about 1 SDS difference between GH treated and non-GH treated) but higher for females (0.7 SDS difference). Bakker et al. found a higher AH relative to PAH both in those with and without GH treatment. This is likely due to the use of a different method to predict AH. They used a model based on individual growth data of children after HSCT before the start of GH treatment to predict growth profiles, whereas we have used the method of B&P. The method used by Bakker et al. likely resulted in a lower PAH because it took into account the individual growth pattern, with growth deflection in those eligible for GH treatment. The method by B&P on the other hand predicts AH based on data from healthy children, likely overestimating the true growth potential of children after HSCT. However, we chose to use the B&P method because it is one of the most widely available and commonly used methods. The current study provides useful data for clinical practice on the degree of overestimation of AH when using this method in this context.

Sanders et al.[10] reported that for GH-deficient children who had undergone HSCT before age 10, GH treatment significantly improved growth. GH-treated patients lost 0.06 SDS on average from GH deficiency diagnosis to AH, compared to 0.53 SDS in non-GH-treated patients. This difference of approximately 0.5 SDS is similar to our finding of 0.7 SDS difference between GH treated and non-GH treated subjects in height loss between start GH treatment and AH.

Other studies reported no significant difference in AH-TH or height loss between HSCT and AH between GH treated and untreated children after HSCT, although longer duration of GH treatment was associated with a smaller loss of height SDS.[4,12] However, these studies only included 17, respectively, 10 GH treated subjects. The results are not directly comparable to those of the current study because different formulas were used to calculate TH.

There was considerable interindividual variation in the response to GH treatment. Although the change in height SDS in the first year of treatment was significantly associated with AH−PAH, the correlation was weak. Therefore, the first-year response cannot be relied upon to predict improvement of AH compared to PAH in practice.

Interestingly, males achieved an AH further below their PAH compared to females, both with and without GH treatment. Less affected growth and better catch-up growth with GH treatment in females has previously been described but no definite explanation has been provided for this phenomenon.[1,2,10,17] In the current study, more boys than girls (78.3% vs. 54.5%) received TBI and TBI was associated with an AH further below PAH, consistent with previous reports of more severe growth impairment after TBI compared to chemotherapy only.[5,18] Bakker et al.[3] suggested that maximum growth velocity may be limited by radiation-induced damage to growth plates and that this may have a larger impact on growth in males, who normally have a higher peak growth velocity than girls. However, among those conditioned without TBI, females also had better growth than males. Conditioning with busulphan combined with cyclophosphamide has also been reported to impair growth in several studies although others did not find a significant impact.[1] Similar to TBI, high-dose chemotherapy might reduce maximum height velocity, thereby affecting males more than females. We did observe a larger decrease of height SDS between onset of puberty and AH in boys (approx. 1 SDS) than girls (approx. 0.5 SDS), both in those with and without GH treatment. An alternative explanation

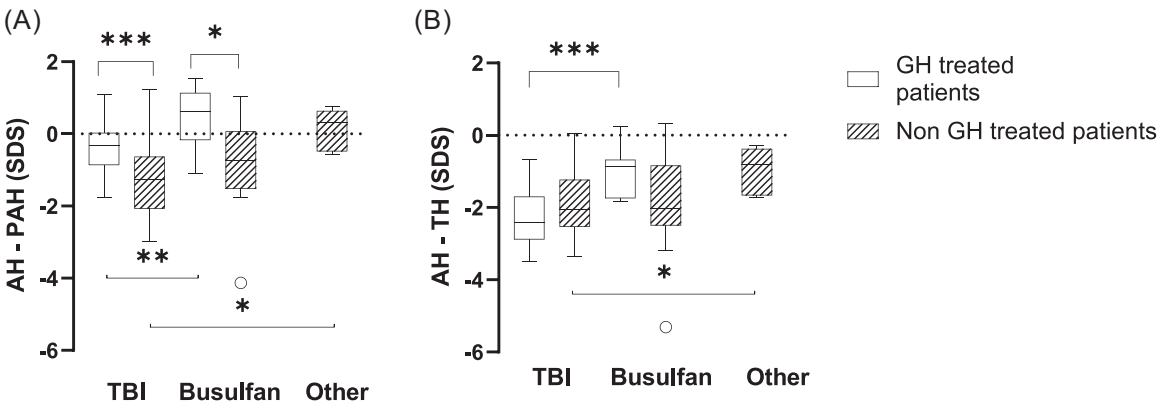

FIGURE 2 Growth outcomes by conditioning regimen. (A) Difference between adult height (AH) SDS and predicted adult height (PAH) SDS at the start of GH treatment or equivalent age in controls. (B) Difference between AH SDS and target height (TH) SDS. Outliers are indicated by circles. *$p < 0.05$, **$p < .01$, ***$p < .001$. GH, growth hormone; SDS, standard deviation score; TBI, total body irradiation.

suggested by Bakker et al. is the fact that more girls than boys require pubertal induction, which was also the case in the current study.[5] A delayed start and slower progression of induced versus spontaneous puberty may result in increased height gain. However, we could not confirm this hypothesis in the current study; a multivariate analysis showed that sex had a significant effect on the difference between AH and PAH whereas the need for pubertal induction did not. Another factor may be treatment adherence. Previous studies, have found that males have poorer adherence to daily medication.[19,20] In this retrospective study we could not assess adherence and its effect on growth outcomes. However, in those without GH treatment, growth outcomes were also better in females than males so other factors must play a more important role.

Despite a positive effect of GH treatment, AH was low compared to the general population and far below TH in all groups, as has previously been found.[3,4,12,17,18,21,22] This is important to take into account when counselling patients about GH treatment, to ensure realistic expectations.

Our study has several limitations. The GH-treated population is small although it is one of the largest populations reported so far of children who reached AH after GH treatment after HSCT. GH secretion status was not investigated in all patients, but a previous study reported that the effect of GH therapy was not correlated to the presence or absence of GH deficiency.[9] In the current study, we also found that the difference between AH and PAH was similar in those with and without GH deficiency. Furthermore, despite matching for indication for HSCT, sex, conditioning and age, the treated and untreated groups had important differences in baseline characteristics. Children who were eligible for GH treatment were shorter and/or had poorer growth velocity and were therefore more likely to achieve a shorter AH. To overcome this, we did not use AH as the main outcome measure but reported how close AH was to PAH at the start of GH treatment or equivalent age in controls. We cannot exclude that some of the observed effect of GHRx was due to regression to the mean. However, GH treatment was not routinely available before 1997, so some short children who fulfilled criteria for treatment but for whom this was not available at the time, also served as controls. More children transplanted in the 1980s were included in the control group than in the GH treated group (17.6% vs. 5.9%); this could have introduced bias because of changes in treatment and supportive care over time that might impact growth. However, we did not find that the decade of transplantation was related to the difference between AH and PAH.

As discussed above, we chose to use the difference between AH and PAH as our primary outcome measure to enable a comparison between GH treated and untreated individuals. However, predicting AH has its own limitations. The formula we used is based on data from healthy children and is likely to overestimate remaining growth in transplanted children whose growth plates may have been damaged by radiation and chemotherapy. However, we expect that this inaccuracy equally applies to the treated and untreated groups, and therefore does not affect comparison of outcomes between these groups.

Lastly, we did not assess safety aspects of GH treatment. Two children were excluded from the study because they had stopped GH therapy within the first year of treatment due to slipped capital femoral epiphysis (SCFE); both had been transplanted because of beta-thalassemia. This complication is an important concern. In addition to GH treatment, chemotherapy and TBI have also been implicated as factors contributing to the increased risk of SCFE after HSCT and in cancer survivors.[23] The exact contribution of GH treatment to the elevated risk is not completely clear; SCFE has also been observed in cancer survivors who had not been treated with GH[23] and in children with beta-thalassemia who had not been transplanted.[24]

A major concern is the elevated risk of malignancies after HSCT and a potential effect of GH treatment on this risk. Previous studies of cohorts of GH treated children after HSCT or after childhood cancer did not find an increased risk of relapse but an increased risk of a secondary malignancy with a rate ratio of 2.15 (95% CI 1.33–2.47) has been reported in childhood cancer survivors.[10,17,25,26] A possibly increased risk of secondary malignancies is important to take into consideration when counselling patients on the option of GH treatment although more data are necessary to establish this risk in individuals who have undergone an HSCT.

5 | CONCLUSION

In conclusion, our study shows a beneficial effect of GH treatment in children after HSCT, with treated children reaching an AH closer to that predicted at the start of treatment compared to children who did not receive GH treatment. Growth was less impaired in females and in children who did not receive TBI. However, AH was far below the population average and below TH in all groups, both with and without GH treatment. Children and their families should be informed of the risk of impaired growth and what AH they might expect, taking into account the overestimation of AH when predicted according to B&P. The results from this study should help to counsel them about the efficacy of GH treatment but more data are needed on its safety, especially concerning the risk of secondary malignancies.

ACKNOWLEDGEMENTS

We would like to thank Dr. Boudewijn Bakker, who performed the overnight GH sampling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hoekx CA, Bresters D, le Cessie S, Oostdijk W, Hannema SE. Improved growth with growth hormone treatment in children after hematopoietic stem cell transplantation. *Clin Endocrinol (Oxf)*. 2022;97:596-603. doi:10.1111/cen.14782