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Final Adult Height after Growth Hormone Treatment in Patients with Turner Syndrome

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Turner syndrome · Treatment outcome · Growth hormone · Short stature

Abstract
Aims: This study aimed to evaluate final adult height (AH) after recombinant human growth hormone (GH) treatment of girls with Turner syndrome (TS) and to elucidate the predicting factors for their growth response. ***Methods:*** We enrolled 73 patients with TS who underwent GH treatment and reached AH and 14 patients who did not undergo treatment. To assess the effectiveness of GH therapy, we evaluated final AH, height gain over the predicted AH, and height gain over the projected AH. In addition, to analyze the factors affecting final AH, we studied correlations between final AH (or height SDS, height gain) and treatment variables. ***Results:*** GH therapy was started at a mean age of 8.87 ± 3.73 years, and the treatment duration was 6.47 ± 3.02 years. The patients in the treated group reached a final AH of 152.03 ± 4.66 cm (final AH SDS for the general population: −1.93 ± 1.03) with a gain over projected AH at the start of treatment of 12.21 ± 4.33 cm. The untreated control subjects had a final AH of 143.57 ± 4.06 cm with a gain over projected AH at the first visit of 3.89 ± 3.80 cm. Final AH and AH SDS were positively correlated to height SDS at the start of treatment. Thirty-five patients out of the 73 GH-treated patients (47.9%) attained to a normal range of height for Korean girls. The patients having attained to a normal height range after GH treatment had shown a higher height SDS at the start of GH treatment, a higher mid-parental height SDS, and a younger age at initiation of estrogen. ***Conclusions:*** Our findings demonstrate that GH treatment at an early age is effective in improving the final height SDS and height SDS gain in TS patients. Therefore, GH administration at an early age is important for final height gain.

Introduction

Turner syndrome (TS) is a chromosomal disorder caused by complete or partial monosomy of the X chromosome in a phenotypic female, which is associated with a short stature and primary ovarian failure. Short stature is the most common clinical feature of TS [1]. Prenatal growth failure followed by impaired childhood growth and the absence of a pubertal growth spurt in patients with TS result in a final height that is approximately 20 cm shorter than that of the normal female population.

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The etiology of growth failure in TS is not well understood. It is supposed that haploinsufficiency of the short stature homeobox-containing (*SHOX*) gene contributes more to short stature than a disturbance of the growth hormone (GH)-insulin-like growth factor (IGF) axis [2].

Although recombinant human GH has been prescribed to improve adult height (AH) in TS patients for decades, the response of patients to GH treatment is variable and depends on the treatment protocol (e.g., dosage, age at initiation of treatment, and age at puberty onset) [3–10]. The guidelines of the Turner Syndrome Study Group recommend that GH should be administered at the US Food and Drug Administration (FDA)-approved dose of 1.125 IU/kg/week (0.375 mg/kg/week); this dose can be adapted according to the growth response and IGF-1 levels [1]. It is also recommended that GH treatment should be considered as soon as growth failure is evident, possibly around 4–6 years of age. Estrogen therapy to induce pubertal development should be started between 11 and 12 years of age [11].

In this retrospective study, we assessed the effect of GH replacement therapy on final AH by comparing the final AHs of TS patients undergoing GH therapy with those of TS patients without GH treatment, as well as height SDS (standard deviation score) gain after treatment. In addition, we analyzed contributing factors determining the effect of GH treatment on final AH.

Subjects and Methods

This retrospective study included 92 patients with TS who were followed up at the Department of Pediatrics of Severance Children's Hospital, South Korea, and reached final AH. The study participants were recruited from the database of the hospital that includes subjects diagnosed with TS based on peripheral blood karyotyping between January 1986 and December 1997. We enrolled 74 patients with TS who underwent GH treatment and reached AH and 18 patients who did not undergo treatment.

Recombinant GH was administered subcutaneously, every evening, at the fixed dose of 1 IU/kg/week (0.33 mg/kg/week) until final AH was reached. The untreated control group included patients visiting the hospital too late to undertake GH treatment. Conjugated estrogens were initiated at a mean age of 14.76 ± 1.96 years in the GH-treated group, and at 17.63 ± 2.96 years in the untreated group. A small daily dose of estradiol valerate (0.25 mg) was given for the first 1 or 2 years, which was gradually increased to 1 mg, followed by cyclic administration of 1 mg of estrogen (estradiol valerate) for 25 days, combined for the last 10 days with progesterone (medroxyprogesterone 10 mg/day).

We evaluated the subjects' height, weight, BMI, and bone age (BA) before and during the GH treatment. The patients visited the outpatient clinic for follow-up every 3 months. At each visit, height (to the nearest 0.1 cm) was measured using a Harpenden Stadiometer, and weight was recorded to the nearest 0.1 kg. Growth parameters, including height, weight, and BMI, are expressed as SDS and were calculated using the growth standard for Korean children and adolescents [12] and the reference growth chart for Korean girls with TS [13]. Mid-parental height (MPH) was defined as the mean of the parental height minus 6.5 cm. BA was assessed according to the Greulich-Pyle method by the same observer [14]. Predicted AH was calculated according to the Bayley-Pinneau method [15]. Projected AH was calculated according to the projected final height method [16] based on the reference growth chart for Korean girls with TS [13]. Final AH was defined as the height observed for at least 1 year without any further increase >1 cm after the discontinuation of GH treatment.

To assess the effectiveness of GH therapy, we evaluated final AH, height SDS gain for the general population and TS (Δ between the final AH SDS and initial height SDS), height gain over the predicted AH (Δ between final AH and predicted AH at baseline), and height gain over the projected AH (Δ between final AH and projected AH at baseline). In addition, to analyze the factors affecting final AH in the GH treatment group, we studied correlations between final AH (or height SDS for the general population and TS, height gain over predicted AH) and baseline and treatment variables. BA, complete blood cell counts, routine chemistry, and thyroid function, as well as hemoglobin A_{1c}, IGF-1, and IGF-binding protein 3 levels were monitored every 6 months.

Statistical Analysis

Continuous variables are expressed as means ± SD for normally distributed data. Multiple regression analysis was used to evaluate the relationship between the height outcomes and clinical parameters. All data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). p values <0.05 were used as the cutoff for statistical significance.

Results

Clinical Characteristics of the Subjects at Baseline and at the Endpoint

We compared the clinical characteristics of the 73 TS patients who underwent human GH treatment to those of the 14 patients who did not undertake GH treatment at baseline and at the endpoint (Table 1). At the first visit, the mean age of the untreated and the treated group was 17.32 ± 2.8 and 8.87 ± 3.73 years, respectively. Although the height SDS for the general population at the first visit were lower in the untreated control group than in the treated group, MPH, height SDS for age-specific TS, predicted AH, and projected AH were not different.

After GH treatment, the final AH was 143.57 ± 4.06 cm in the untreated control group and 152.03 ± 4.66 cm in the treated group. The mean duration of GH treatment was 6.47 ± 3.02 years. According to the growth standard for Korean children and adolescents, the final AH SDS was −3.87 and −1.93 in the untreated and the treated group, respectively. According to the reference growth chart for

Table 1. Baseline characteristics and final adult height of the patients with Turner syndrome with and without GH treatment

	Treated group (n = 73)	Untreated controls (n = 14)
At first visit		
Chronological age, years	8.87±3.73	17.32±2.8
Bone age, years	8.06±3.48	14.00±1.46
Height, cm	114.41±21.3	137.8±5.89
Mid-parental height, cm	158.50±3.41	158.17±5.80
Height SDS (general population)	−2.71±1.03	−4.48±1.04
Height SDS (age-specific Turner syndrome)	0.33±1.03	0.10±1.04
Predicted adult height, cm	144.39±7.81	141.30±5.34
Projected adult height, cm	139.82±0.63	139.67±0.67
45,X karyotype, *n* (%)	26/73 (35)	0/14 (0)
At attainment of adult height		
Chronological age, years	15.40±1.46	20.31±2.23
Bone age, years	14.78±0.55	15.78±0.43
Height, cm	152.03±4.66	143.57±4.06
Height SDS (general population)	−1.93±1.03	−3.87±0.98
Height SDS (age-specific Turner syndrome)	1.60±0.59	0.51±0.52
Treatment duration, years	6.47±3.02	–
Height SDS gain (general population)	0.79±1.05	0.60±0.59
Height SDS gain (age-specific Turner syndrome)	1.27±0.84	0.41±0.91
Height gain from predicted adult height, cm	7.6±6.44	2.26±3.85
Height gain from projected adult height, cm	12.21±4.33	3.89±3.80

GH, growth hormone; SDS, standard deviation score.

Korean girls with TS, it was 0.51 and 1.60, respectively. Final AH and height SDS had significantly increased in the subjects with GH treatment. The height SDS gain for age-specific TS was 0.41 ± 0.91 and 1.27 ± 0.84 in the untreated and the treated group, respectively. Final AH was 7.6 cm above the Bayley-Pinneau prediction at baseline, and 12.21 cm above the projected AH at baseline.

Figure 1 shows the baseline height and final AH for all subjects. Thirty-five (47.9%) of the 73 recipients of GH (Fig. 1a) had heights above the 3rd percentile on the growth chart for normal Korean girls, whereas no one in the untreated group attained heights above the 3rd percentile for normal Korean girls (Fig. 1b).

Predictors of Final AH in Patients with TS Undergoing GH Treatment

We analyzed the factors affecting the final growth outcome in the GH treatment group. AH in centimeters as well as height SDS for the general population and age-specific TS were correlated with only height SDS at the start of GH treatment. AH in centimeters or SDS for the general population and age-specific TS did not show any correlation with chronological age at the start of GH treatment, MPH SDS, duration of therapy, and age at initiation of estrogen. No correlation was found between the gain over projected AH and chronological age at the start of GH treatment, height SDS at the start, MPH SDS, and duration of therapy (Table 2).

Comparison of the Clinical Characteristics between the Group Having Attained to a Normal Height Range and the Group Who Did Not after GH Treatment

We compared the clinical characteristics between the group having attained to a normal height range (higher than the 3rd percentile on the growth chart for normal Korean girls) and the group who did not (below the 3rd percentile on the growth chart for normal Korean girls) after GH treatment. Thirty-five patients out of the 73 GH-treated patients (47.9%) attained to a normal height range on the growth chart for normal Korean girls. The patients having attained to a normal height range after GH treatment (n = 35) showed a higher height SDS at the start of GH treatment, a higher MPH SDS, and a younger age at initiation of estrogen (Table 3).

Table 2. Correlation between growth outcome and clinical characteristics in the GH-treated group

	AH, cm		Height SDS (general population)		Height SDS (Turner syndrome)		Gain over projected AH, cm	
	R^2	*p* value	R^2	*p* value	R^2	*p* value	R^2	*p* value
Chronological age at start, years	0.202	0.364	0.198	0.375	0.206	0.354	–0.4	0.078
Height SDS at start	0.504	0.036	0.481	0.046	0.511	0.036	0.204	0.349
MPH SDS	0.192	0.084	0.201	0.073	0.192	0.085	–0.121	0.344
Treatment duration, years	0.029	0.890	0.028	0.897	0.030	0.887	–0.429	0.061

GH, growth hormone; SDS, standard deviation score; AH, adult height; MPH, mid-parental height.

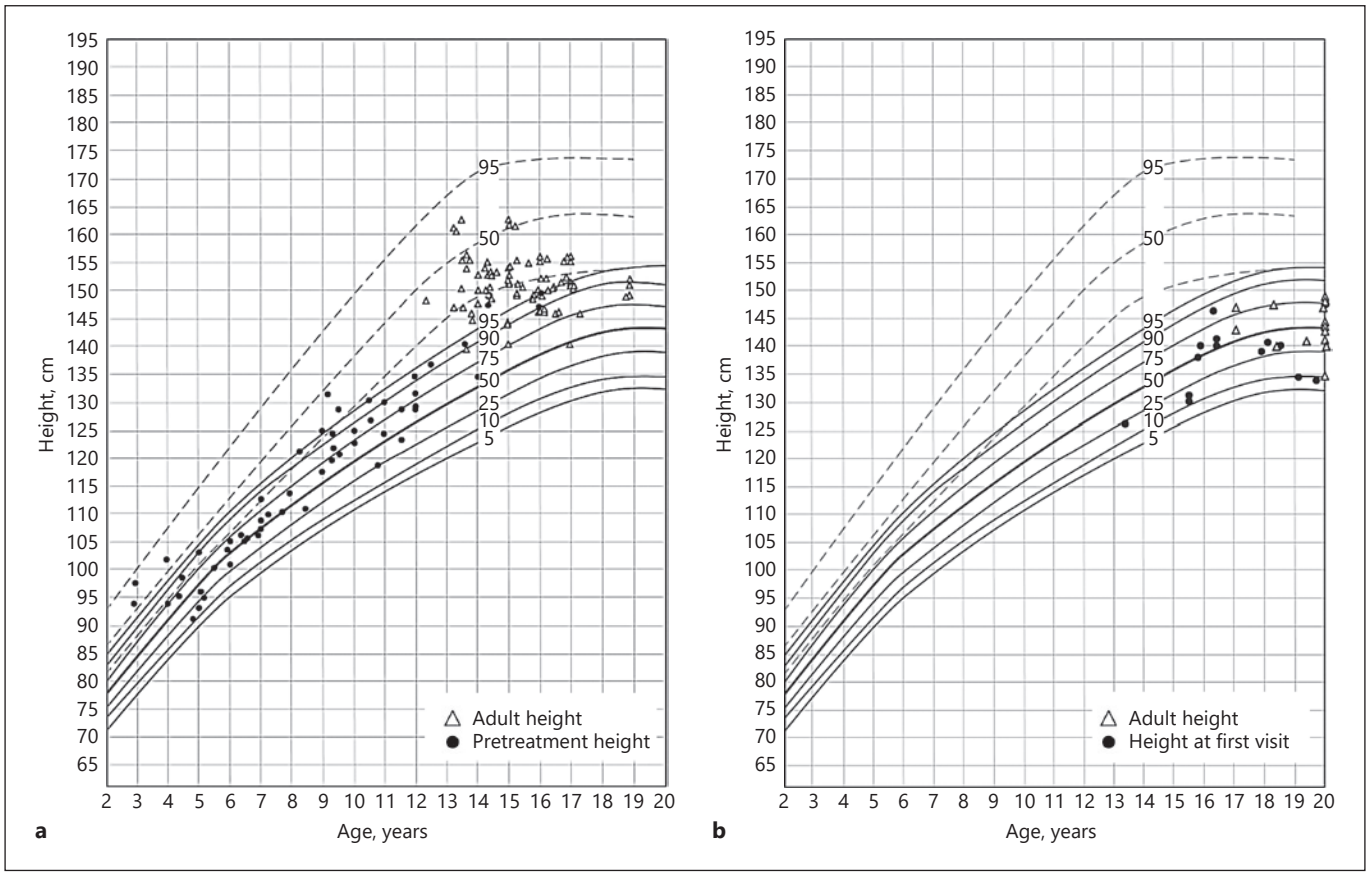

Fig. 1. Height of Turner syndrome patients plotted on the growth curve for normal girls (dashed lines) and for Turner syndrome girls (solid lines). Height before treatment (filled circles) and after treatment (triangles) in growth hormone-treated patients (**a**), and height at the first visit (filled circles) and at adult age (triangles) in untreated patients (**b**).

Discussion

In this study we analyzed final AH in patients with TS who underwent GH treatment or not. The mean final AH in the GH-treated group was 152.03 cm, which is 12.21 ± 4.33 cm taller than their projected AH based on Korean TS-specific data, and 7.6 ± 6.44 cm taller than their predicted AH based on the Bayley-Pinneau prediction method. The final AH in our study is comparable to previous reports of AHs of girls with GH-treated TS from France (147.8 cm) [4], the Netherlands (151.3 cm) [4], Germany (151.9 cm) [4], the UK (150.7 cm) [4], Norway (151.7 cm)

Table 3. Comparison of the clinical characteristics between the group having attained to a normal height range and the group who did not after GH treatment

	Group having attained to a normal height range (n = 35)	Group not having attained to a normal height range (n = 38)	p value
Chronological age at start, years	8.80±3.30	8.86±4.13	0.874
Height at start, cm	118.39±15.23	110.75±25.32	0.127
Height SDS at start (general population)	–2.3±1.0	–3.09±0.92	0.001
Height SDS at start (Turner syndrome)	0.77±0.97	–0.07±0.92	0.000
MPH SDS	–0.28±1.0	–1.0±0.9	0.002
BA – CA	–0.97±1.01	–0.67±1.60	0.328
Treatment duration, years	6.28±2.66	6.65±3.35	0.616
Age at initiation of estrogen, years	14.7±1.17	15.48±1.43	0.017
45,X karyotype, %	56.7	51.2	0.416
Adult height, cm	155.72±2.77	148.6±3.24	0.000
Adult height SDS (general population)	–1.11±0.58	–2.68±0.75	0.000
Adult height SDS (Turner syndrome)	2.07±0.35	1.17±0.42	0.000
Height SDS gain (general population)	1.19±0.83	0.41±1.1	0.001
Height SDS gain (Turner syndrome)	1.30±0.83	1.23±0.86	0.741
Height gain over predicted adult height, cm	7.18±6.58	8.0±0.64	0.631
Height gain over projected adult height, cm	15.62±2.5	9.06±3.09	0.000

GH, growth hormone; SDS, standard deviation score; MPH, mid-parental height; BA, bone age; CA, chronological age.

[4], Japan (144.3 cm) [17], and the USA (150.4 cm) [18], as well as population-based cohort studies from France (149.9 cm) [19] and Italy (151 cm) [20]. Although the previous studies were undertaken in different years (1980–1990s) and with slightly different treatment protocols, they demonstrated a similar final AH attained and that there was a beneficial effect of GH on final AH.

Meanwhile, it is noteworthy that the height gain over the projected AH at the start observed in our study (12.21 cm) exceeded those observed in other countries (range: 1.8–9.0 cm), as did the height gain over the predicted AH at the start (7.6 cm in this study; 3.3 cm in other countries) [4, 19, 20]. The greater height gain over the projected or the predicted AH seen in our study compared to other countries might be due to the younger age of the subjects at the start of therapy (8.87 years in this study; 10.9–14.6 years in other countries), the longer duration of treatment (6.47 years in this study; 4.5–7.6 years in other countries), and the larger dose of GH (1.0 IU/kg/week in this study; 0.7–1.0 IU/kg/week in other countries) [4, 17–20].

In our study, we selected as the untreated control group those patients having visited the hospital too late to undertake GH treatment, and they were matched for the same MPH and projected AH at the first visit, though not in a randomized fashion. The mean final AH in the untreated group was 143.57 cm, which was 3.89 ± 3.80 cm taller than their projected AH based on Korean TS-specific data, and 2.26 ± 3.85 cm taller than their predicted AH based on the Bayley-Pinneau prediction method. The mean final AH of Korean girls with untreated TS was similar to those reported in previous studies from other countries, i.e., the UK (142.9 cm) [16], the USA (144.2 cm) [18], Italy (144.3 cm) [20], Germany (146.8 cm) [21], 12 European countries (144.3 cm) [9], Japan (136.8 cm) [22], and China (141.46 cm) [23]. In our study, the height gains over the projected or predicted AH at the start in the GH-treated group were greater than those in the untreated controls, suggesting that GH treatment of patients with TS augments the final AH.

Previous studies have demonstrated that the growth response after GH treatment for TS was related to height and height SDS at the start of treatment [4, 20], MPH or target height [4, 19, 20, 24], BA delay [4, 19, 24], GH dosage [4, 19], duration of treatment [19, 24], age at the start of treatment [19, 24], and age at pubertal onset [19, 24]. In our study, only height SDS at the start of treatment was correlated with AH in centimeters, and AH SDS for the general population and TS. When the clinical characteristics were compared between the group having attained to a normal range of height in the general population and the group who did not after GH treatment, those patients with a higher height SDS at the start of GH treatment, a higher MPH SDS, and a younger age at initiation of estro-

gen tended to attain to a normal range of height. In contrast, chronological age at the start of treatment, BA delay, and duration of therapy did not influence attainment to a normal range of height after treatment.

These discrepancies between factors affecting the determination of final AH may derive from differences in study population size, ethnicity, and treatment protocol. Our data suggest that final AH in TS is correlated with height SDS at the start of treatment, and attainment to a normal range of height in the general population is mainly determined by factors that reflect the genetically determined growth channel, such as MPH and height SDS at the start of treatment, which is similar to the results of a previous study [4].

In our study, initiation of estrogen at an earlier age seems to have been more effective for attainment to a normal height range in the general population. However, we could not determine the exact effect of early initiation of estrogen because of the very late initiation of estrogen treatment in our retrospective study. A previous study on the impact of age at estrogen replacement on final height showed that patients in whom estrogen treatment had been initiated at the age of 15 years had gained 3.3 cm more AH than those in whom estrogen treatment had been initiated at the age of 12 years [25], whereas other cohort studies found no effect of age at estrogen replacement [26, 27]. A more recent randomized study on whether to begin estrogen treatment early (at 12.0–12.9 years of age) or late (at 14.0–14.9 years of age) showed that very-low-dose estrogen replacement permits age-appropriate feminization without interfering with the effect of GH on TS [28]. Another study, a double-blind, placebo-controlled, randomized trial on optimizing estrogen replacement, demonstrated that combining childhood ultralow-dose estrogen with GH may improve growth and other potential benefits associated with early initiation of estrogen replacement [29].

In conclusion, our study shows that GH treatment initiated at an early age increases the final AH and height gain in patients with TS. The data also show that nearly half of the patients attain to an AH in the normal range of height for the normal population after GH treatment. In our study, attainment to a normal height after treatment depended on height SDS at the start of treatment, the genetically determined growth potential (MPH SDS), and earlier replacement of estrogen.

Statement of Ethics

This study was approved by the Institutional Review Board of Severance Children's Hospital (No. 4-2018-0142). The research has been conducted according to the principles expressed in the Declaration of Helsinki.

Disclosure Statement

The authors have no potential conflicts of interest to disclose.

References

1 Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007 Jan;92(1):10–25.
2 Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet. 1997 May;16(1):54–63.
3 Rosenfeld RG; Genentech National Cooperative Study Group. Long-term results of GH therapy in Turner syndrome. In: Hibi I, Takano K, editors. Basic and Clinical Approach to Turner Syndrome. Amsterdam: Elsevier; 1993. pp. 339–44.
4 Van den Broeck J, Massa GG, Attanasio A, Matranga A, Chaussain JL, Price DA, et al.; European Study Group. Final height after long-term growth hormone treatment in Turner syndrome. J Pediatr. 1995 Nov;127(5):729–35.
5 Attanasio A, James D, Reinhardt R, Rekers-Mombarg L. Final height and long-term outcome after growth hormone therapy in Turner syndrome: results of a German multicentre trial. Horm Res. 1995;43(4):147–9.
6 Massa G, Otten BJ, de Muinck Keizer-Schrama SM, Delemarre-van de Waal HA, Jansen M, Vulsma T, et al.; Dutch Growth Hormone Working Group. Treatment with two growth hormone regimens in girls with Turner syndrome: final height results. Horm Res. 1995;43(4):144–6.
7 Rochiccioli P, Battin J, Bertrand AM, Bost M, Cabrol S, le Bouc Y, et al. Final height in Turner syndrome patients treated with growth hormone. Horm Res. 1995;44(4):172–6.
8 Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, et al. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab. 1996 Feb;81(2):635–40.
9 Ranke MB, Grauer ML. Adult height in Turner syndrome: results of a multinational survey 1993. Horm Res. 1994;42(3):90–4.
10 Chung SC, Park MJ, Kim DH. Final adult height in patients with Turner syndrome. J Korean Soc Pediatr Endocrinol. 1997;2(1):60–9.
11 Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al.; International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017 Sep;177(3):G1–70.
12 Korea Center for Disease Control and Prevention, The Korean Pediatric Society, The Committee for the Development of Growth Standard for Korean Children and Adolescents. 2007 Korean children and adolescents growth standard (commentary for the development of 2007 growth chart) [government report online]. Seoul: Division of Chronic Disease Surveillance; 2007.

13 Shin JH. Spontaneous growth in Korean patients with Turner syndrome. J Korean Soc Pediatr Endocrinol. 1998;3(1):1–6.
14 Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press; 1959. https://doi.org/10.1097/00000441-195909000-00030.
15 Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr. 1952 Apr;40(4):423–41.
16 Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child. 1985 Oct;60(10):932–5.
17 Takano K, Ogawa M, Tanaka T, Tachibana K, Fujita K, Hizuka N; The Committee for the Treatment of Turner's Syndrome. Clinical trials of GH treatment in patients with Turner's syndrome in Japan – a consideration of final height. Eur J Endocrinol. 1997 Aug;137(2):138–45.
18 Rosenfeld RG, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF, et al. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. J Pediatr. 1998 Feb;132(2):319–24.
19 Soriano-Guillen L, Coste J, Ecosse E, Léger J, Tauber M, Cabrol S, et al. Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. J Clin Endocrinol Metab. 2005 Sep;90(9):5197–204.
20 Pasquino AM, Pucarelli I, Segni M, Tarani L, Calcaterra V, Larizza D. Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. J Endocrinol Invest. 2005 Apr;28(4):350–6.
21 Ranke MB, Pflüger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, et al. Turner syndrome: spontaneous growth in 150 cases and review of the literature. Eur J Pediatr. 1983 Dec;141(2):81–8.
22 Takano K, Shizume K, Hibi I, Suwa S, Okada Y. Cross-sectional growth study in patients with Turner's syndrome. Endocrinol Jpn. 1988 Aug;35(4):631–8.
23 Low LC, Sham C, Kwan E, Karlberg J, Tang G, Cheung PT, et al. Spontaneous growth in Chinese patients with Turner's syndrome and influence of karyotype. Acta Paediatr. 1997 Jan;86(1):18–21.
24 Plotnick L, Attie KM, Blethen SL, Sy JP. Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. Pediatrics. 1998 Aug;102(2 Pt 3):479–81.
25 Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. J Clin Endocrinol Metab. 2000 Jul;85(7):2439–45.
26 Ranke MB, Partsch CJ, Lindberg A, Dorr HG, Bettendorf M, Hauffa BP, et al. Adult height after GH therapy in 188 Ullrich-Turner syndrome patients: results of the German IGLU Follow-Up Study 2001. Eur J Endocrinol. 2002 Nov;147(5):625–33.
27 Massa G, Heinrichs C, Verlinde S, Thomas M, Bourguignon JP, Craen M, et al.; Belgian Study Group for Pediatric Endocrinology. Late or delayed induced or spontaneous puberty in girls with Turner syndrome treated with growth hormone does not affect final height. J Clin Endocrinol Metab. 2003 Sep;88(9):4168–74.
28 Rosenfield RL, Devine N, Hunold JJ, Mauras N, Moshang T Jr, Root AW. Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome. J Clin Endocrinol Metab. 2005 Dec;90(12):6424–30.
29 Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, et al. Growth hormone plus childhood low-dose estrogen in Turner's syndrome. N Engl J Med. 2011 Mar;364(13):1230–42.