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# Wpływ terapii hormonalnej na tempo wzrastania i progresję wieku kostnego u pacjentek zespołem Turnera

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**Streszczenie**

Celem pracy była ocean skuteczności leczenia hormonalnego u pacjentek z zespołem Turnera (TS) poprzez analizę tempa wzrastania i progresji wieku kostnego w trakcie stosowania hormonu wzrostu (GH), oxandrolonu (Ox) i estrogenów (E). 62 pacjentki z TS w zależności od rodzaju zastosowanej terapii podzielono na pięć grup: grupę GH (n=11); GH+Ox (n=18); GH+Ox+E (n=7); Ox+E (n=6) oraz grupę 0, którą stanowiły pacjentki nie leczone. Wzrost pacjentek wyrażano w wartościach standaryzowanych obliczonych według siatek dla TS (hSDST), a wiek kostny (BA) oceniano metodą Greulich-Pyle. Wyniki: Średnie wartości ΔhSDST uzyskane w poszczególnych grupach w pierwszym i drugim roku terapii różniły się znamiennie, co wynikało z istotnie wyższych wartości ΔhSDST w grupie GH+Ox. Na podstawie analizy regresji pomiędzy przyrostem wieku metrykalnego w trakcie terapii (ΔCA) a przyrostem wieku kostnego w tym czasie (ΔBA) uzyskano w poszczególnych grupach współczynniki kierunkowe α równania ΔBA=α x ΔCA, które różniły się istotnie, co wynikło ze znamiennie wyższych ich wartości w grupie GH niż w grupie 0 i GH+Ox. Tylko w grupie GH+Ox stwierdzono ujemną korelację pomiędzy początkowych CA a ΔBA. Wnioski: Wszystkie formy terapii przyczyniły się do poprawy tempa wzrastania u naszych pacjentek, jednak największy przyrost wzrostu przy najmniejszej progresji wieku kostnego obserwowano w grupie GH+Ox.

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***Słowa kluczowe:*** *zespół Turnera, terapia hormonalna, tempo wzrastania, wiek kostny*

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# Influence of hormonal therapy on growth rate and bone age progression in patients with Turner syndrome

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**Summary**

The efficacy of growth promoting hormonal therapy is assessed on the basis of growth rate as well as bone age progression until the patients reach their final height. The aim of our study was to investigate which hormonal therapy influences in most appropriate way height velocity and bone age progression in patients with Turner syndrome (TS) and to establish the optimal age to initiate treatment. Patients were divided into five groups according to the type of hormonal therapy: 1) 11 patients treated with growth hormone (GH); 2) 18 patients treated with GH and oxandrolone (Ox); 3) 7 patients treated with GH, Ox and estrogens (E); 4) 6 patients treated with OX and E; and the control group (Group 0) of 62 untreated patients. The patients height was expressed in hSDS calculated on the basis of growth chart for patients with TS (hSDST). Bone age (BA) was assessed according to Greulich-Pyle method. Results: The mean values of ΔhSDST in the first and second year of therapy in individual groups were significantly different. The difference resulted from significantly higher value of ΔhSDST in group treated with GH+Ox. Analysis of regression between ΔCA and ΔBA revealed regression coefficients α of equation ΔBA= α x ΔCA: in group 0: 0.817; group GH: 1.233; group GH+Ox: 0.861; group GH+Ox+E: 0.997; group Ox+E: 1.141. There was significant difference between regression coefficients in studied groups. It resulted from significantly higher value of α in group treated with GH than in a group 0 and treated with GH+Ox. Only group treated with GH+Ox showed a significant negative correlation between baseline CA and ΔBA during the therapy. We can conclude that all regimens of hormonal therapy improved height in our patients but the highest increase of height during the therapy and the smallest progression of the bone age in the same time were observed in patients treated with GH+Ox.

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***Key words:*** *Turner syndrome, hormonal therapy, growth rate, bone age*

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## Introduction

Turner syndrome (TS) is a chromosomal disorder caused by complete or partial absence of one of the two sex chromosomes, presented in all or only in some of the cell lines. The frequency of TS is 1:2000 to 1:5000 newborn females [1, 2].

The most typical clinical feature of Turner syndrome is a significant growth deficiency that is present in 95% of all TS patients [3]. The mechanisms contributing to growth deficiency have yet to be fully understood. It has been hypothesized that the characteristic short stature of Turner patients is due to inappropriate secretion of endogenous growth hormone (GH) [4-7]. Reports about improved growth rate and final height after administration of GH in a higher dose than applied in growth hormone deficiency might suggest target tissue resistance [6, 8].

The essential aim of therapy in Turner syndrome (TS) is to improve final height. Escamilla et al. (1960) was the first to show a positive effect of the therapy with human growth hormone (hGH) in a 14-year old TS patient [9]. Presently, therapy includes recombinant growth hormone in monotherapy or in combination with Oxandrolone (Ox) and/or estrogen (E). However, the clinical studies in TS have not conclusively established the optimal therapeutic regimen due to significant differences in treatment protocols. Important considerations involve not only the doses of hGH (with or without adjunctive treatment), but also the optimal patient's age for beginning therapy.

The aim of this study was to evaluate different hormonal therapies with respect of height velocity increase and bone age progression, as well as to establish the optimal age to initiate treatment.

## Materials and Methods

The study was carried out in 62 patients with TS. The average time of the follow up was 1.82 years (max.=6.12 years). The mean age of the patient at the beginning of the study was 10.79 ±4.39 SD years (min.=1.84, max.=18.36).

Recombinant growth hormone (Genotropin®, 1 IU/kg/wk, applied as a daily s.c. injection) was used in patients with bone age ≤13 years and a height <3rd percentile (based on the Kurniewicz-Witczakowa growth chart) [10]. Oxandrolone® (oral doses between 0.05 - 0.0625 mg/kg/d) was used as adjunctive treatment for GH therapy in patients >9 years old.

According to the experts recommendations transdermal estrogen (Estraderm 25MX®) followed by the estrogen-progesterone (Estracomb TTS®) treatment should be instituted when the bone age exceed 11 years of age. The treatment protocol consisted of half a patch of Estraderm 25MX® (new patches applied twice a week) for two months, followed by one full patch of Estraderm 25MX® (new patch applied twice a week) until the first vaginal bleeding, then changing to Estracomb TTS®.

Criteria for finishing GH therapy and Ox were bone age of ≥14 years and/or growth rate <2 cm/yr and/or the decision to terminate therapy by either the patient or the patient's parents.

Based upon chronological age (CA) and bone age (BA), as well as due to the financial limitations in providing GH treatment prior to 1999 in Poland, the 62 patients with TS could be assigned to the following groups:

- Group **GH** – 11 patients treated with GH (≤9 years of age);
- Group **GH+Ox** – 18 patients treated with GH+Ox (>9 years of age);
- Group **GH+Ox+E** – 7 patients treated with GH+Ox+E (BA ≥11 years);
- Group **Ox+E** – 6 patients treated with Ox+E (BA ≥11 years with no GH available);
- Group **0** - 62 patients without therapy at the baseline.

In Group 0 all 62 patients were followed before therapeutic regimens were initiated. Forty two of them were subsequently assigned to one of the treatment groups. Group 0 was regarded as a control group for verifying height growth chart designed for girls with TS. The number of patients followed each year within the individual groups is presented in table I.

All patients were reevaluated every 2-6 months. Height was measured in Frankfurt's position [11], without shoes, before noon, using Harpenden stadiometer by the same well trained person. All measurements were performed three times and the mean value was calculated. The height was expressed as standardized values (hSDS) based on growth chart for a population of healthy Polish girls, published by Kurniewicz-Witczakowa et al (hSDSN) [10], and growth chart for a population of girls with TS, published by Ranke (hSDST) [12]. Bone age was estimated based upon x-rays of the hand and wrist, according to Greulich & Pyle [13].

***Table I.*** *Number of patients observed each year within the individual groups*

| GROUP | YEAR 1 | YEAR 2 | YEAR 3 |
|---|---|---|---|
| **O** | 39 | 9 | 3 |
| **GH** | 11 | 5 | 2 |
| **GH+Ox** | 18 | 10 | 5 |
| **GH+Ox+E** | 7 | 3 | - |
| **Ox+E** | 6 | 3 | - |

### Statistical analysis

The results were analyzed using the following statistical tests: one-way ANOVA, Kruskall-Wallis ANOVA, Regression Analysis and Multiple Regression Analysis, Test of Homogeneity of regression coefficients (Test of Parallelism).

Group values are expressed as mean ±SD (range). The differences with p-value of <0.05 were considered significant. The STATISTICA 6.0 for Windows and Microsoft Office was used to evaluate all data.

## Results

Baseline characteristics of subjects in all groups are presented in table II.

There were significant statistical differences between mean baseline values for CA (p=0.0001), BA (p<0.0001), and BMI (p=0.021) (Kruskall-Wallis ANOVA). Mean values of hSDSN were significantly different (p=0.033, ANOVA). The Less Significant Difference test (LSD) showed the difference resulted from higher mean values in GH treated group. There were no significant differences between mean values (p>0.05) of the other parameters.

### Influence of hormonal therapy on growth rate (ΔhSDST).

Comparison of the mean values of ΔhSDST in Group 0 during the 3-year follow up period showed no statistical difference (p=0.97). The means were also not significantly different from 0 (p=0.08; 0.51; 0.59; respectively) (fig. 1). The ANOVA test showed mean values of ΔhSDST in Group GH+Ox during the 3-years to be significantly different (p=0.0016). This difference was the consequence of higher ΔhSDST values during the first year of therapy as compared to the second and third year of treatment (p<0.05). Mean values of ΔhSDST in the second and third year of therapy were not significantly different

***Table II.*** *Mean Baseline Anthropometric Measurements, Perinatal Lenght and Weight Measurements, and Mid-parental Height (Mean±SD)*

| GROUP | N | BA (yrs) | CA (yrs) | BA/CA | hSDST | hSDSN | BMI (kg/m²) | BW (g) | BL (cm) | mphSDS |
|---|---|---|---|---|---|---|---|---|---|---|
| **O** | 62 | 10.8±4.4 | 8.9±3.8 | 0.83±0.11 | 0.20±0.92 | –4.05±1.50 | 19.5±4.0 | 2884±448 | 52.4±2.7 | –0.21±0.99 |
| **GH** | 11 | 7.0±1.2 | 5.6±1.9 | 0.78±0.16 | 0.15±0.88 | –3.28±0.98 | 15±1.0 | 2964±474 | 51±3.2 | –0.06±0.88 |
| **GH+Ox** | 18 | 12.0±1.9 | 10.1±1.5 | 0.85±0.10 | –0.16±0.85 | –4.52±1.42 | 20.6±3.8 | 2854±332 | 52.6±2.8 | –0.47±0.91 |
| **GH+Ox+E** | 7 | 14.9±1.2 | 12.4±0.9 | 0.83±0.07 | 0.36±0.77 | –5.21±1.13 | 21.6±3.3 | 2831±463 | 53.1±1.8 | –0.51±0.57 |
| **Ox+E** | 6 | 16.4±1.1 | 12.4±1.0 | 0.76±0.05 | 0.26±0.77 | –4.78±1.42 | 20.7±2.3 | 2922±429 | 51.5±1.4 | –0.07±1.02 |
| **No Therapy** | 20 | 10.0±5.7 | 8.6±5.0 | 0.89±0.16 | 0.55±1.03 | –3.29±1.49 | 20.3±4.6 | 2877±581 | 52.8±2.9 | 0.11±1.21 |

*CA -- Chronological Age*
*BA -- Bone Age*
*hSDST – hSDS estimated according to Turner syndrome – specific growth chart by Ranke*
*hSDSN -- hSDS based on healthy polish girls (Kurniewicz-Witczakowa et al.)*
*BMI -- Body Mass Index*
*BW -- Birth Weight*
*BL -- Birth Lenght*
*mphSDS – Mid-parental Height*

(p>0.05) (fig. 1). A t-test (used only for groups followed for 2 years) showed significant differences in mean values of ΔhSDST between the first and the second year of therapy between Groups GH (p=0.03) and Ox+E (p=0.04), but there was no significant difference with respect to Group GH+Ox+E (p=0.057) (fig. 1).

The Kruskall-Wallis ANOVA test was used to compare the mean values of ΔhSDST at the first year of therapy between groups. The values were significantly different at p level <0.0001. These differences were due to the significantly higher increase of hSDST during the first year of treatment in Group GH+Ox (p=0.0051), while Group 0 showed significantly lower values as compared to all other groups. There were no significant differences in the mean values of hSDST in the first year of treatment between Groups GH, GH+Ox+E, and Ox+E (p=0.29) (fig. 1).

Significant differences in ΔhSDST were present also during the second year of therapy between all groups (p<0.0001, ANOVA). This difference was significant due to the higher value recorded in Group GH+Ox with respect to the other groups. Moreover, the mean value of ΔhSDST in the second year of therapy in Group GH was significantly higher than in Group 0 (p=0.002) (fig. 1).

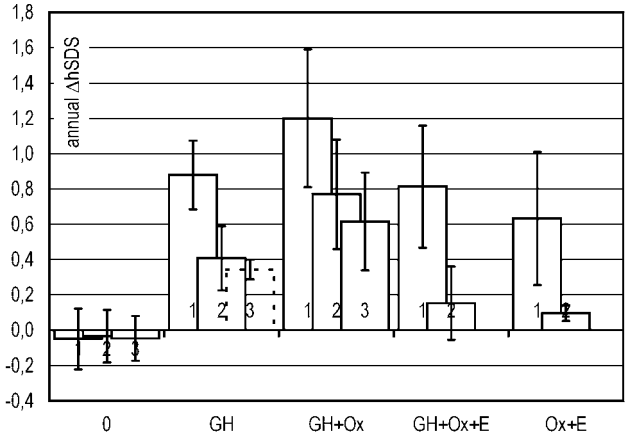


***Fig. 1*** *Mean annual values of ΔhSDST in each group during the observation period (mean±SD).*

**Correlation between CA versus BA in untreated patients with TS.**

Statistical analysis comparing baseline values of BA and CA in 62 patients with TS demonstrated a significant correlation (r=0.95; p<0.0001) as described by the regression equation (fig. 2).

BA=0.814 x CA + 0.24

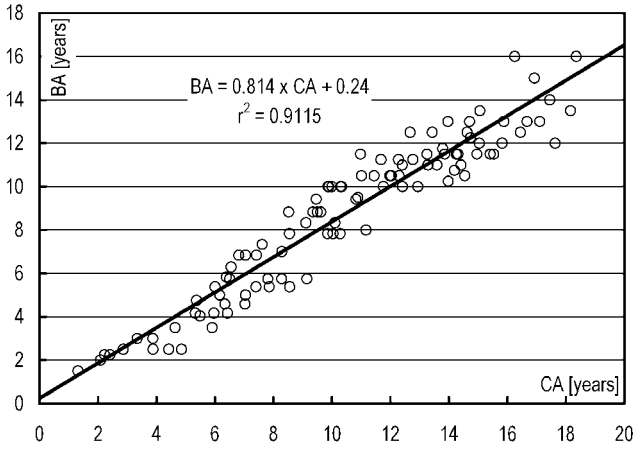


***Fig. 2*** *Correlation between CA and BA values before therapy.*

**Evaluation of different types of hormonal therapy on BA progression (ΔBA).**

Evaluating BA progression during different ways of hormone therapy was performed by regression analysis between the time of treatment (ΔCA) and BA progression (ΔBA).

The regression coefficients were as follows: **Group 0:** 0.817; **GH Group:** 1.233; **GH+Ox Group:** 0.861; **GH+Ox+E Group:** 0.997; **Ox+E Group:** 1.141; with an intercept =0 (fig. 3). These values were analyzed using the homogeneity of regression coefficients test. The results showed significant differences (p=0.007) in regression coefficients between Group GH and Groups 0 & GH+Ox.

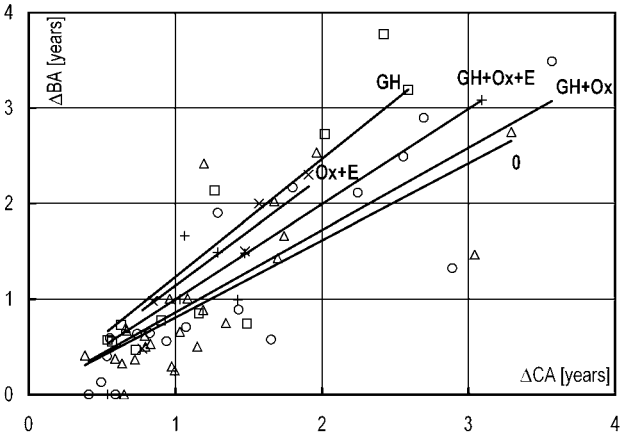


*Fig. 3 Correlation between time of treatment (ΔCA) and BA progression (ΔBA) in group 0 (r, ΔBA=0.817*ΔCA, $r^2$=0.58), GH (□, ΔBA=1.233*ΔCA, $r^2$=0.81), GH+Ox (○, ΔBA=0.861*ΔCA, $r^2$=0.77), GH+Ox+E (É, ΔBA=0.997*ΔCA, $r^2$=0.83), Ox+E (Î, ΔBA=1.141*ΔCA, $r^2$=0.88). The coefficients are significantly different, p=0.007.*

**Analysis of baseline CA, baseline bone age retardation (baseline BA/CA; baseline CA-BA); and baseline hSDST and the subsequent increase in height value during the first year of therapy.**

Linear regression analysis showed no statistically significant correlation between baseline CA and ΔhSDST in the first year of therapy in all groups, which started hormonal therapy (**GH:** r=0.26; p=0.43; **GH+Ox:** r=-0.28; p=0.27; **GH+Ox+E:** r=-0.27; p=0.55; **Ox+E:** r=-0,65; p=0.0,16).

When the analysis of the relationship between ΔhSDST in the first year of therapy in all patients and the baseline values of BA/CA was performed, there were no statistically significant correlations (r=0.13; p=0.31). Further analysis of these parameters within the individual groups did no show significant differences (**GH:** r=0.29; p=0.38; **GH+Ox:** r=0.33; p=0.19; **GH+Ox+E:** r=-0.53; p=0.21; **Ox+E:** r=-0.13; p=0.80).

There were also no significant differences between baseline growth retardation (CA – BA) and ΔhSDST in the first year of therapy in all patients (r=-0.05; p=0.68), as well as in each individual group (**GH:** r=-0.33; p=0.32; **GH+Ox:** r=-0.27; p=0.29; **GH+Ox+E:** r=0.40; p=0.37; **Ox+E:** r=-0.05; p=0.91).

Moreover, none of the treated groups revealed significant correlation between baseline hSDST and ΔhSDST during the first year of therapy (**GH:** r=0.48; p=0.13; **GH+Ox:** r=0.04; p=0.84; **GH+Ox+E:** r=-0.72; p=0.07; **Ox+E:** r=0.04; p=0.94).

**Influence of baseline CA on BA progression (ΔBA) during therapy.**

Only Group GH+Ox showed a significant negative correlation between baseline CA and ΔBA in the first year of therapy (r=-0.62, p=0.007), as well as during the entire therapeutic regimen (ΔBA/ΔCA) (r=-0.71, p=0.001) (fig. 4 and 5). Data analysis of all treated patients yielded a statistically significant negative correlation between baseline CA and BA progression throughout the therapy (r=-0.36, p=0.019) (fig. 6).

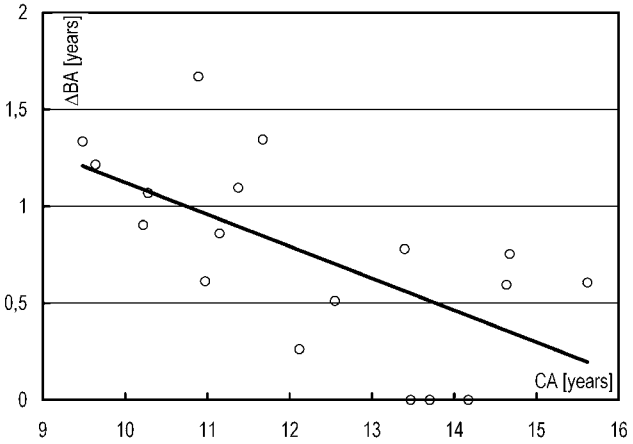


*Fig. 4 Correlation between baseline CA and BA progression in group GH+Ox during the first year of therapy ($r^2$=0.40; p=0.007).*

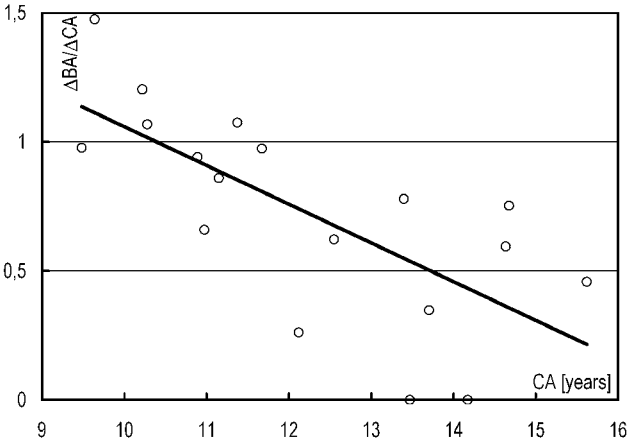


*Fig. 5 Correlation between baseline CA and BA progression velocity (ΔBA/ΔCA) in group GH+Ox during entire therapy ($r^2$=0.49; p=0.001).*

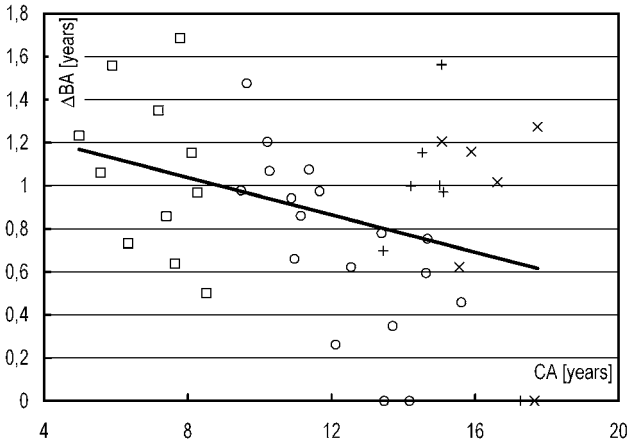


*Fig. 6 Correlation between baseline CA and BA progression in all treated groups ($r^2$=0.13; p=0.019; groups: GH-□, GH+Ox-○, GH+Ox+E-É, Ox+E-Î).*

**The influence of baseline BA retardation on BA progression during hormonal therapy (ΔBA).**

No significant correlations were found in any of the study groups during baseline analysis between BA retardation, expressed as BA/CA and as CA – BA, and BA progression during hormonal therapy (ΔBA/ΔCA) (BA/CA on ΔBA: all groups: r=-0.06; p=0.60; **GH:** r=-0.34; p=0.30; **GH+Ox:** r=0.23; p=0.36; **GH+Ox+E:** r=0.19; p=0.68; **Ox+E:** r=-0.29; p=0.57; CA-BA on ΔBA: all groups: r=-0.21; p=0.09; **GH:** r=0.32; p=0.34; **GH+Ox:** r=-0.37; p=0.15; **GH+Ox+E:** r=-0.44; p=0.32; **Ox+E:** r=0.32; p=0.53).

## Discussion

**Therapeutic protocol of hormonal therapy in TS**

There are numerous forms of heterogeneous therapies for girls with Turner syndrome presented in the literature, making comparative studies very difficult to interpret. Therefore only suggestions about therapeutic protocols for TS are available. Before final height data is available, the benefits of hormone therapy are estimated based on the analysis of growth velocity and progression of bone age.

**The influence of different protocols of hormonal therapy on improving height velocity for girls with TS.**

Several years long follow ups of girls with TS showed that height velocity (HV) and improved height standard deviation scores (ΔhSDST) depended on the dose of GH and the number of GH injections per week. Higher doses of GH induced a greater HV [14-16] and improved ΔhSDS [17-20].

The data from the literature suggest that higher doses of GH yield higher hSDS, but with proportionally much less final height improvement [21]. In some studies GH was used in doses similar to that applied in GH deficiency (~0.5 IU/kg/wk), and it increased ΔhSDST during the first year of treatment of approximately 0.3-0.5 [17, 22]. When GH in doses higher than 0.5 IU/kg/wk, but less than 1.0 IU/kg/wk was used, there was an increase in hSDS of approximately 0.5-0.7 [17, 23-25]. Doses close to 1.0 IU/kg/wk increased ΔhSDST by 0.7-1.2 in the first year of treatment [16, 26, 27]. In the study protocols using higher than 1.0 IU/kg/wk doses no statistically significant changes in growth velocities in the first year of therapy (ΔhSDST was ~0.9) was noted [28]. At present most pediatric endocrinologists believe that beyond the maximal dose of approximately 1.0 IU/kg/wk, there is no significant improvement in growth velocity or improvement of the final height [29, 30].

Many studies documented that combination therapy of GH+Ox stimulated growth velocity better than GH therapy alone [24, 31-35]. However, the combination of GH+E does not always enhance growth rates relative to GH alone [27, 36]. Beginning estrogen therapy too early enhances hSDST initially, however it may compromise the final height [37]. The combination of Ox+E also improves growth velocity, especially during the first year of therapy [38]. Polytherapy (GH+Ox±E) was found to improve height velocity relative to mono-therapy with GH, even when lower doses of GH are applied [37].

There is a substantial body of evidence that many regimens of therapy (mono-, combined-, and polytherapy) have improved growth rate in TS, particularly during the first year of treatment [16, 20, 24, 25, 28, 32, 36, 37]. The positive correlation between the number of GH injections (max of 7 times/wk) and the growth rate [15, 23, 39] as well as standard deviation of height was also documented [19].

The patients' nationality had substantial influence on height velocity as German and Swedish TS girls had significantly higher height velocities than TS patients from France, UK and Japan [24]. The age of the subjects was also investigated, with significantly better growth rates demonstrated in younger patients [17, 23, 27, 28, 31, 36, 40].

According to some clinicians, the greater the baseline growth retardation, the greater the height velocity during the first year of therapy [28]. Better therapeutic responses were also recorded with greater BA retardation, which has been expressed as growth rate improvement [36, 40] and as increase of standard deviation height values [27, 28, 41]. On the other side the karyotype had no impact on growth rate or standard deviation of height values [24].

All the girls in this study were Caucasian and of Polish origin. The therapeutic results confirmed the data of the recent literature reviews. The height improvement by means of GH+Ox treatment was better than seen in other groups. However height improvement were also achieved in the other groups in the first year of therapy. In the second year only GH+Ox and GH therapy provided significant improvements in hSDS relative to untreated patients. The most improved growth rates were noted in the first year of therapy in all groups (except for a tendency towards significance in GH+Ox+E).

Improvement in hSDST in all our study groups was similar to previous studies on hormone therapy. In contrast to other authors [17, 23, 27, 28, 31, 36, 40], the younger patients in our study did not show better improvements in height than the older patients. We were also unable to find the relation between the baseline height and the degree of BA retardation and height improvement.

**Influence of different types of hormone therapy on bone age progression.**

Ranke developed a model for the natural progression of growth in girls with TS and described four

stages, which differ in growth rate and BA evolution. These two variables are closely related to stages II and IV of spontaneous growth, which corresponds to the development before 3 and after 12 years of age [12, 42]. The lower BA progression during this age period, the more significant was BA retardation. BA progression was unaffected by endogenous GH secretion [26]. With only a few exceptions [26], the research data confirm that hormone therapy increases BA progression. However higher doses of GH had no further influence on BA progression [17, 22].

More pronounced BA progression during therapy was documented in the patients who were initially treated with estrogens (together with GH and Ox) [37], those in whom estrogen therapy was started prior to GH administration [43] and those in whom estrogen therapy was started in the younger age [39, 44]. Bone age progression was also noted in younger girls receiving only GH, as compared to the older girls treated by the combination therapy regimen (GH+E). It was therefore argued that estrogen therapy should be used only after BA reaches 11 years [44]. Even smaller doses of estrogens, which did not accelerate BA during the first year of therapy, could have negative impact on BA progression during the second year of treatment [36]. Some authors found BA progression more pronounced with combination therapy (e.g., GH+Ox) as compared to monotherapy (e.g., GH or Ox), especially during the first year of treatment [34].

Several studies showed that the younger the age at the initiation of therapy the higher rates of BA progression [16, 23, 27, 28, 32, 36, 37, 44]. Bone age progression was proportional to baseline bone age delay [16, 28]. Sas et al. found no differences between the patients treated with the stable GH dose or with progressively higher doses of GH [30]. In Van Teunenbroek et al. study there was a lack of correlation between the GH dose and BA progression [16].

In our patients before therapy BA was retarded. The average yearly BA progression before therapy was 0.8 year. BA progression was significantly increased with hormonal therapy. The highest BA progression was found in patients treated with GH only, and it was significantly different from BA progression in patients from Group 0 and Group GH+Ox. Only Group GH+Ox yielded a significant negative correlation between CA and BA progression. The youngest patient in Group GH+Ox had the greatest BA progression – similar to Group GH; and the oldest patients from Group GH+Ox were found to have the lowest BA progression – similar to Group 0. This indicates that baseline age, rather than the type of therapy, was the most influencing variable in BA progression for Group GH+Ox.

Bone age progression in Groups GH+Ox and 0 were not significantly different. Addition of estrogen to the therapy induced higher BA progression, and this rate was increased only slightly in Group Ox+E. Bone age delay in relation to CA did not have any influence on BA progression.

Presently, the greatest concern in girls with TS is a late diagnosis [45-47]. This is likely due to a non-specific or non-pathognomonic phenotype, as well as a lack of parental or sometimes physician's concern when characteristic clinical signs of TS are present. The most common reason for TS girls to visit their doctor is a short stature – usually about 20 cm below the average healthy peer.

There are ongoing discussions about the age of beginning of therapy to correct height deficits in girls with TS. Our study, as well as other studies data, show that beginning therapy too early may result in disproportionate BA progression.

## Conclusions

1. All regimens of hormone therapy improved height in girls with TS. The greatest improvement as well as the lowest bone age progression were seen in patients treated with growth hormone and oxandrolone.
2. Chronological age at which treatment was initiated had no influence on height improvement during therapy.
3. Bone age progression during hormone therapy was most pronounced in the younger patients.
4. A degree of bone age delay before therapy did not influenced height velocity or further bone age progression.

### References


1. Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Milunsky A, ed. Genetic disorders and the fetus. Baltimore: The John Hopkins University Press, 1998; 179-248.
2. Farias JL, Davenport ML. Health supervision for children with Turner syndrome. Pediatrics 2003; 111: 692-702.
3. Saenger P, Albertsson Wikland K, Conway GS, Davenport M, Gravholt CH, Hintz R, Hovatta O, Hultcrantz M, Landin-Wilhelmsen K, Lin A, Lippe B, Pasquino AM, Ranke MB, Rosenfeld R, Silberbach M. Recommendation for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metab 2001; 86: 3061-3069.
4. Albertsson-Wikland K, Rosberg S. Pattern of spontaneous growth hormone secretion in Turner syndrome. In: Ranke MB, Rosenfeld RG, eds. Turner syndrome: growth promoting therapies. Proceedings of the 2nd International Symposium on Turner syndrome, Frankfurt / Main. Amsterdam: Excerpta Medica, 1991: 23-28.
5. Blethen SL, Albertsson-Wikland K, Faklis E, Chsalow F. Circulating growth hormone isoforms in girls with Turner's syndrome. J Clin Endocrinol Metab 1994; 78: 1439-1443.
6. Massarano AA, Brook CGD, Hindmarsh PC, Pringle PJ, Teale JD, Stanhope R, Preece MA. Growth hormone secretion in Turner's syndrome and influence of oxandrolone and ethinyl oestradiol. Arch Dis Child 1989; 64: 587-592.
7. Ross JL, Long LM, Loriaux DL, Cutler GBJr. Growth hormone secretory dynamics in Turner syndrome. J Pediatr 1985; 106: 202-206.

8. Hochberg Z, Pollack S, Aviram M. Resistance to insulin-like growth factor 1 in Turner syndrome. In: Hibi I, Takano K, eds. Basic and clinical approach to Turner syndrome. Proceedings of the 3rd International Symposium on Turner Syndrome, Chiba, Japan, 8-10 July 1992. Amsterdam: Excerpta Medica, 1993: 233-237.
9. Escamilla RF, Hutchings JJ, Deamer WC, Li CH. Clinical experiences with human growth hormone (LI) in pituitary infantilism and in gonadal dysgenesis. Acta Endocrinol 1960; 35 (Suppl 51): 253 (Abstr).
10. Kurniewicz-Witczakowa R, Mięsowicz I, Niedźwiecka Z, Pietrzak M. Growth chart for Warsaw girls. Instytut Matki i Dziecka. Zakład Rozwoju Dzieci i Młodzieży. Warszawa 1980.
11. Gerver WJM, de Bruin R. Paediatric Morphometrics. A Reference Manual. Utrecht, the Netherlands: Wetenschappelijke uitgeverij Bunge 1996.
12. Ranke MB, Stubbe P, Majewski F, Bierich JR. Spontaneous growth in Turner's syndrome. Acta Paediatr Scan (Suppl.) 1988; 343: 22-30.
13. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. Stanford, California: Stanford University Press 1952.
14. Carel J-C, Mathivon L, Gendrel C, Ducret J- P, Chaussain J-L. Near normalization of final height with adapted doses of growth hormone in Turner's syndrome. J Clin Endocrinol Metab 1998; 83: 1462-1466.
15. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price AD. Prediction of long-term response to recombinant humane growth hormone in Turner syndrome: development and validation of mathematical models. J Clin Endocrinol Metab 2000; 85: 4212-4218.
16. Van Teunenbroek A, de Muinck Keizer-Schrama SMPF, Stijnen T, Jansen M, Otten JB, Delemarre-van de Waal HA, Vulsma T, Wit JM, Rouwe CW, Reeser HM, Gosen JJ, Rongen-Westerlaken C, Drop SLS. Yearly stepwise increments of the growth hormone dose results in a better growth response after four years in girls with Turner syndrome. J Clin Endocrinol Metab 1996; 81: 4013-4021.
17. Bertrand AM, Chaussain JL, Job B, Mariani R, Ponte C, Rappaport R, Rochiccioli P, Chatelain P on behalf of the French Pediatric Clinics and Sanofi-Winthrop (France). Three years of GH treatment in Turner's syndrome: complex effect of GH dosage on growth parameters. Clin Endocrinol 1996; 44: 665-671.
18. Betts PR, Butler GE, Donaldson MDC, Dunger DB, Johnston DI, Kelnar CJH, Kirk J, Price DA, Wilton P, the UK KIGS Executive Group on behalf of the participating centres. A decade of growth hormone treatment in girls with Turner syndrome in the UK. Arch Dis Child 1999; 80: 221-225.
19. Ranke MB, Guilbaud O, Lindberg A, Cole T on behalf of the International Board of the Kabi Pharmacia International Growth Study. Prediction of the growth response in children with various growth disorders treated with growth hormone: analyses of data from the Kabi Pharmacia Internationl Growth Study. Acta Paediatr Suppl 1993; 391: 82-88.
20. Takano K, Ogawa M, Tanaka T, Tachibana K, Fujita K, Hizuka N and the Members of 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; 137: 138-145.
21. van Pareren YK, de Muinck Keizer-Schrama SMPF, Stijnen T, Sas TCJ, Jansen M, Otten BJ, Hoorweg-Nijman JJG, Vulsma T, Stokvis-Brantsma WH, Rouve CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SLS. Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab 2003; 88: 1119-1125.
22. Haeusler G, Frisch H, Schmitt K, Blümel P, Plöchl E, Zachmann M, Waldhör T. Treatment of patients with Ullrich-Turner syndrome with conventional doses of growth hormone and the combination with testosterone or oxandrolone: effect on growth, IGF-1 and IGFBP-3 concentrations. Eur J Pediatr 1995; 154: 437-444.
23. De Schepper J, Craen M, Massa G, Heinrichs C, Meas M, du Caju M, Rausin L, Bourguignon JP. Growth hormone therapy in Turner's syndrome: one versus two daily injections. J Clin Endocrinol Metab 1994; 79: 489-494.
24. Price DA, Albertson-Wikland K on behalf of the International Board of the Kabi Pharmacia International Growth Study. Demography, auxology and response to recombinant human growth hormone treatment in girls with Turner's syndrome in the Kabi Pharmacia International Growth Study. Acta Paediatr Suppl 1993; 391: 69-74.
25. Schweizer R, Ranke MB, Binder G, Herdach F, Zapadlo M, Grauer ML, Schwarze CP, Wollmann HA. Experience with growth hormone therapy in Turner syndrome in a single centre: low total height gain, no further gains after puberty onset and unchanged body proportions. Horm Res 2000; 53: 228-238.
26. Massa G, Vanderschueren-Lodeweyckx M, Craen M, Vandeweghe M, van Vliet G. Growth hormone treatment of Turner syndrome patients with insufficiency growth hormone response to pharmacological stimulation tests. Eur J Pediatr 1991; 150: 460-463.
27. Vanderschueren-Lodeweyckx M, Massa G, Maes M, Craen M, van Vliet G, Heinrichs C, Malvaux P. Growth-promoting effect of growth hormone and low dose ethinyl estradiol in girls with Turner's syndrome. J Clin Endocrinol Metab 1990; 70 (1): 122-126.
28. Van Teunenbroek A, de Muinck Keizer-Schrama S, Stijnen T, Waelkens J, Wit J. M, Vulsma T, Gerver WJ, Reeser H, Delemarre-van de Waal H, Jansen M, Drop S (Dutch Working Group on Growth Hormone). Growth response and levels of growth factors after two years growth hormone treatment are similar for a once and twice daily injection in girls with Turner syndrome. Clin Endocrinol 1997; 46: 451-459.
29. 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: 147-149.
30. Sas TCJ, de Muinck Keizer-Schrama SMPF, Stijnen Th, Jansen M, Otten BJ, Hoorweg-Nijman JJG, Vulsma T, Massa GG, Rouwe CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SLS. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. J Clin Endocrinol Metab 1999; 84: 4607-4612.
31. Haeusler G, Schmitt K, Blümel P, Plöchl E, Waldhör T, Frisch H. Growth hormone in combination with anabolic steroids in patients with Turner syndrome: effect on bone maturation and final height. Acta Paediatr 1996; 85: 1408-1414.
32. Joss EE, Mullis PE, Werder EA, Partsch CJ, Sippell WG. Growth promoting and Turner-specific bone age after therapy with growth hormone and in combination with oxandrolone: when should therapy be started in Turner syndrome? Horm Res 1997; 47: 102-109.
33. Rosenfeld RG, Frane J, Attie KM, Brasel JA, Burstein S, Cara JF, Chernausek S, Gotlin RW, Kuntze J, Lippe BM, Mahoney PC, Moore WV, Saenger P, Johanson AJ. Six-year results of a randomized, prospective trial of human growth hormone and oxnadrolone in Turner syndrome. J Pediatr 1992; 121: 49-55.
34. Rosenfeld RG, Hintz RL, Johanson AJ, Brasel JA, Burstein S, Chernausek SD, Clabots T, Frane J, Gotlin RW, Kuntze J, Lippe BM, Mahoney PC, Moore WV, New MI, Saenger P, Stoner E, Sybert V. Methionyl human growth hormone and oxandrolone in Turner syndrome: Preliminary results of a prospective randomized trial. J Pediatr 1986; 109: 936-943.
35. Rosenfeld RG, Hintz RL, Johanson AJ, Sherman B, Brasel JA, Burstein S, Chernausek S, Compton P, Frane J, Gotlin RW, Kuntze J, Lippe BM, Mahoney PC, Moore WV, New MI, Saenger P, Sybert V. Three-year results of a randomized prospective trial of methionyl human growth hormone and oxandrolone in Turner syndrome. J Pediatr 1988; 113: 393-400.
36. Massa G, Maes M, Heinrichs C, Vandeweghe M, Craen M, Vanderschueren-Lodeweyckx M. Influence of spontaneous

or induced puberty on the growth promoting effect of treatment with growth hormone in girls with Turner's syndrome. Clin Endocrinol 1993; 38: 253-260.
37. Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, Häger A, Ivarsson SA, Karlberg J, Kriström B, Marcus C, Moell C, Ritzen M, Tuvemo T, Wattsgard C, Westgren U, Westphal O, Aman J. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab 1996; 81: 635-640.
38. Bareille P, Massarano AA, Stanhope R. Final height outcome in girls with Turner syndrome treated with a combination of low dose oestrogen and oxandrolone. Eur J Pediatr 1997; 156: 358-362.
39. Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J and the Genentech, INC, Collaborative Study Group. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. J Clin Endocrinol Metab 2000; 85: 2439-2445.
40. Dacou-Voutetakis C, Karavanaki-Karanassiou K, Petrou V, Georgopoulos N, Maniati-Christidi M, Mavrou A. The growth pattern and final height of girls with Turner syndrome with and without human growth hormone treatment. Pediatrics 1998; 101: 663-668.
41. Plotnick L, Attie KM, Blethen SL, Sy JP. Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study Experience. Pediatrics 1998; 102: 479-481.
42. Ranke MB, Pflüger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, Majewski F. Turner syndrome: Spontaneous growth in 150 cases and review of the literature. Eur J Pediatr; 1983, 141: 81-88.
43. Johnston DI, Betts P, Dunger D, Barnes N, Swift PGF, Buckler JMH, Butler GE. A multicentre trial of recombinant growth hormone and low dose oestrogen in Turner syndrome: near final height analysis. Arch Dis Child 2001; 84: 76-81.
45. Massa GG, Vanderschueren-Lodeweyckx M. Age and height at diagnosis in Turner syndrome: influence of parental height. Pediatrics 1991; 88: 1148-1152.
44. Naeraa RW, Nielsen J, Kastrup KW. Growth hormone and 17β-oestradiol treatment of Turner girls - 2-year results. Eur J Pediatr 1994; 153: 72-77.
46. Partsch C-J, Raffenberg U, Sippell WG. Screening for Turner's syndrome by chromosome analysis of all girls with short stature. J Pediatr 2002; 140 (1): 140-141.
47. Sävendahl L, Davenport ML. Delayed diagnosis of Turner's syndrome: proposed guidelines for change. J Pediatr 2000; 137: 455-459.