Growth and Adult Height in Girls With Turner Syndrome Following IGF-1 Titrated Growth Hormone Treatment

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Context: Girls with Turner syndrome (TS) suffer linear growth failure, and TS is a registered indication for growth hormone (GH) treatment. GH is classically dosed according to body weight, and serum insulin-like growth factor-1 (IGF-1) concentrations are recommended to be kept within references according to international guidelines.

Objective: To assess the effect of long-term GH treatment in girls with TS following GH dosing by IGF-1 titration.

Design and setting: A retrospective, real-world evidence, observational study consisting of data collected in a single tertiary center from 1991 to 2018.

Patients: A cohort of 63 girls with TS treated with GH by IGF-1 titration with a median duration of 6.7 years (interquartile range [IQR]: 3.4-9.7 years).

Main outcome measures: Longitudinal measurements of height, IGF-1, and adult height (AH) following GH treatment were evaluated and compared between the different karyotypes (45,X, 45,X/46,XX, or miscellaneous).

Results: Using GH dose titration according to IGF-1, only 6% of girls with TS had supranormal IGF-1 levels. Median dose was 33 µg/kg/day (IQR: 28-39 µg/kg/day) with no difference between the karyotype groups. AH was reached for 73% who attained a median AH of 1.25 standard deviation score (SDS) for age specific TS references (IQR: 0.64-1.50 SDS), and a median gain in height (ΔHSDS: AH SDS minus baseline height SDS of TS references) of 0.50 SDS, equal to 3.2 cm (SD 7.68) for all karyotypes.

Conclusion: Our real-world evidence study suggested that titration of GH dose to keep IGF-1 levels within the normal range resulted in a lower AH gain than in studies where a fixed dose was used. **(*J Clin Endocrinol Metab* 105: 2566–2574, 2020)**

Key Words: Turner syndrome, adult height, IGF-1 titration, growth hormone

Turner syndrome (TS) is found in 1 per 2500 live born females (1), and this chromosomal abnormality is known to cause numerous clinical manifestations such as heart and kidney malformations, hearing loss, primary amenorrhea, and short stature. Girls with TS often suffer linear growth failure due to haploinsufficiency of the short stature homeobox-containing gene resulting in low adult height (AH) about 20 cm shorter than a normal reference population (2). TS is an approved indication of treatment with recombinant human growth hormone (GH) leading to a reported increase in AH of 5 to 8 cm at a dosage of 42 to 50 µg/kg/d, but with

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large individual variation in growth response (2-7). The present recommended GH dose for girls with TS is 45 to 50 µg/kg/day. An increase of the dose up to 68 µg/kg/day may be considered if AH potential is substantially compromised (8). However, dosage of GH in TS patients is still a matter of debate.

GH stimulates a direct production of insulin-like growth factor-1 (IGF-1), which mediates many of the growth-promoting actions of GH on linear growth. Most TS patients are not GH deficient, and GH treatment is given at supraphysiological levels, which may result in elevated concentrations of IGF-1 during treatment. Current international guidelines for GH treatment in girls with TS recommend to keep IGF-1 levels below +2 standard deviation scores (SDS) and to decrease GH dose if IGF-1 levels are above +3 SDS (8).

Large epidemiological studies of adults from the general population have shown that both low and high levels of IGF-1 concentrations were associated with increased cancer mortality and all-cause mortality (9,10). However, no studies have evaluated the morbidity or mortality in children with increased IGF-1 levels during GH treatment.

The use of serum IGF-1 values to adjust GH dosing has been debated (11). In a study comparing IGF-1 titration to weight-based dosing in both short prepubertal children and GH-deficient children, a significantly greater linear growth was found in the group of patients where IGF-1 was titrated to the higher level of the normal range compared to traditional weight-based dosing (12). IGF-1 titration of GH dose seems as a reasonable approach in terms of efficacy and safety (12, 13), especially in GH-deficient children.

To our knowledge IGF-1 titration of GH doses in girls with TS has not previously been investigated in detail. In this large single-center study, we evaluated for the first time growth and AH in 63 TS patients where GH doses were adjusted according to the IGF-1 concentrations.

Methods

Patients

Ninety-two patients with a TS diagnosis were identified from the patient registry at our department based on the *International Classification of Diseases 10* codes (Q96-Q96.9). The patients were followed in a single tertiary center (Department of Growth and Reproduction at Rigshospitalet, Copenhagen University Hospital, Denmark) from 1991 to 2018.

Of the 92 patients 16 were excluded either due to a male phenotype (n = 14) or missing medical notes (n = 2). Of the remaining 76 patients with TS, 63 patients were treated with IGF-1-titrated GH, and 13 did not receive GH therapy. Forty-six of the 63 patients (73%) treated with GH achieved an AH during the study period; near AH was defined as height velocity <2 cm per year.

Clinical examination, data, and medical history

This study was a retrospective analysis using the medical record files of the girls with TS. They attended routine clinical visits with a trained pediatric endocrinologist every 4 months during the period of treatment where the clinical and auxological progress was monitored. Standing height was measured to the nearest 0.1 cm with a wall-mounted Harpenden stadiometer (Holtain Limited, Pembrokeshire, UK), and weight on a Seca delta model 707 digital electronic scale (Seca, Hamburg, Germany) while wearing light clothes and no shoes, with a 0.1 kg precision. Pubertal development was evaluated by inspection and palpation according to Marshall and Tanner (14). Body mass index was calculated as weight (kg) divided by squared height (m^2). Target height was calculated as the mean of the height SDS of the mother and the father. The anthropometric measurements were expressed as SDS according to the Danish national reference (15). AH SDS is expressed in SDS for the end of growth 18+ years for both general population and age specific TS references. Bone age was determined according to the methods of Greulich and Pyle (16). Predicted AH was calculated using BoneXpert Adult Height Predictor (Visiana, Holte, Denmark). Projected AH was calculated based on the reference growth chart for northern European girls with TS (17) assuming that the TS girls would follow their baseline growth HSDS until final height without treatment. To assess the effectiveness of the GH treatment we used changes in height SDS (ΔHSDS) according to a TS reference (AH SDS minus height SDS at baseline), changes in height gain over projected AH (AH [cm] minus projected AH [cm]), and height gain over the predicted AH (AH [cm] minus predicted AH [cm]).

Karyotypes

The diagnosis of TS was validated and confirmed by a clinical geneticist by karyotyping using routine G-banding, including counting of at least 30 metaphases. All phenotypic female patients diagnosed with TS karyotypes were included. Phenotypic male patients with 45,X/46,XY were excluded. The included girls with TS were divided into 3 groups depending on their karyotype: 45,X (n = 25), Turner mosaicism 45,X/46,XX (n = 8), and miscellaneous (ie, 45,X/46,X,r(X) and 45,X/46,X,i(X)(q10)) (n = 29).

Analysis of insulin-like growth factor-1 hormone assays

Nonfasting blood samples were drawn between 8 AM to 5 PM from an antecubital vein, clotted, and centrifuged, and hormone analyses were performed. Serum IGF-1 was measured using 3 different assays during the study period. From 1991, a highly sensitive in-house radioimmunoassay, as previously described by Juul et al (18) was used, with an intra- and inter-assay coefficients of variation of 3.9% and 8.7%, respectively. From 2008, the IGF-1 levels were determined using IMMUNULITE 2000 IGF-1 conventional immunoassays (Siemens Healthcare Diagnostics, Los Angeles, CA, US), and the intra- and inter-assay coefficients were less than 4% and 9%, respectively (19). From 2013, the IGF-1 levels were determined using IDS-iSYS Multidiscipline Automated Analyser.

The assays available for IGF-1 changed during the 27-year study period, and the assays were compared one by one before changing in 2008 and 2013, respectively.

IGF-1 titration

At the Department of Growth and Reproduction, Rigshospitalet, the treatment with GH of all patients was titrated using the IGF-1 (SDS) levels in serum. GH starting dose was 12.5 µg/kg/day for 4 weeks, and thereafter GH dose was increased to 25 µg/kg/day until first visit at 3 months. Thereafter, the dose was titrated up and down according to height changes and IGF-1 levels measured every 3 to 6 months. GH doses were titrated to obtain IGF-1 levels above 0 standard deviations (SD) and preferably to reach levels just below +2 SD in girls with reasonable growth responses. In cases of poor responses to GH, supranormal IGF-1 levels (up to +3 SD) have been accepted. GH doses have been increased or decreased with 0.1 to 0.2 mg to obtain levels of IGF-1 at the preferred levels.

Statistical analysis

The data are displayed as medians with interquartile ranges (IQR); the 25th to 75th percentile. Comparisons between the 3 groups of karyotypes was performed using a Kruskal-Wallis test. A multiple regression analysis was performed, expressing regression coefficients (B), standard error (SE). All statistical analyses were performed using SPSS software, version 22 (IBM Corporation, Armonk, NY, US). A *P*-value below 0.05 was considered statistically significant.

Ethical considerations

This retrospective study was based on patient record files, including clinical data and blood samples collected as part of the routine clinical follow-up. The use of data was approved by the Danish Health Authority (3-3013-2022/1) and the Danish Data Protection Agency (RH-2016-177, I-Suite number: 04732). Our clinical data from individual patients cannot be uploaded in any form to an open repository and shared according to GDPR and Danish law.

Results

Birth characteristics from all GH-treated girls with TS (n = 63) did not differ between karyotype subgroups (Table 1). Age at baseline was significantly different between karyotype subgroups; 6.0 years (5.2-7.6 years) in the 45,X group, 11.9 years (8.3-13.3 years) in the 45,X/46,XX group, and 9.4 years (5.4-13.5 years) in the miscellaneous group ($P = 0.02$) (Table 1).

Median IGF-1 at baseline was –0.47 SDS (–1.11to 0.33 SDS) for all patients, with a trend towards lower IGF-1 levels in the 45,X group, however, the difference was only borderline significant ($P = 0.05$) (Table 2). Throughout the period of GH treatment, a total of 923 measurements of serum IGF-1 were collected from the girls with TS. The IGF-1 concentration was below mean in 29% of the measurements (N = 264), between mean and +2SDS in 52% of the measurements (N = 484),

Table 1. Clinical characteristics at birth and at baseline in the 3 groups of karyotypes

	All Patients		Karyotypes				
	N		45,X	45,X/46,XX	Miscellaneous		
N	63	63	25	8	30		*P*-value
At birth							
Birth weight (SDS)	48	–0.82 (–1.66 to –0.13)	–0.92 (–1.26 to –0.20)	–0.29 (–1.91 to 0.34)	–0.86 (–1.73 to –0.16)		0.90
Birth length (SDS)	42	–0.33 (–1.21 to 0.47)	–0.09 (–1.21 to 0.28)	–0.09 (–1.21 to 1.03)	–0.52 (–1.21 to 0.33)		0.79
Gestational age (WK)	39	39 (38 to 40)	39.00 (38 to 40)	40	39 (38 to 40)		0.34
Mother's height (SDS)	62	–0.77 (–1.48 to 0.09)	–0.79 (–1.32 to –0.05)	–0.69 (–1.58 to 0.22)	–0.86 (–1.59 to 0.15)		0.91
Father's height (SDS)	60	–0.20 (–0.81 to 0.57)	–0.42 (–0.78 to 0.05)	–0.73 (–1.58 to 0.41)	–0.06 (–0.81 to 0.75)		0.17
Target height (SDS)[a]	62	–0.64 (–1.08 to 0.09)	–0.66 (–0.99 to –0.10)	–0.98 (–1.46 to 0.18)	–0.44 (–1.10 to 0.35)		0.64
At baseline							
Age (year)	63	7.59 (5.36 to 11.97)	5.97 (5.17 to 7.63)	11.86 (8.29 to 13.31)	9.41 (5.36 to 13.53)		**0.02**
Height (SDS) general population	60	–2.54 (–3.11 to –2.23)	–2.55 (–3.05 to –2.20)	–2.27 (–2.68 to –1.69)	–2.55 (–3.31 to –2.29)		0.10
Weight (SDS)	58	–1.36 (–2.06 to –0.57)	–1.31 (–2.16 to –0.85)	–0.89 (–1.25 to –0.10)	–1.53 (–2.24 to –0.52)		0.33
Body mass index (SDS)	58	0.38 (–0.26 to 1.00)	0.40 (–0.24 to 0.86)	0.14 (–0.23 to 0.78)	0.35 (–0.54 to 1.33)		0.16
Bone age (years)	29	7.83 (3.75 to 10.90)	6.00 (3.70 to 9.12)	11.20 (5.18 to 11.68)	9.15 (3.88 to 11.75)		0.28
Height (SDS) TS reference	60	0.50 (–0.25 to 1.25)	0.50 (–0.63 to 0.88)	1.38 (0.88 to 2.38)	0.50 (–0.25 to 1.00)		**0.02**

Data are presented as medians (interquartile range with 25th to 75th percentiles). Significant values are presented in bold.
[a]Target height: mean (paternal height SDS + maternal height SDS).

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Table 2. Clinical characteristics during growth hormone treatment in the 3 groups of karyotypes

	All Patients		Karyotypes			
	N		45,X	45,X/46,XX	Miscellaneous	P-value
N	63		25	8	30	
GH treatment						
Age at start of GH (years)	63	7.59 (5.36 to 11.97)	5.97 (5.17 to 7.63)	11.86 (8.29 to 13.31)	9.41 (5.36 to 13.53)	**0.02**
Age at cessation of GH (years)	46	15.54 (14.63 to 16.88)	15.59 (14.30 to 16.88)	15.53 (14.05 to 16.73)	15.49 (15.07 to 17.19)	0.53
Duration (years)	46	6.72 (3.36 to 9.72)	9.05 (6.98 to 10.20)	2.66 (1.97 to 3.41)	5.35 (1.71 to 8.87)	**0.001**
HV at baseline (SDS)	18	−1.15 (−1.90 to −0.50)	−1.00 (−1.31 to −0.60)	−1.00 (−3.45 to 1.45)	−1.53 (−2.01 to −0.92)	0.52
HV during GH (SDS)	31	0.44 (0.05 to 1.18)	0.08 (−0.17 to 0.38)	1.27 (0.48 to 2.05)	0.33 (−0.02 to 1.36)	0.71
AH (cm)[a]	46	153.7 (5.54)	153.67 (5.17)	156.30 (8.65)	152.98 (4.86)	0.73
AH (SDS) general population	46	−2.35 (−2.99 to −2.12)	−2.35 (−2.96 to −2.13)	−2.21 (−3.37 to −0.54)	−2.51 (−2.87 to −2.16)	0.73
AH (SDS) TS reference	46	1.25 (0.64 to 1.50)	1.25 (0.53 to 1.50)	1.38 (0.25 to 3.00)	1.00 (0.75 to 1.50)	0.67
ΔHeight (SDS) TS reference[a]	43	0.50 (−0.25 to 1.30)	0.75 (0.50 to 1.30)	−0.70 (−1.75 to 0.25)	0.50 (−0.37 to 1.62)	**0.03**
Predicted AH (cm)	18	150.22 (8.38)	148.90 (7.55)	164.95 (11.98)	147.71 (4.12)	0.14
Predicted AH (SDS)	18	−2.66 (−3.14 to −2.21)	−2.41 (−3.25 to −2.25)	−0.73 (−2.06 to 0.61)	−2.88 (−3.03 to −2.66)	0.08
AH (cm) – Predicted AH (cm)	18	3.63 (6.06)	6.33 (4.72)	−7.65 (0.89)	3.38 (4.55)	0.05
Projected AH (cm)	43	150.38 (9.06)	148.41 (6.84)	161.15 (9.16)	148.85 (8.88)	**0.01**
AH (cm) – Projected AH (cm)	43	3.20 (7.68)	4.97 (4.66)	−4.85 (6.98)	4.06 (8.83)	**0.02**
IGF-I						
IGF-1 at baseline (SDS)	57	−0.47 (−1.11 to 0.33)	−0.86 (−1.82 to −0.10)	0.08 (−0.70 to 0.62)	−0.33 (−1.01 to 0.83)	0.05
IGF-1 during GH (SDS)						
RIA	26	0.14 (−0.35 to 1.09)	−0.03 (−0.60 to 0.18)	0.87 (0.65 to 1.08)	0.37 (−0.12 to 1.12)	0.30
IML	33	1.37 (0.88 to 1.75)	1.36 (0.92 to 1.66)	0.02 (−0.73 to 0.20)	1.45 (1.19 to 2.13)	**0.03**
iSYS	18	1.46 (0.64 to 2.10)	0.99 (0.58 to 1.15)	0.78 (0.53 to 1.61)	2.03 (1.19 to 2.25)	0.09

Data are presented as medians (interquartile with 25th to 75th percentiles), except data measured in cm, which are represented as means (standard deviation). Significant values are presented in bold.
Abbreviation: HV, height velocity; RIA, radioimmunoassay.
[a]Adult height: Height velocity <2 cm/year.
[b]ΔHSDS: AH SDS (TS reference) – height SDS baseline (TS reference).

and exceeded +2 SDS in 19% of the measurements (N = 175). In total only 6% of all IGF-1 measurements exceeded +3 SD during GH treatment (N = 51) (20). IGF-1 SDS during GH treatment divided into the 3 different assays showed the variabilities in the measurements throughout the period, (Table 2).

The median duration of treatment with GH was 6.7 (3.4-9.7) years, which differed according to karyotype: 45,X: 9.1 (7.0-10.2) years; 45,X/46,XX: 2.3 (2.0-3.4) years; and miscellaneous: 5.4 (1.7–8.9) years ($P = 0.001$) (Table 2). The median GH dose was 33 µg/kg/day (28-39 µg/kg/day). Dividing the cohort into tertiles according to received GH dose (median of tertiles: 41 µg/kg/day, 33 µg/kg/day, and 26 µg/kg/day, respectively) showed that AH (Fig. 1) and gain in HSDS (Fig. 2) during GH treatment were not related to average GH doses. However, a multiple regression analysis showed a significant positive association between GH dose and gain in height (SDS) even after adjustment for age at start and duration of treatment (B = 0.04, SE = 0.01, $P = 0.009$). A multiple regression analysis with AH as primary outcome (adjusted for age at start and duration of GH treatment) also showed a positive association but this did not reach statistical significance (B = 0.03, SE = 0.02, $P = 0.06$).

AH was reached in 73% of the girls with TS (n = 46), who attained a AH of –2.35 SDS (–2.99 to –2.12 SDS), and 40% of these patients (N = 18) attained a height within the reference range of the general population (greater than –2 SDS) (Fig. 3). Height velocity SDS at baseline was –1.15 SDS and 0.44 SDS during GH treatment for all karyotypes (Table 2). Median height gain for all karyotypes (ΔHSDS) was of 0.50 SDS (–0.25 to 1.30 SDS), with a significant difference between the 3 groups of karyotypes ($P = 0.03$). Height gain was largest for the girls with a 45,X or miscellaneous karyotype and lowest for those with a 45,X/46,XX karyotype (Table 2)

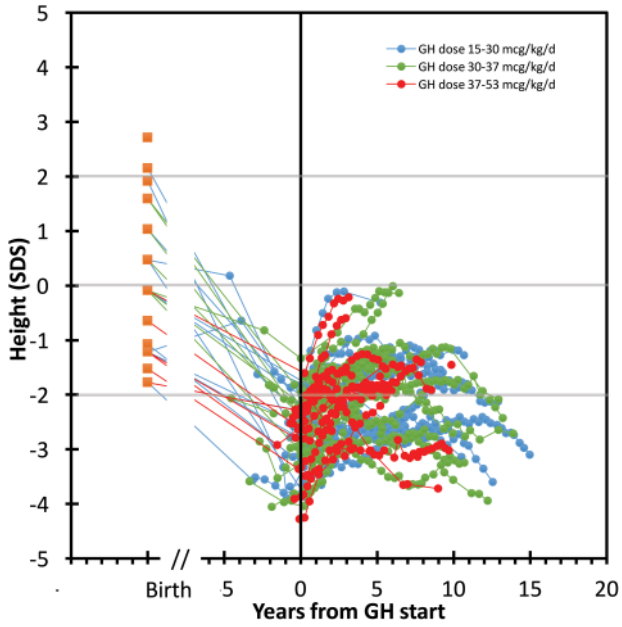

Figure 1. Height changes (SDS) before and during GH treatment, according to 3 different groups of mean GH doses.

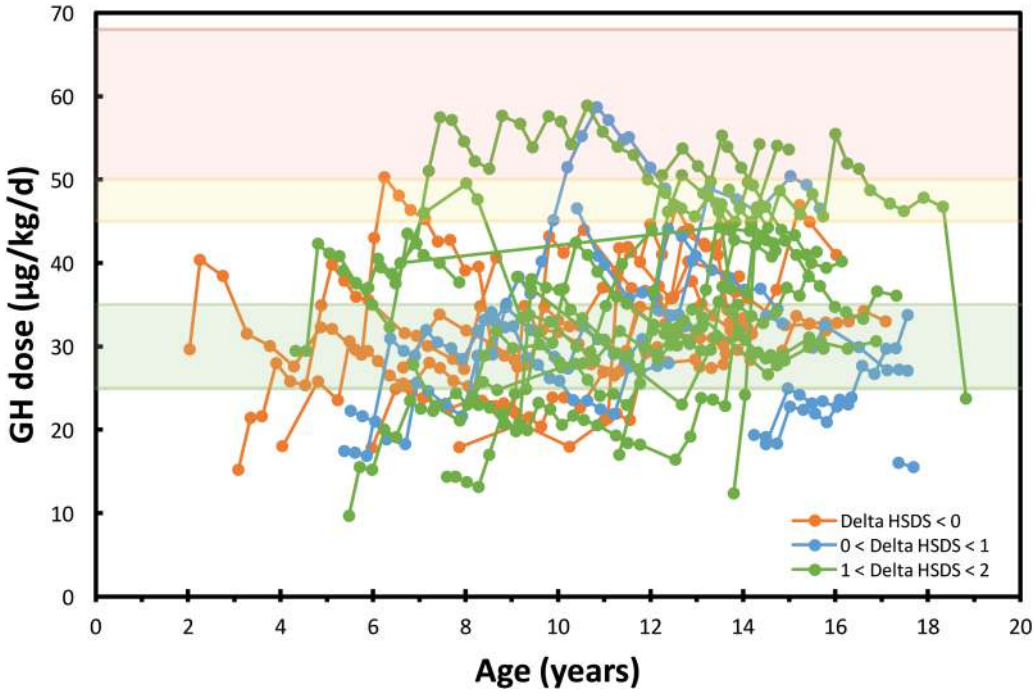

Figure 2. Gain in height changes (ΔHSDS for TS references) during treatment in tertiles, according to their received GH doses. Yellow area represents recommended dose of GH doses for girls with TS (45-50 µg/kg/day). Red area represents the highest recommended dose (up to 68 µg/kg/day). Green area represents recommended dose for patients with GH deficiency (25-35 µg/kg/day).

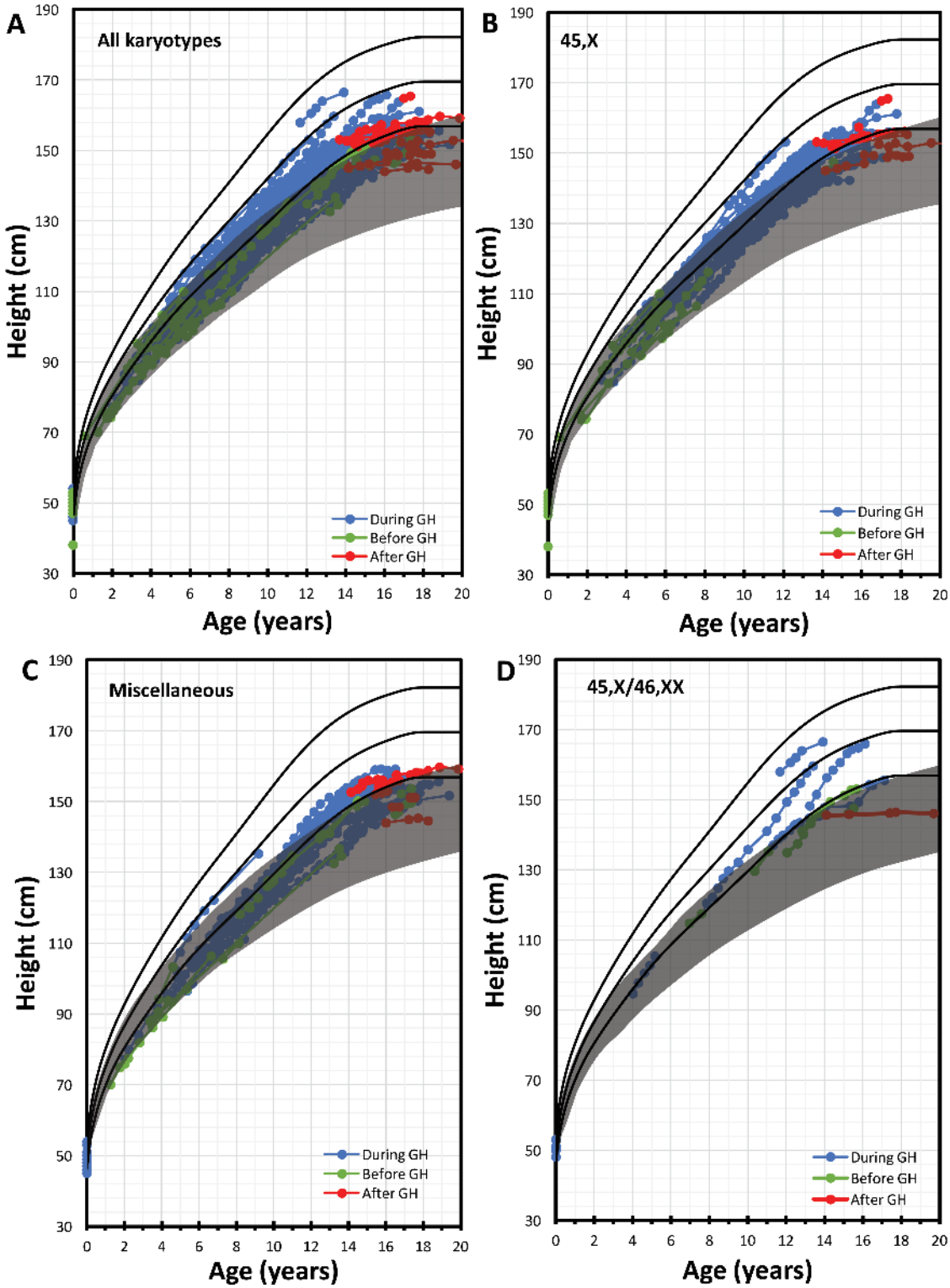

Figure 3. Height (cm) according to age (years) in TS patients treated with GH (blue lines: on treatment; green lines: before treatment; red lines: after treatment). (A) All patients, (B) karyotype 45,X, (C) karyotype 45,X/46,XX, and (D) miscellaneous karyotypes. Grey area represents height references of GH untreated TS girls ± 2 SD.

(Fig. 4), but this difference may be caused by the large difference in duration of treatment (Table 2). Height gain (cm) was assessed by AH (cm) minus projected AH (cm), which showed a mean increase of 3.20 cm (SD = 7.68) for all karyotypes, with a significant difference between the 3 karyotypes groups (P = 0.02) (Table 2). AH (cm) minus predicted AH (cm) showed a similar response in mean height gain of 3.63 cm (–0.250.30 to 7.45) for all karyotypes, but only with a borderline significant difference (P = 0.05). Among the untreated girls with TS, 3

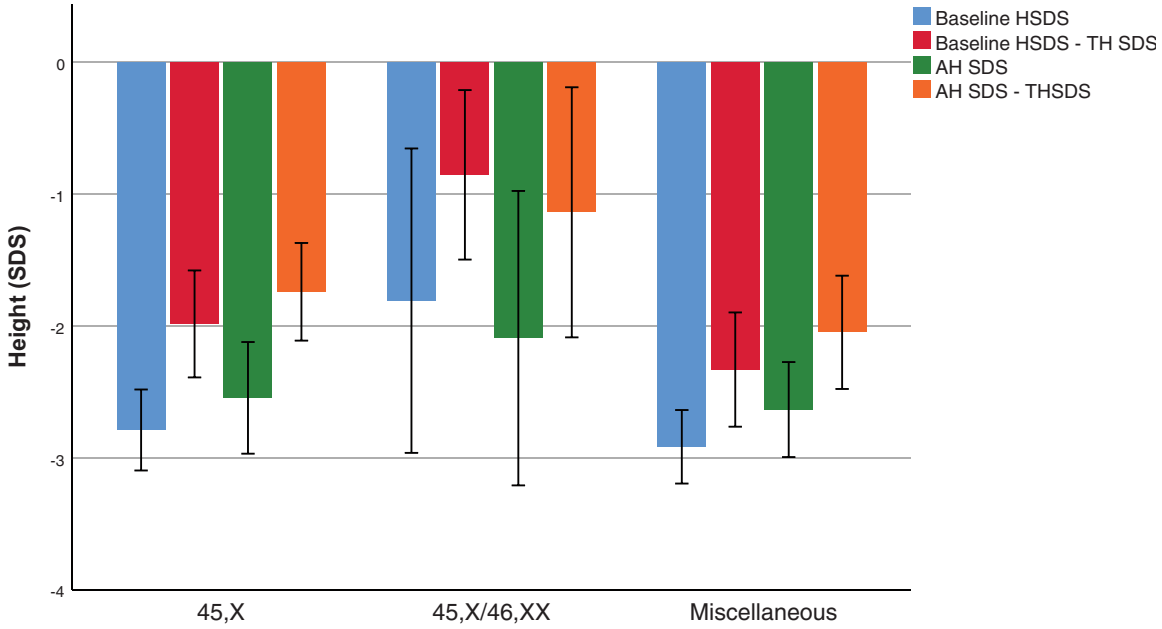

Figure 4. Height SD score during GH treatment divided by karyotype groups, at baseline (blue bars), at baseline minus target height (TH) (red bars), AH (green bars), and AH minus TH (orange bars). Bars represent mean ±2 standard error.

out of 13 untreated girls achieved an AH comparable to TS girls treated with GH (all 3 patients were miscellaneous: 45X/46XX/47XXX; 45X,46XY,idic(Y)(q11); and 45X,t(x;5)(q13;p15.3)dn). The remaining girls have not yet reached an AH and are not candidates for GH treatment due to their age-appropriate growth at present (21).

Forty-eight of the 59 (81%) girls above 10 years of age received estrogen treatment during treatment with GH. E2 was administered as transdermally (56%), orally (29%), or both (15%) (Table 3). The median age at start of estrogen treatment was 12.3 years (11.2-13.8 years; median of 4.7 years after initiation of GH) and did not differ between karyotypes (P = 0.12) (Table 3). The majority of patients experienced pubertal growth spurt with increased HSDS after initiation of E2 treatment (22). However, the effect of E2 varied considerably between patients during the first 2 years after initiation of E2 treatment, with a median gain in height of 0.3 SDS (0.07-0.53 SDS).

Discussion

In this large single-center study, we evaluated the effect on AH following long-term GH treatment with dose titration by IGF-1 levels in 63 girls with TS. We succeeded in attaining IGF-1 levels within the recommended target range in the majority of the girls using an average GH dose of 33 µg/kg/day. We report an AH gain of 3.20 cm in our real-world evidence study, which is below the findings observed in randomized controlled trials.

Improvement of AH in girls with TS treated with the traditional weight-based GH dosing regimen usually ranges between 5 and 8 cm at GH doses ranging from 42 to 50 µg/kg/d, although a Dutch study reported of gain in AH of 11 to 16 cm using much higher GH doses (45-90 µg/kg/d) (23). However, large interindividual variation in AH gain was apparent in all studies (3-7). In the current study, AH gain was evaluated using a reference material for untreated TS girls and the gain in height was slightly reduced using an IGF-1 titration regimen compared with the results reported in previous studies. There was a significant difference between the karyotypes as the mosaic group (45,X/46,XX) had lower gain in height following GH treatment. However, this group had a higher baseline height (SDS) according to the TS reference population (1.38 SDS) and thereby also a higher projected AH, which they reached. Predicted AH is determined by the height and bone age at baseline with a prediction model based on a normal reference population (24). This method has not been validated for TS girls, but in our study the predicted AH and the projected AH were quite similar, suggesting that the prediction model could give substantial information on the height potential in untreated TS girls.

The latest international clinical guidelines recommend to keep IGF-1 levels below +2 SDS and to decrease the GH dose if IGF-1 levels are above +3 SDS. Importantly, our present results showed that IGF-1 titration of the GH dose in girls with TS may lead to lower doses of GH than recommended (8) and that the gain in height in our study was lower than previously reported results. These findings underline the great variability in growth response to GH treatment in girls with TS and that numerous factors may influence the efficacy of the

Table 3. Administration of estrogen in the 3 groups of karyotypes

	All Patients		Karyotypes			
	N		45,X	45,X/46,XX	Miscellaneous	
N			25	8	30	P-value
Age at start of E2 treatment	48	12.26 (11.22 to 13.78)	12.08 (11.08 to 13.17)	14.64 (14.25 to 15.03)	12.84 (11.30 to 14.60)	0.12
E2 treated, n (%)[a]	48	48 (81.36)	24 (100)	2 (25)	22 (81.48)	**<0.001**[b]
E2 TD administration, n (%)	27	27 (56.25)	14 (58.33)	1 (50)	12 (54.55)	
E2 PO administration, n (%)	14	14 (29.17)	7 (29.17)	1 (50)	6 (27.27)	
E2 both TD and PO, n (%)	7	7 (14.58)	3 (12.50)	0	4 (18.18)	

Data are presented as medians (interquartile with 25th to 75th percentiles). Significant values are presented in bold.
Abbreviations: E2, estrogen; PO, oral; TD, transdermal.
[a]Only girls above 10 years of age (n = 59).
[b]Calculated by Chi-Squared test.

treatment, such as early initiation of GH treatment (25). The dose of GH was decreased when IGF-1 levels exceeded +2 SD according to a normal reference. However, following the international recommended guidelines, decreasing GH doses when IGF-1 levels exceeded +3 SD might have resulted in a more significant effect of the titration regime. In a growth prediction model of girls with TS, GH dose was the most influential variable for first year growth response as well as an important factor for the growth response the following years on treatment (26). Girls with TS are not GH deficient, and many of them will have IGF-1 levels within the normal reference before start of GH treatment and may therefore experience a rise in IGF-1 to supraphysiological levels during GH treatment. We and others have previously shown that keeping IGF-1 levels below +2 SDS by titration of the GH dose was less effective in terms of height gain in small for gestational age children than current dosing regimens (27). Thus, it can be speculated that the effect of GH treatment in non-GHD children may depend on continuous supraphysiological levels of IGF-1 to maintain a sufficient growth response.

In the current study, the pubertal growth spurt was evident in most of the patients irrespectively of spontaneous or induced puberty. Administration of estrogen and GH and its combined effect on height is a matter of debate and has not yet reached consensus. One study reported that low-dose treatment with E2 in mid-childhood does not improve gain of near-AH in TS patients (28) whereas another study concluded that combining childhood ultralow-dose estrogen with GH may improve growth in girls with TS (5). Early treatment with low-dose estrogen combined with IGF-1 titration of GH in girls with TS has never been investigated.

This study has some limitations mostly because it is a retrospective study design, which did not allow us to compare our results with a control group. We therefore compared our cohort of GH-treated girls with TS to a previously published study on a group of untreated girls with TS. Another limitation of our study is the methodology of IGF-1 measurements changed throughout the period. However, compared to other studies, we have a large cohort of TS girls followed closely with many routine visits at a single tertiary center, assuring a uniform treatment strategy.

In this single-center study of GH treated girls with TS, we found that lower GH doses were adequate to obtain IGF-1 levels within the normal range as recommended in the clinical guidelines. However, our real-world evidence suggested that IGF-1 titrated GH dosing in girls with TS resulted in a lower AH gain compared to previous studies of weight-based GH dosing.

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Additional Information

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