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Long-Term Results of Growth Hormone Therapy in Turner Syndrome

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Short stature is one of the main features of Turner syndrome. Today, most patients are treated with growth hormone (GH) to improve adult height. We have reviewed the literature reporting adult height in patients with Turner syndrome treated with GH alone or in combination with oxandrolone. The reported adult heights as well as the height gain over projected or predicted height are still preliminary and vary considerably among studies. There is some evidence that the age of onset of therapy, dose of GH, duration of GH therapy, target height, time of estrogen substitution, or concurrent treatment with oxandrolone affect adult height. The reported height gains over projected height range from –0.20 to +16.0 cm (median: 5.1 cm) in patients treated with GH and from +0.68 cm to +10.3 (median: 6.40 cm) in patients treated with GH and oxandrolone. Thus, the presently available data are extremely varied and need further detailed analysis after all ongoing clinical trials have published the final results of all patients included in the study.

Key Words: Turner syndrome; growth hormone; oxandrolone; adult height.

Introduction

Short stature, ovarian failure, and a variety of distinct clinical features are characteristic of Turner syndrome. Numerous studies have attempted to improve adult height in patients with Turner syndrome using replacement doses of pituitary growth hormone (GH) or various doses of oxandrolone or estrogens *(1–4)*. After an initial catch-up growth, a gain of 5.1 cm in adult height was demonstrated in a pair-matched controlled study after 2 yr of oxandrolone therapy *(3)*. Moore et al. *(5)* and Urban et al. *(6)* claimed similar benefits of oxandrolone therapy, whereas others were unable to document a significant or clinically relevant gain in adult height *(4,7)*.

With the advent of biosynthetic GH therapy, several clinical trials have been initiated to assess the effects of higher doses of GH in girls with Turner syndrome. Most of the studies have shown an acceleration in short-term growth and variable increases in adult height when height before therapy was compared with projected, predicted, or target height *(8–29)*. It is a major disadvantage of most studies that changes in growth velocity and adult height have been compared with only historical controls, thus not accounting for a possible secular acceleration of growth and adult height in untreated patients. The only multicenter, prospective, randomized, nonplacebo controlled study was started in Canada in 1989, with preliminary results published recently *(12)*.

The present review was undertaken to document final height outcome in patients with Turner syndrome treated with GH alone or GH and oxandrolone combined. The effects of different treatment regimens, age of starting substitution therapy with estrogens, duration of therapy, and influence of target height were evaluated.

Results

Many studies have documented that girls with Turner syndrome have acceleration of short-term growth velocity during GH therapy alone *(30–32)* or during GH therapy in combination with oxandrolone *(33)* or estrogens *(34–36)*. Adult height data of some of these studies have been published recently. Many studies were randomized to different treatment regimens, i.e., the dose of GH, age of onset of GH therapy, and use of estrogens or anabolic steroids. None except the Canadian Randomized Trial of Growth Hormone in Turner's Syndrome included a prospectively randomized untreated control group for more than 1 or 2 yr *(12)*.

The results of the present review are presented in two parts: (1) a summary of published reports with final height data using GH alone in different doses, and (2) an analysis of adult height data of studies in patients who received GH in combination with oxandrolone.

GH Treatment in Turner Syndrome

Previous reviews have been published by Donaldson *(37)* in 1998 and by Guyda *(29)* in 1999. Additonal reports with final height data have appeared subsequently (Table 1). In the present review, the mean final height of 1188 girls with Turner syndrome treated with GH alone is 150.2 ± 5.5 cm, which is 5.8 ± 4.3 cm (median: 5.1 cm) above the projected (n = 1188) and 4.6 ± 2.0 cm above the predicted height (n =

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Table 1
Characteristics and Treatment Results of Patients with Turner Syndrome Treated with GH

Author	Country	Year	No. of patients	hGH dose (mg/[kg.wk]) (mean)	hGH start (yr) Mean	hGH start (yr) SD	Projected height (cm) Mean	Projected height (cm) SD	Target height (cm) (mean)	Final height (cm) Mean	Final height (cm) SD	Estrogen start (yr) (mean)	Final height–projected height (cm) (mean)[c]	Target height–final height (cm) (mean)	Duration of hGH therapy
van den Broeck	5 countries[d]	1995	56	0.400[a]	11.7[b]					150..7	4.9	14.5	2.90 (R)		
van den Broeck	5 countries[d]	1995	22	4.400[a]	11.7[b]					148.5	5.1	14.5	3.00 (R)		
Attanasio	Germany	1995	6	0.311[a]	15.4	1.00	151.1	6.20	162.9	150.9	4.7				4.4
Massa	Holland	1995	45	0.400[a]	12.0[b]		149.7	5.70		152.3	5.3	12.1	2.60 (R)		
Taback	Canada	1996	17	0.350	10.2	1.60	148.2		170.0	148.0		13.3	−0.20		
Chu	Scotland	1997	11	0.256[a]	12.8	1.59	140.9	6.70		141.3	6.2	12.9	0.41 (L)		4.0
Takano	Japan	1997	15	0.167	10.0					142.2	6.5	16.0[b]			
Takano	Japan	1997	15	0.333	10.0					144.3	3.9	16.0[b]			
Dacou-Voutetakis	Greece	1998	35	0.233	12.0	1.80	145.0	9.80	158.3	146.1	6.6	15.6	1.10 (R)	12.6	2.7
Carel	France	1998	17	0.300[a]	11.0	1.30	143.1	5.20		148.3	6.0	14.0	5.20 (L)		5.2
Plotnick	United States	1998	622	0.330	12.9	2.50	141.9	6.20		148.3	5.6		6.40 (L)		3.7
Rosenfeld	United States	1998	17	0.375	9.1	2.10	142.0	5.90	164.5	150.4	5.5	15.2	8.40 (L)		7.6
Sas	Holland	1998	9	0.467	13.3	1.70	146.7	6.00	166.5	154.3	5.2		7.60 (T)	12.2	4.0
Sas	Holland	1998	10	0.467[a]	13.8	1.80	151.5	6.90	168.3	156.5	5.6		5.10 (T)	11.8	3.2
Carel	France	1998	12	0.700[a]	10.2	2.50	144.6	3.10		155.3	4.2	15.3	10.60 (L)		6.0
Betts	United Kingdom	1999	52	0.260	10.7	1.56							4.15 (L)		5.8
Hochberg	Israel	1999	25	0.273	10.7	1.40	142.6	5.20	163.3	147.3	4.9	13.2	4.70 (R)	16	6.0
Cacciari	Italy	1999	47	0.333	12.6	2.30	142.9	5.70		148.5	7.1	14.1[b]	5.60 (B)		5.1
Cacciari	Italy	1999	10	0.333	10.8	1.80	141.6	5.30		143.0	5.3	14.1[b]	1.40 (B)		
Sas	Holland	1999	10	0.315	7.9	0.90	146.2	7.50	169.7	158.8	7.1	12.1	12.50 (T)	10.9	7.8
Sas	Holland	1999	10	0.473[a]	8.6	1.60	146.6	4.50	170.5	161.0	6.8	13.3	14.50 (T)	9.5	6.8
Sas	Holland	1999	12	0.630[a]	8.1	1.40	146.2	5.30	169.0	162.3	6.1	12.9	16.00 (T)	6.7	7.3
Chernausek	United States	2000	26	0.375	9.6	1.00	141.9	5.40	161.9	147.0	6.1	12.3	5.10 (L)	14.9	5.6
Chernausek	United States	2000	29	0.375	9.4	1.09	142.0	6.10	163.6	150.4	6.0	15.0	8.40 (L)	13.2	6.1
Chernausek	United States	2000	51	0.375	12.7	1.30	143.8	5.30	162.9	148.5	5.5	13.7	4.70 (L)	14.4	3.8
Stahnke	Germany	2001	7	0.311[a]	11.5	1.20	148.1	3.80	165.1	151.7	3.1		3.60 (R)	13.4	4.8

[a] Indicates the highest dose of hGH, when different doses of hGH were used in the study.
[b] Indicates the earliest mean chronologic age or the chronologic age before GH or estrogen therapy was started.
[c] L, R, T, B: data according to Lyon et al. *(39)*, Ranke et al. *(38)*, Teunenbroek et al. *(46)*, and Bernasconi et al. *(50)*.
[d] France, The Netherlands, Germany, United Kingdom, and Norway.

142). The individual variability was marked in all studies. Some girls remained very short with a minimum final height of 128.0 cm in a Japanese study *(28)*, 132.0 cm in a study from Italy *(11)*, and 133.4 cm in a report from Scotland *(15)*. Maximum adult height varied considerably as well—150.0 cm in Scotland *(15)*, 152.1 cm in Japan *(28)*, and 172.4 cm in the Netherlands *(23)*—documenting an adult height either below or well within the normal range of the population.

The doses of GH extended from 0.167 to 0.700 mg/(kg·wk). The mean dose was 0.326 ± 0.071 mg/(kg·wk) in the 26 studies under review. The effects of different doses of GH on adult height are shown in Fig. 1. The data suggest that higher doses have a more favorable effect on adult height, especially when hGH doses above 0.400 mg/(kg·wk) are used.

Duration of GH therapy or commencement of therapy at an early chronologic age have been implicated in the outcome of GH therapy. The mean chronologic age before therapy has been 11.0 ± 1.9 yr with a mean minimum age of 7.9 and a mean maximum age of 15.4 yr (Table 1). Adult heights have not been published from a larger group of patients starting GH therapy before the age of 6 yr. The effects of an early vs a late start of GH therapy are therefore only preliminary. The present data indicate that a longer duration of treatment has a somewhat favorable effect on adult height (Fig. 2) but correlates more positively with the gain in final height over projected height (Fig. 3) than will adult height (Fig. 2).

The age of onset of estrogen substitution therapy could be another important variable affecting adult height. The effects on height gain over projected height are demonstrated in Fig. 4 and indicate that in contrast to some studies *(14)* delaying estrogen substitution therapy does not necessarily increase adult height.

Eleven studies have documented the difference between target height and adult height. The mean difference is 12.3 ± 2.6 cm with a minimum of 6.7 cm and a maximum of 16.0 cm. As a group, patients with Turner syndrome did not reach their target height. Target height is correlated to final height (Fig. 5) and to the gain in adult height over projected height (Fig. 6).

GH and Oxandrolone Treatment in Turner Syndrome

The number of patients treated with GH in combination with oxandrolone is considerably smaller. The adult height of 288 patients was 150.5 ± 3.8 cm, with a mean minimum height of 143.5 cm *(15)* and a mean maximum height of 155.1 cm *(26)*. The height gain over projected height was 5.7 ± 3.3 cm (median: 6.40 cm). The mean dosages of GH and oxandrolone were 0.261 ± 0.064 mg/(kg·wk) and 0.074 ± 0025 mg/(kg·d). Within the small hGH dosage range of

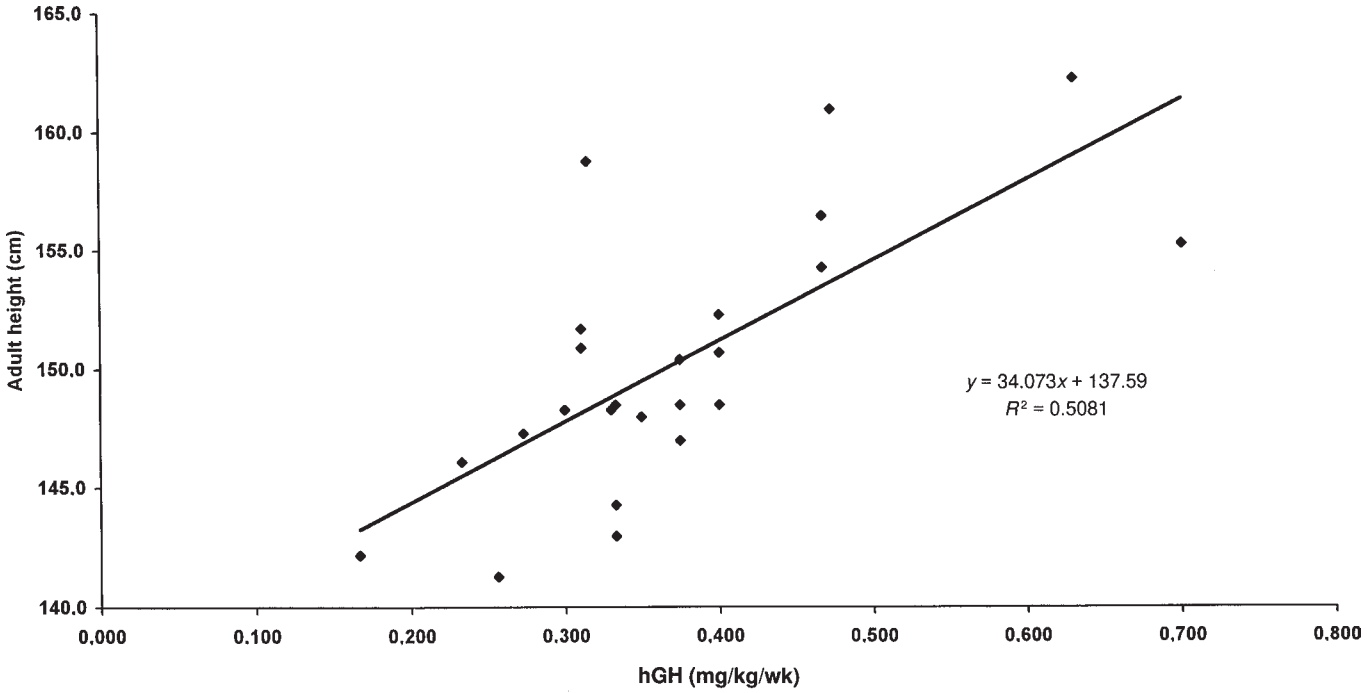

Fig. 1. Dose of GH and adult height in Turner patients treated with GH. Mean values of 24 different studies are given.

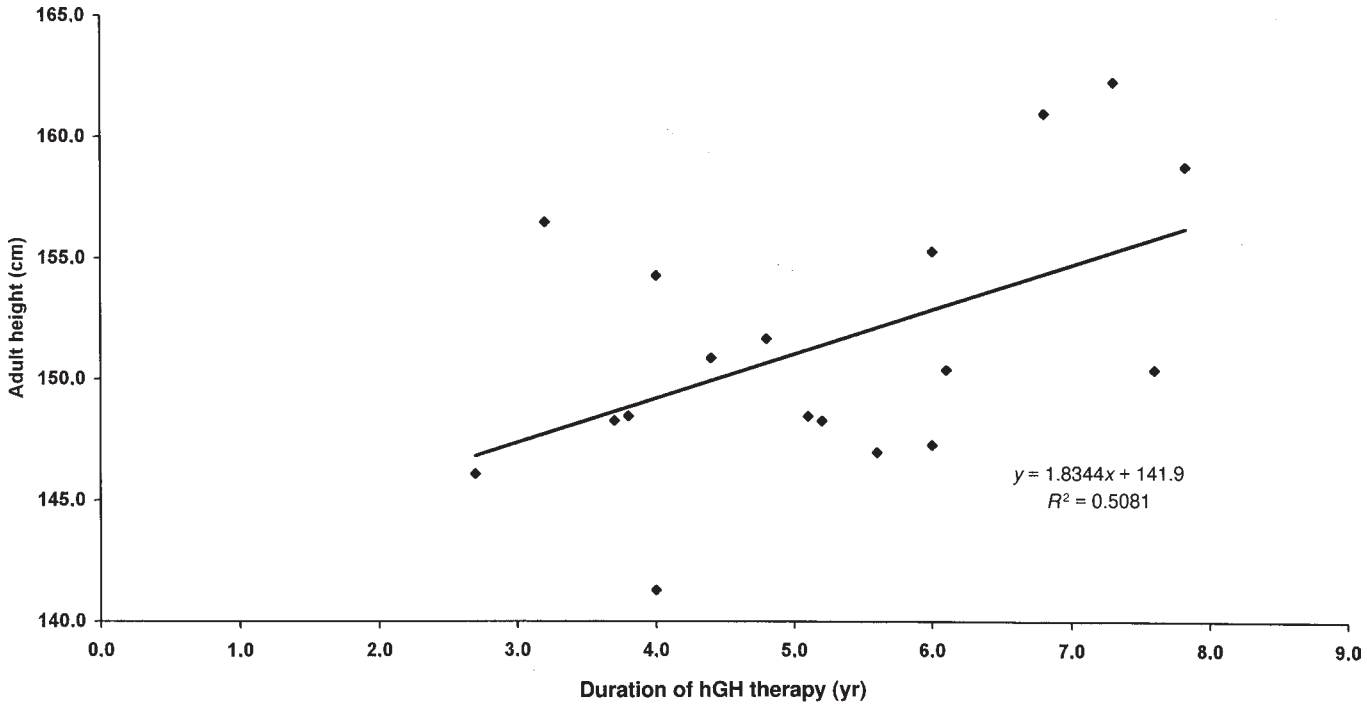

Fig. 2. Duration of GH therapy and final height in Turner patients. Mean values of 18 different studies are given.

0.200–0.375 mg/(kg·wk), there was no correlation of the dose of GH to the attained adult height (Fig. 7), but there was a correlation to the duration of GH therapy (Fig. 8). The chronologic age before therapy was rather late (11.82 ± 0.74 yr), and the duration of therapy (4.66 ± 0.92 yr) was shorter than the 5.3 ± 1.5 yr documented in the patients treated with GH only (Table 2).

Discussion

Twenty-six studies have reported adult height in girls with Turner syndrome treated with GH alone, and twelve studies reported adult heights in girls treated with GH and oxandrolone. In most studies, data are still preliminary because final heights were not available in all patients, especially the younger patients. Final height was 150.2 ± 5.5 cm

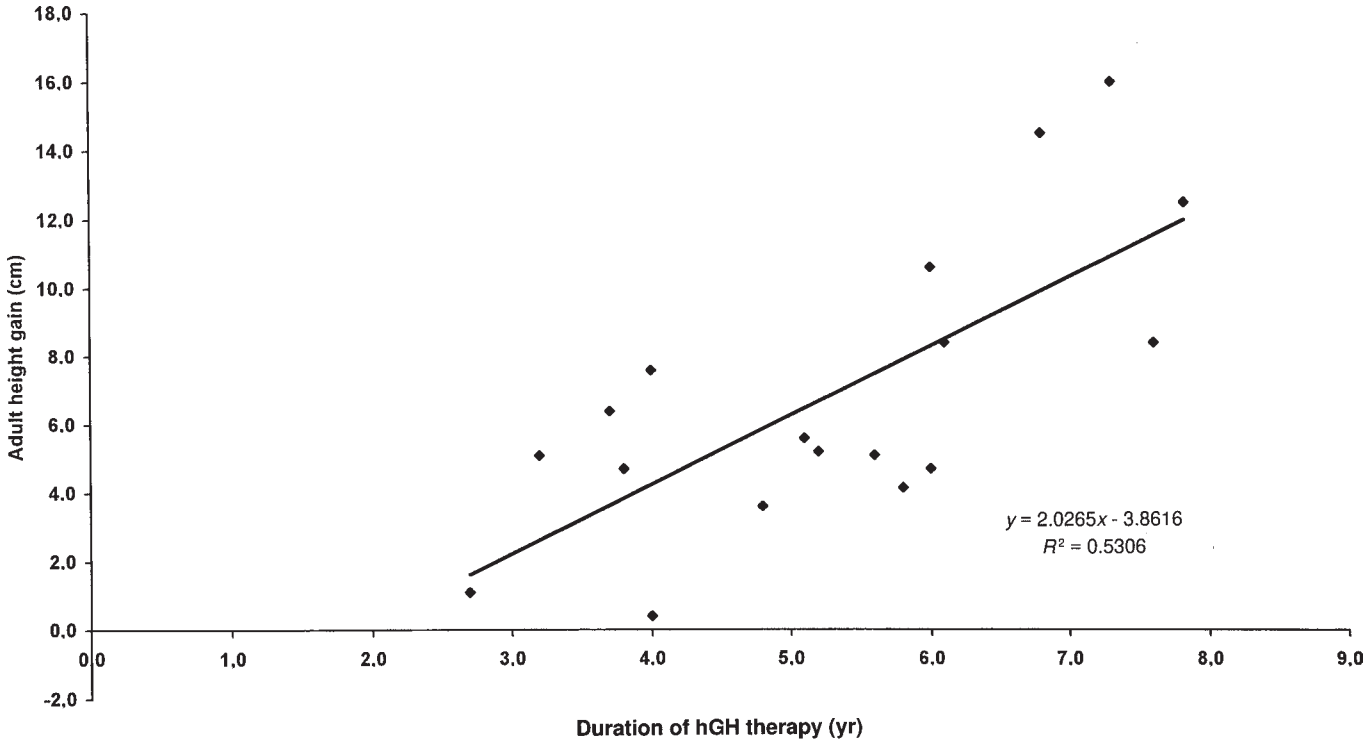

Fig. 3. Duration of GH therapy and adult height gain over projected height in Turner patients treated with GH. Mean values of 18 different studies are given.

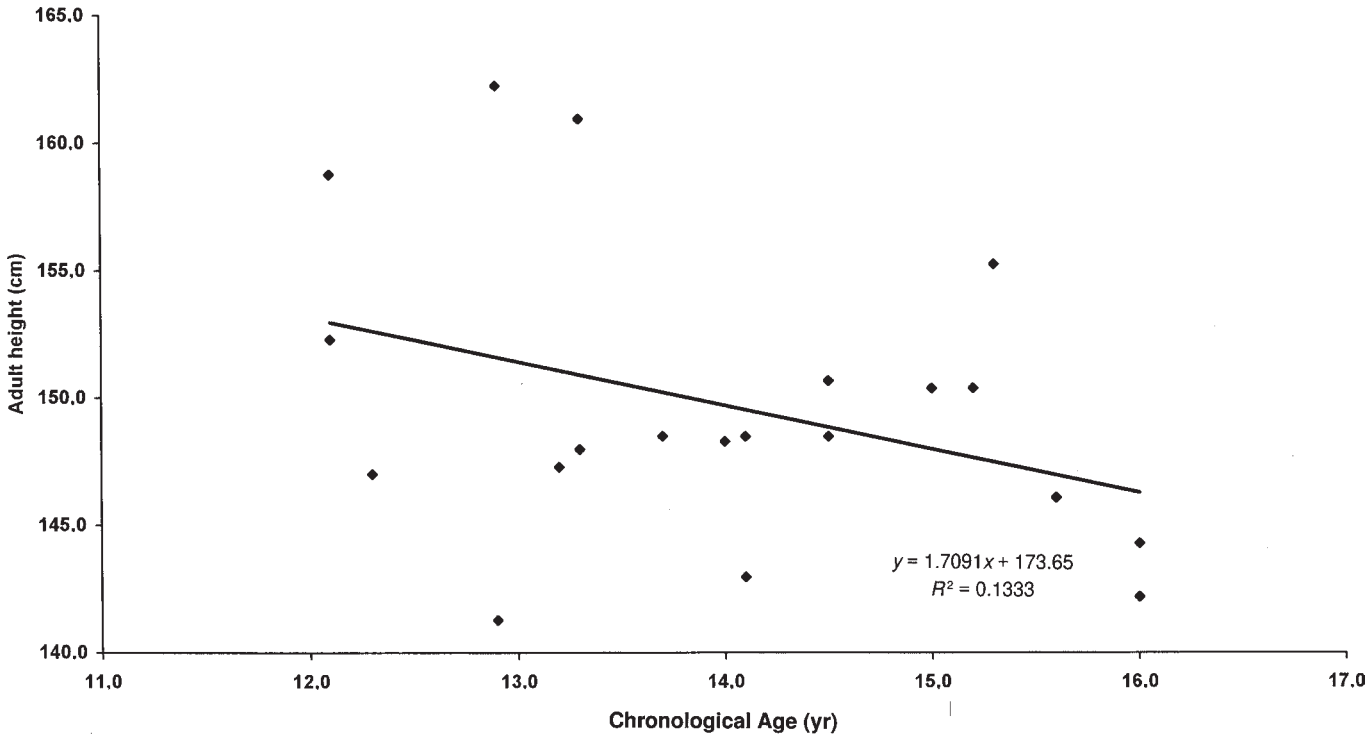

Fig. 4. Chronologic age at estrogen substitution and adult height in Turner patients treated with GH. Mean values of 20 different studies are given.

in 1188 girls treated with GH and 150.5 ± 3.8 cm in 288 girls treated with a combination of GH and oxandrolone. Various outcome measures have been used to assess the effects of therapy on final height.

The final height in these two patient groups is taller than the mean adult height of 146.8 ± 5.8 cm reported by Ranke et al. *(38)* and 142.9 ± 6.7 cm published by Lyon et al. *(39)* in adult patients with Turner syndrome not treated with

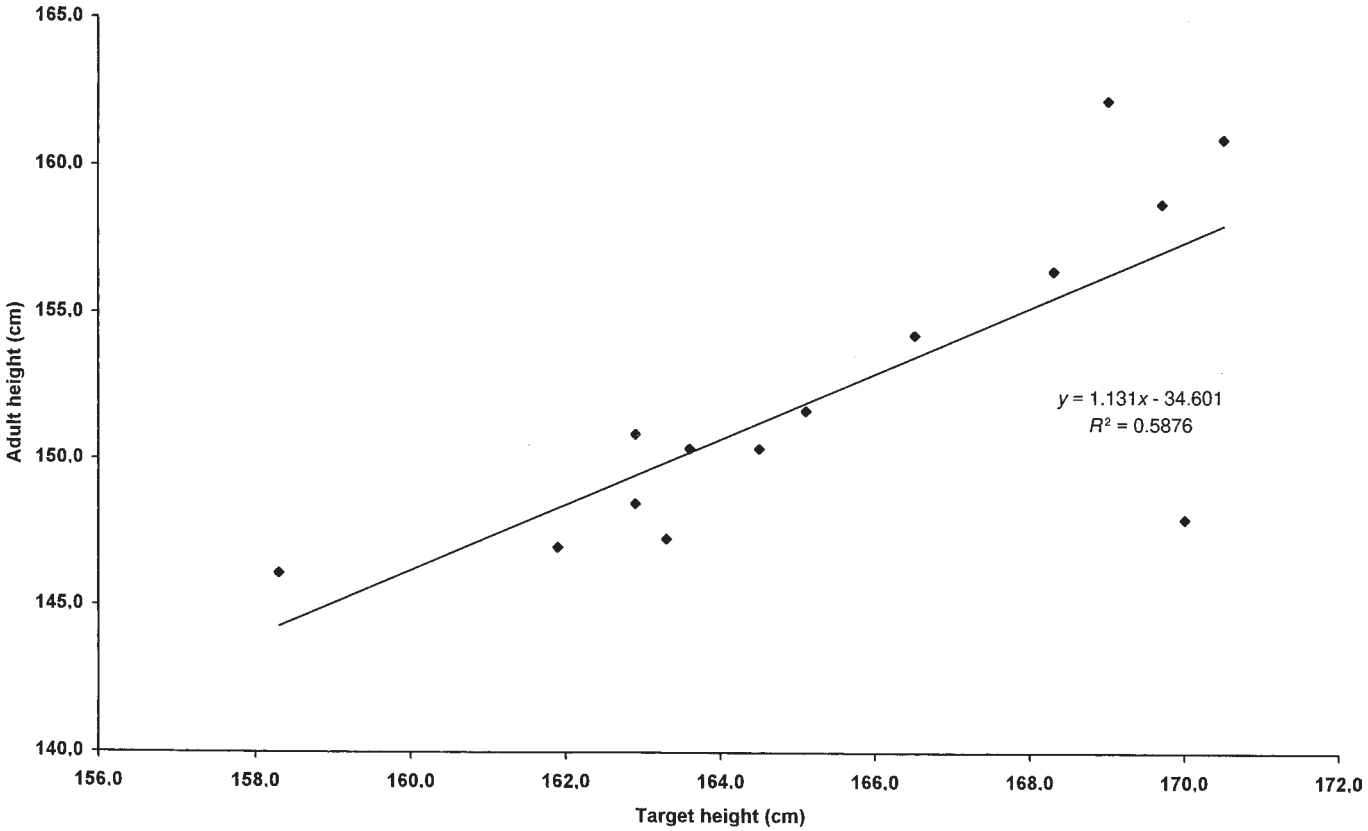

Fig. 5. Target height and adult height in Turner patients treated with GH. Mean values of 14 different studies are given.

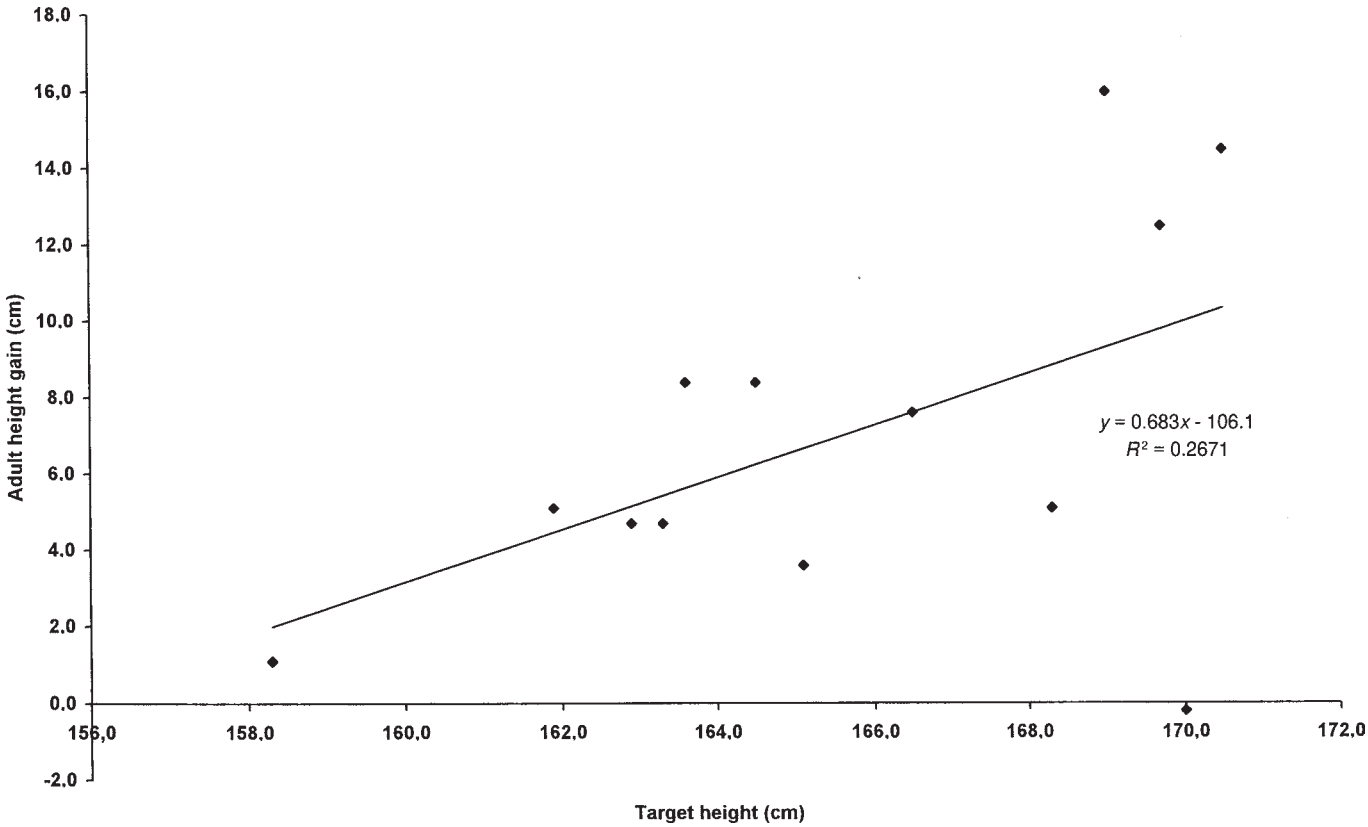

Fig. 6. Target height and adult height gain over projected height in Turner patients treated with GH. Mean values of 21 different studies are given.

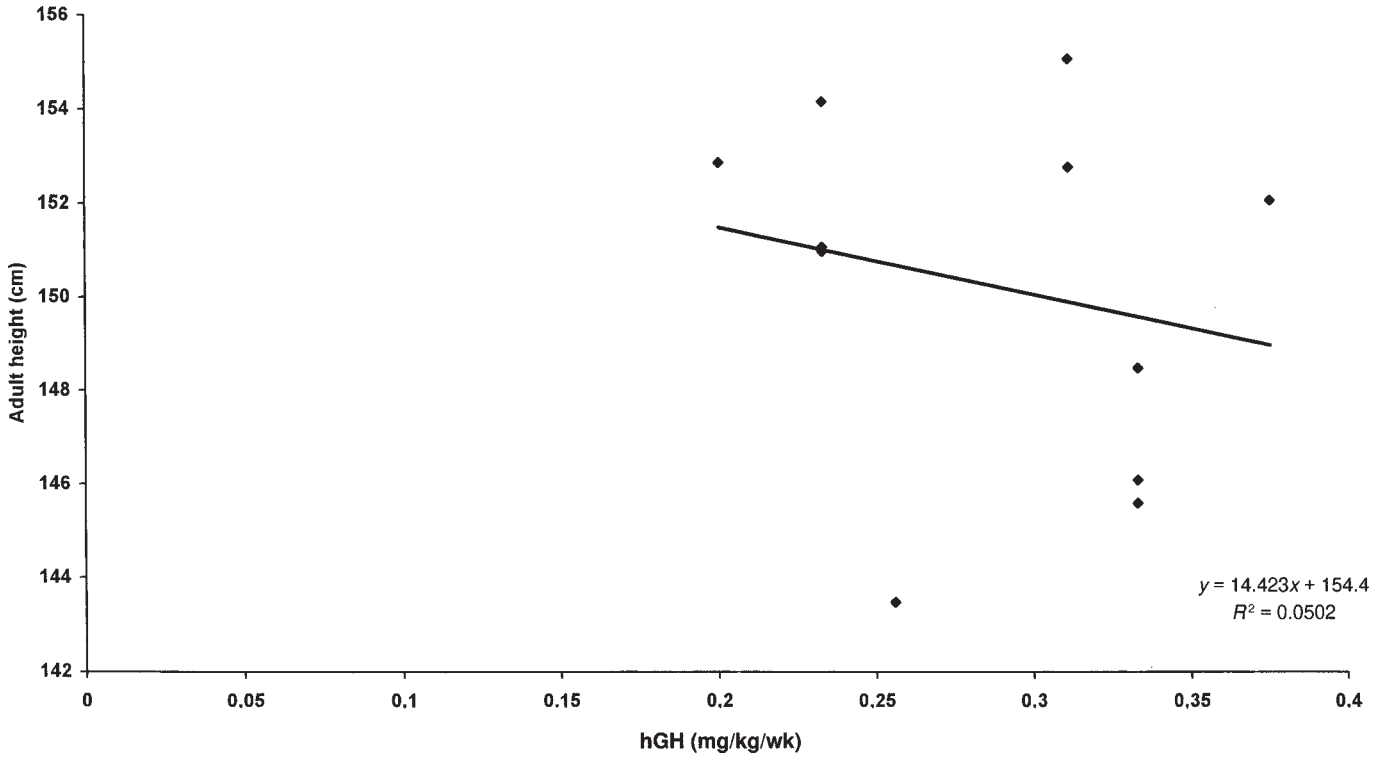

Fig. 7. Dose of GH and adult height in Turner patients treated with GH and oxandrolone. Mean values of 11 different studies are given.

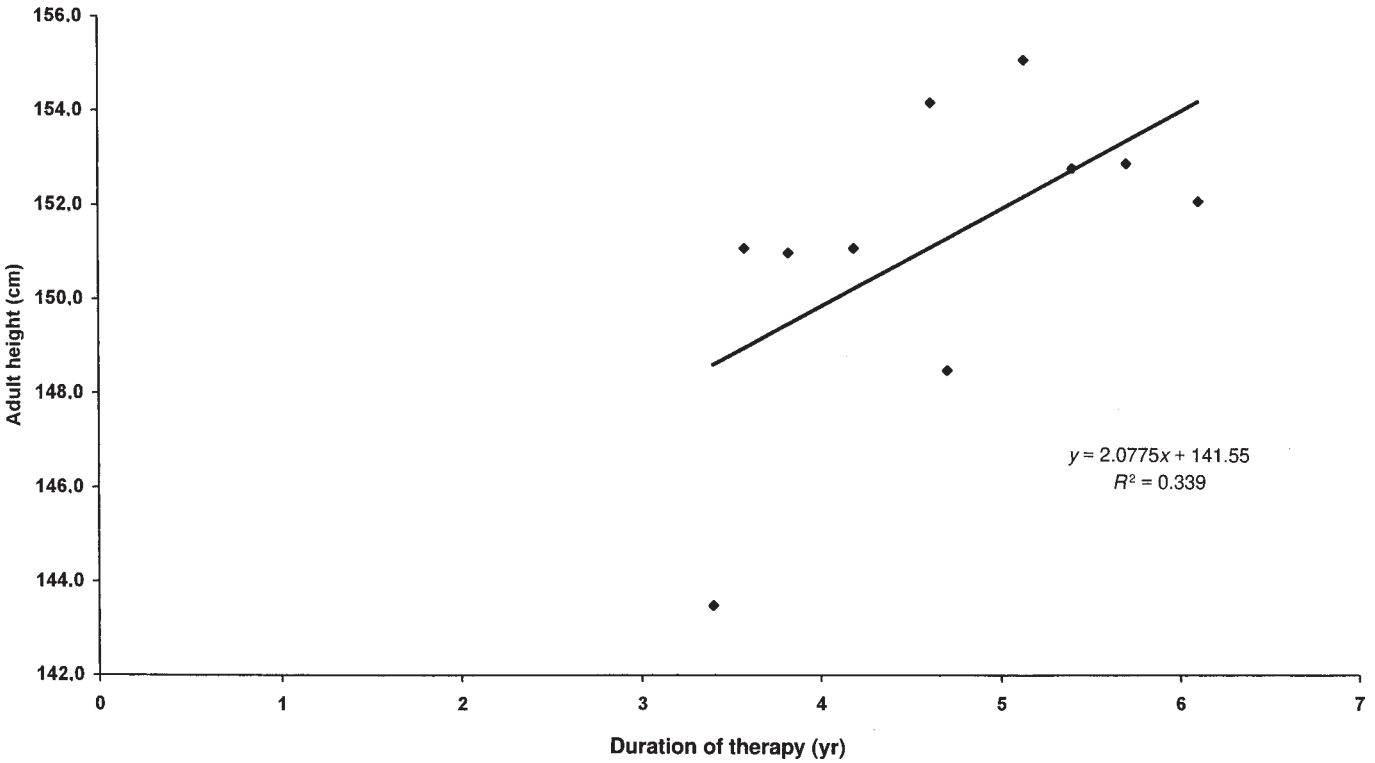

Fig. 8. Duration of GH therapy and final height in Turner patients treated with GH and oxandrolone. Mean values of 10 different studies are given.

Table 2
Characteristics and Treatment Results of Patients with Turner Syndrome Treated with GH and Oxandrolone

Author	Country	Year	No. of patients	hGH dose (mg/[kg·wk]) (mean)	Oxandrolone (mg/[kg·wk]) (mean)	hGH start (yr) Mean	hGH start (yr) SD	Projected height (cm) Mean	Projected height (cm) SD	Target height (cm) (mean)	Final height (cm) Mean	Final height (cm) SD	Final height–projected height (cm) (mean)[b]	Target height–final height (cm) (mean)	Duration of hGH therapy (yr) (mean)
Cacciari	Italy	1999	47	0.333[a]	0.05	12.6	2.3	142.9	5.7		148.5	7.1	5.60 (B)		4.70
Cacciari	Italy	1999	27	0.333[a]	0.05	11.0	2.6	142.8	7.3		146.1	5.1	3.40 (B)		
Cacciari	Italy	1999	51	0.333[a]	0.05	12.4	2.5	144.2	6.8		145.6	5.7	1.40 (B)		
Chu	Scotland	1997	15	0.256[a]	0.05	11.6	1.7	142.9	5.5		143.5	5.3	0.68 (B)		3.40
Hauessler	Austria	1996	20	0.200[a]	0.0625	11.8	2.4	143.7	4.0	162.6	152.9	3.5	9.30 (H)	9.6	5.70
Nilsson	Sweden	1996	6	0.233	0.1	12.3	1.7	143.6	5.9		151.0	6.7	7.40 (K)		3.82
Nilsson	Sweden	1996	7	0.233	0.1	12.3	1.7	146.8	3.7		151.1	5.4	4.30 (K)		3.58
Nilsson	Sweden	1996	17	0.233	0.1	12.1	1.7	145.7	5.0		154.2	6.6	8.50 (K)		4.61
Nilsson	Sweden	1996	15	0.233	0.1	12.3	12.3	148.1	6.2		151.1	4.6	3.00 (K)		4.18
Rosenfeld	United States	1998	43	0.375	0.125[a]	9.9	2.3	141.8	5.9	162.6	152.1	5.9	10.30 (L)	10.5	6.10
Stahnke	Germany	2001	15	0.311[a]	0.1[a]	11.8	2.0	147.2	5.6	166.9	155.1	4.5	7.90 (R)	11.8	5.13
Stahnke	Germany	2001	25	0.311[a]	0.1[a]	11.7	1.8	146.4	4.8	163.6	152.8	3.8	6.40 (R)	10.8	5.40

[a]Indicates the highest dose of hGH or oxandrolone, when different doses of hGH were used in the study.
[b]L, R, K, H, B: data according to Lyon et al. *(39)*, Ranke et al. *(38)*, Karlberg et al. *(51)*, Haeussler et al. *(52)*, and Bernasconi et al. *(50)*.

growth-promoting agents. With a mean height difference of 3.9 cm between these two adult heights, reference to the Lyon data will obviously give better results.

Treated patients do not reach the mean height of 164.6 ± 5.9 cm of adult females in the Zurich Longitudinal Growth Study *(40)*. The difference to this population mean is –14.4 cm in patients treated with GH and –14.1 cm in patients treated with GH and oxandrolone. Thus, the mean adult height is still below the population 3rd percentile in most studies. An exception are the girls in the Dutch dose-response study in which the mean adult height in the three treatment groups was 158.8 ± 7.1 cm (n = 10), 161.0 ± 6.8 cm (n = 10), and 162.3 ± 6.1 cm (n = 12). The – 2 height standard deviation score of the female Dutch population is 157.6 cm according to the reference data of the 1997 fourth nationwide growth study *(41)*. Only one girl had a height <150 cm, 17 had a height >160 cm, and 5 had a height >170 cm.

A distinct growth pattern and adult heights specific to the country of origin have been documented in Turner syndrome *(42,43)*. Most studies contain historical data and did not encounter a secular trend in final height. In addition, it is very likely that at that time relatively high doses of estrogens were given for the induction of puberty. These doses might have accelerated bone age and therefore reduced the adult height potential. Today, lower estrogen doses are used. If they have the expected additional positive effect on adult height, then the reported height gains in treated patients would be of lesser magnitude.

The effects of growth-promoting therapies are also expressed as height gain over projected height before treatment. The mean height gain was 5.82 ± 4.31 cm in girls treated with GH and 5.69 ± 3.29 cm in girls treated with the combination therapy. This height gain is similar to the 5.34 ± 3.89 cm preliminarily reported from the Canadian Randomized Trial of Growth Hormone in Turner Syndrome in which adult height in GH-treated patients was compared with that of a randomized untreated group of patients *(12)*. Mean final height gains vary from a disappointing –0.2 cm *(27)*, 0.40 ± 4.3 cm *(15)*, or 2.90 ± 3.8 cm *(10)* to an exciting 10.6 ± 3.8 *(13)* or 16.0 ± 4.1 cm *(23)*.

This difference, however, is only partially explained by the age of onset or the duration of therapy, the dose of GH, or the chronologic age when estrogen substitution therapy was started. It has been suggested that the gain in final height over the baseline projected height is higher in patients who receive higher doses of GH. The dose of GH varied considerably among the 28 studies, with some researchers using 0.167 mg/(kg·wk) *(28)* and others up to 0.700 mg/(kg·wk) *(13)*. In two studies the dose of GH was increased during therapy either up to 0.700 mg/(kg·wk) depending on height velocity in a French study *(13)*, or in a fixed dose-response regimen from 0.308 to 0.469 mg/(kg·wk) or from 0.308 to 0.469–0.623 mg/(kg·wk) in a Dutch study *(23)*. In both studies the response to therapy was compared with that of a fixed-dose group receiving 0.300 mg/(kg·wk) *(13)* or 0.315 mg/(kg·wk) *(23)*. The gain in height over projected height in the higher vs lower dosage groups was 10.6 vs 5.2 cm in the French and 14.5 and 16.0 vs 12.5 cm in the Dutch study. There is no explanation for the different gains in height between the two low-dose treatment regimens except the differences in the age of onset of therapy or target height. The Dutch researchers consider this difference in adult height gain between the two treatment regimens quite small in proportion to the difference in the GH dose. They recommend using the "standard dose" of 0.311 mg/(kg·wk) or 4 IU/(m^2·d) but suggest that therapy starts at a relatively young age to achieve a normal height already in the first years of therapy.

The dose-response relationship documented in these two studies is not as evident in other studies and in this review in the dosage range up to 0.400 mg/(kg·wk) (Fig. 2), so that other variables such as patient selection, age at start and duration of therapy, target height, and age at start of estrogen substitution therapy could be important.

The dose of GH was considerably lower in patients treated with GH and oxandrolone varying from 0.200 to 0.375 mg/

(kg·wk) (Table 2). It appears that a comparable height gain of 5.69 ± 3.29 cm can be achieved when oxandrolone is added to a lower-dose GH treatment regimen. The height gain is even more remarkable when the shorter duration of therapy of 4.82 ± 0.98 yr and the older chronologic age of 11.61 ± 0.81 yr are taken into account. The final height of 150.5 ± 3.8 cm is similar to the adult height of 150.2 ± 5.5 cm in patients treated with GH alone.

Early reports indicated that a close correlation exists between parents' height and the adult height of patients with Turner syndrome *(44)*. Several studies have documented the difference between adult height and target height in treated patients. They vary from 6.7 *(23)* to 14.9 cm *(14)* in patients treated with GH alone and from 9.6 *(17)* to 11.8 cm *(26)* in patients treated with GH and oxandrolone. A close relationship between target height and adult height (Fig. 5) or adult height gain over projected height (Fig. 6) was demonstrated, suggesting that target height is a major determinant of final height even in GH-treated patients.

In 10–15% of adolescents with Turner syndrome, puberty commences spontaneously, and in 85–90% puberty has to be induced with synthetic or natural estrogens, preferably at a normal pubertal age. There is some concern that early institution of estrogen therapy causes bone age acceleration and reduction of adult height *(14)*. For this reason, some researchers have suggested that estrogen therapy be postponed to a later chronologic age so that the growth period is prolonged and adult height is improved. However, the delay of pubertal development may cause serious psychosocial problems in self-esteem and interaction with peer groups. In addition, it has not been clearly documented that adult height is significantly taller in late vs normal institution of estrogen therapy. A recent article by Chernausek et al. *(14)* and a previuos one by Nilsson et al. *(20)* found a significantly taller adult height in patients starting estrogen therapy at a later chronologic age. By contrast, in a study by Sas et al. *(23)*, estrogen therapy was started at a normal pubertal age of 12 yr, and most of their patients reached an adult height above 150 cm. They suggest that puberty can be induced at the appropriate chronologic age when GH therapy is started at 6 to 7 yr and a "normal" or "near normal height" is attained already during the prepubertal years.

The presently available data on GH therapy in Turner syndrome are encouraging, although still controversial. It is hoped that widespread optimism will be substantiated after all ongoing clinical trials, including the randomized clinical trial initiated in Canada *(12)*, have published their final results. Today, there is also some concern about the financial implications of prescribing extremely high doses of GH *(13,23)* to every girl with Turner syndrome, especially when similar height gains can be obtained with less expensive as well as lower-dose treatment regimens *(3,22, 26)*. In addition, it will be necessary to establish whether in relation to the documented effect of GH therapy a psychosocial benefit is obtained during and at the end of therapy and maintained during the years after treatment *(45)*.

Materials and Methods

Peer-reviewed publications reporting final height data after different treatment regimens in Turner syndrome were collected from a literature search. Additional peer-reviewed publications were selected from references cited in the reviewed articles.

We included only studies that fulfilled the following criteria. Chronologic age before and at the end of therapy or the duration of therapy were documented. Height data were presented at diagnosis and at adult height. Adult height was defined at a bone age of at least 15 yr or a growth rate of <2.5 cm/yr. To evaluate the effects of different treatment regimens on final height, the methods of height projection and/or height prediction or the references to the adult height of an untreated group of patients had to be included in the article.

Height projections were performed according to the method of Lyon et al. *(39)* or the modified Lyon method of Teunenbroek et al. *(46)*. Most studies used population-specific height standards for patients with Turner syndrome. The Bayley Pinneau *(47)* method or specific modifications of the Bayley Pinneau method for patients with Turner syndrome were used to predict adult height *(46)*. Target height was documented as midparent height minus 6.5 cm with or without the allowance of a secular trend *(2,23,48,49)*.

The different treatment regimens had to include the dose of GH or other growth-promoting agents used solely or in combination. The dose of GH was converted to mg/(kg·wk) under the assumption that 3 IU are equivalent to 1 mg of GH. When the dose of GH was prescribed as square meters per day or week, 30 kg was used for 1 m^2.

The possible effect of estrogens on adult height was evaluated when the onset, dose, and form of estrogen substitution therapy was stated.

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