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Menke, L.A.

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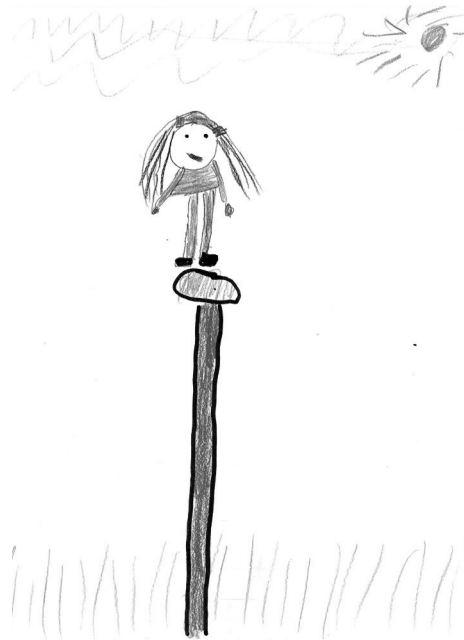
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The effect of oxandrolone on body proportions and body composition in growth hormone-treated girls with Turner syndrome



Leonie A. Menke, Theo C.J. Sas, Gladys R.J. Zandwijken, Maria A.J. de Ridder, Theo Stijnen, Sabine M.P.F. de Muinck Keizer-Schrama, Barto J. Otten, Jan M. Wit

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Summary

Objective Untreated girls with Turner syndrome (TS) have short stature, relatively broad shoulders, a broad pelvis, short legs, a high fat mass, and low muscle mass. Our objective was to assess the effect of the weak androgen oxandrolone (Ox) on body proportions and composition in growth hormone (GH)-treated girls with TS.

Design/Patients 133 patients were included in a randomised, placebo-controlled, double-blind study.

Methods Patients were treated with GH (1.33mg/m²/day) from baseline, combined with placebo (Pl) or Ox in a low (0.03mg/kg/day) or previously conventional (0.06mg/kg/day) dose from the age of eight, and oestrogens from the age of twelve. Sitting height, biacromial and biiliacal distances compared with height (i.e. shape values), BMI, waist circumference, sum of 4 skinfolds (sum4skin), and upper arm muscle area (UAMA) SD scores (SDS) were assessed half-yearly.

Results Compared with GH+Pl, adult shape values on GH+Ox tended to be higher for sitting height (Ox0.03, P=0.2; Ox0.06, P=0.02) and biacromial distance (Ox0.03, P=0.2; Ox0.06, P=0.07), and lower for biiliacal distance (Ox0.03, P=0.004; Ox0.06, P=0.08). Sum4skin SDS tended to decrease more (Ox0.03, P=0.2; Ox0.06, P=0.005), while UAMA SDS increased more (Ox0.03, P<0.001; Ox0.06, P<0.001) than on GH+Pl. The increase in BMI and waist circumference SDS was comparable between the dosage groups.

Conclusions In GH-treated girls with TS, Ox 0.06 increases sitting height and tends to increase biacromial distance and decrease biiliacal distance, while Ox 0.03 significantly decreases biiliacal distance compared with height. Furthermore, Ox 0.06 reduces subcutaneous fat mass, and both Ox dosages increase muscle mass.

Introduction

Untreated girls with Turner syndrome (TS) have a reduced height, broad shoulders, a broad pelvis, and relatively short legs.^{1,2} Growth hormone (GH) therapy somewhat improves the disproportion between sitting height and legs, but higher GH dosages may also slightly increase the size of the feet compared with the height.¹ Patients with TS also have a profoundly altered body composition, with a relatively high fat mass and low skeletal muscle mass.³ Although GH therapy lowers fat mass and increases lean body mass, fat mass remains higher than in healthy individuals.⁴ The effect of oxandrolone (Ox) on body proportions and body composition in girls with TS is still unclear. Studies in other patient groups indicate that Ox may strongly reduce fat mass and increase muscle mass.⁵⁻⁷

To assess the effect of Ox in a low (0.03 mg/kg/day) and a previously conventional dosage (0.06 mg/kg/day) in GH-treated girls with TS we conducted a randomised, placebo-controlled, double-blind study. In a previous report, we showed that the addition of Ox 0.03 to GH moderately increases adult height gain (adult height minus predicted adult height), whereas Ox 0.06 does not significantly increase adult height gain.⁸ In the present article, we describe the effects of Ox on body proportions and body composition.

Patients and methods

Study setting and participants

Participants were recruited in ten pediatric endocrine centers in the Netherlands from December 1991 to June 2003. Inclusion criteria were a karyotype associated with TS (except for cytogenetical evidence of Y-chromosomal material); a calendar age between 2.00 and 15.99 years; and a bone age younger than 12.00 years.⁹ Exclusion criteria were growth failure due to other causes; use of drugs that could interfere with growth; and previous GH, sex hormone, or androgen therapy. The study was performed in accordance with the World Medical Association Declaration of Helsinki and approved by the ethics committee of each participating centre. Before enrolment, written informed consent was obtained for each patient.

Treatment

Patients were included in age group 1 (2.00-7.99 years), 2 (8.00-11.99 years), or 3 (12.00-15.99 years). After stratification for calendar age and height SD score (SDS),¹⁰ they were randomised by a computer-generated schedule, and blindly assigned to receive, after reaching the age of 8 years Ox 0.03 mg/kg/day (Ox 0.03) (S.p.A., Milano, Italy), Ox 0.06 mg/kg/day (Ox 0.06), or a similar appearing placebo (PI) orally at bedtime. The capsules were manufactured and distributed by one hospital pharmacy. All patients and doctors were blinded for the allocation of the patients until the last patient finished the study. Only the independent pharmacist (Dr. C.M.A. Rademaker), the statistician (M.A.d.R.), and data analyst (L.A.M., from 2008 onwards) saw unblinded data, but none of them had any contact with the participants. From baseline onwards, biosynthetic human GH (1.33 mg/m² body-surface/day, at 1 m² equivalent to 46 µg/kg/day) was administered subcutaneously at bedtime: Genotropin[®] (Pfizer Inc, New York, NY) was used in age groups 1 and 2, and Humatrope[®] (Eli Lilly, Indianapolis, IN) in age group 3. Ox/PI was started at the age of eight after a number of complete years of GH therapy (i.e. at their 'year-visit') in age group 1, and at inclusion in age groups 2 and 3 (i.e. between the age of 8.0-16.0 years). In the absence of spontaneous puberty (Tanner breast stage < 2 (B2)¹¹), oestrogens were started at the age of 12.0-12.99 after a number of complete years of GH therapy in age groups 1 and 2, and at inclusion in age group 3 (i.e. between the age of 12.0-16.0 years). 17-β-estradiol was prescribed in age groups 1 and 2, and ethinyl-estradiol in age group 3 (5 and 0.05 µg/kg/day orally, increased to 10 and 0.1 µg/kg/day after two years, respectively). When ethinyl-estradiol became unavailable after March 2002, 17-β-estradiol was also prescribed in age group 3. Cyclic progesterone was added after at least two years of oestrogen therapy. Doses were adjusted every six months, and GH+Ox/PI were stopped when height velocity was less than 1 cm per six months, or when patients decided to stop because they were satisfied with their height.

Assessments

Two trained observers performed all measurements during the total duration of the study. Measurements were taken half-yearly from baseline until six months after

discontinuing GH+Ox/PI therapy. Height and sitting height were obtained using a Harpenden stadiometer and a sitting height table, and biacromial and biiliacal distances were obtained with a Harpenden anthropometer. All measurements were taken according to the procedures described by Cameron.¹² Height was measured four times per visit, sitting height was measured twice and biacromial and biiliacal distances three times per visit. The mean of each measure was expressed as SDS for age and sex using the data of the Dutch Oosterwolde study¹³ that had been transformed to LMS-parameters. The LMS method (L stands for lambda, M for mean, and S for standard deviation) transforms the reference data at each age to a Gaussian distribution.¹⁴ To prevent adult body proportions from being overestimated in patients that stopped growing at an earlier age than the reference group, reference data for the age of 18 rather than the actual age were used in calculating adult SDS. Similarly, adult subischial leg length (height minus sitting height) SDS was calculated using reference data for the age of 21 from the Dutch Nation-Wide Survey.¹⁵ To adjust for height SDS, shape values were calculated using the formula (*e.g.* for sitting height): sitting height shape value = (sitting height SDS - height SDS) / $\sqrt{(2 - 2r)}$, in which *r* is the correlation coefficient between height and sitting height in the reference population.¹⁶ Values above 2 and below -2 were considered outside the normal range. Shape values from our study were compared with previously reported values of untreated adult women with TS (aged 35.7±9.3 years).²

Body weight was measured on an electronic scale, with the patient in underwear and barefooted. Body mass index (BMI) was calculated as weight(kg) divided by height(m) squared. Waist circumference was measured in the standing position, midway between the lowest rib and the iliac crest using a non-extensible measure tape. Mid upper arm circumference (MUAC) was measured midway between the tip of the acromion and olecranon process with the left arm hanging relaxed. Skinfold thickness was measured three times with a Harpenden skinfold caliper at four sites on the left side of the body: biceps and triceps skinfolds in the biceps and triceps region, respectively, midway between elbow and shoulder; the subscapular skinfold at the lower tip of the scapula; and the supra-iliacal skinfold over the iliac crest. The mean of each skinfold was used for calculating the sum of the four skinfolds (sum4skin). The upper arm muscle area (UAMA) was computed using the equation

of Frisancho: $UAMA = ((MUAC - \pi \times \text{triceps skinfold thickness}) \times (MUAC - \pi \times \text{triceps})) / 4\pi$.¹⁷ BMI,¹⁸ waist circumference,¹⁹ sum4skin,¹³ and UAMA¹⁷ were expressed as SDS for age and sex using Dutch references. Reference values were transformed to LMS-parameters before calculating sum4skin SDS and UAMA SDS.¹⁴

All adverse events reported by the patient, parent, or medical doctor concerning muscularity and broadening of the shoulders and/or thorax were noted.

Statistical analysis

We performed a modified intention-to-treat analysis in which patients who refused to start Ox/PI therapy were excluded. When Ox/PI was discontinued before GH, the moment GH was discontinued was identified as 'at discontinuing GH+Ox/PI'. 'At the last measurement' was defined as the most recent visit, at or after discontinuing GH+Ox/PI, at which parameters were measured. Means were compared with zero by a one-sample t test, and with pre-treatment values by a paired t test. Differences between the dosage groups for measurements at one time-point (i.e. adult body proportion parameters corrected for values at baseline) were tested by linear regression using two dummies (for GH+Ox 0.03 and GH+Ox 0.06). Differences in change of outcome variables during the study period (i.e. body composition parameters) were assessed by repeated measurements analysis using linear mixed models with a random intercept and slope per patient. To assess whether the effects were comparable between the three age groups, interaction terms between the age groups and dosage groups were used.

Results

Characteristics of the patients

Fig. 1 shows the 133 patients that were randomised. Four patients were lost to follow-up, nine were still treated when the analysis started, and the parents of eight girls refused to start Ox/PI therapy. Leaving out these patients, 112 patients were left for the analysis. Table 1 shows the baseline characteristics, which were similar between the three dosage groups.

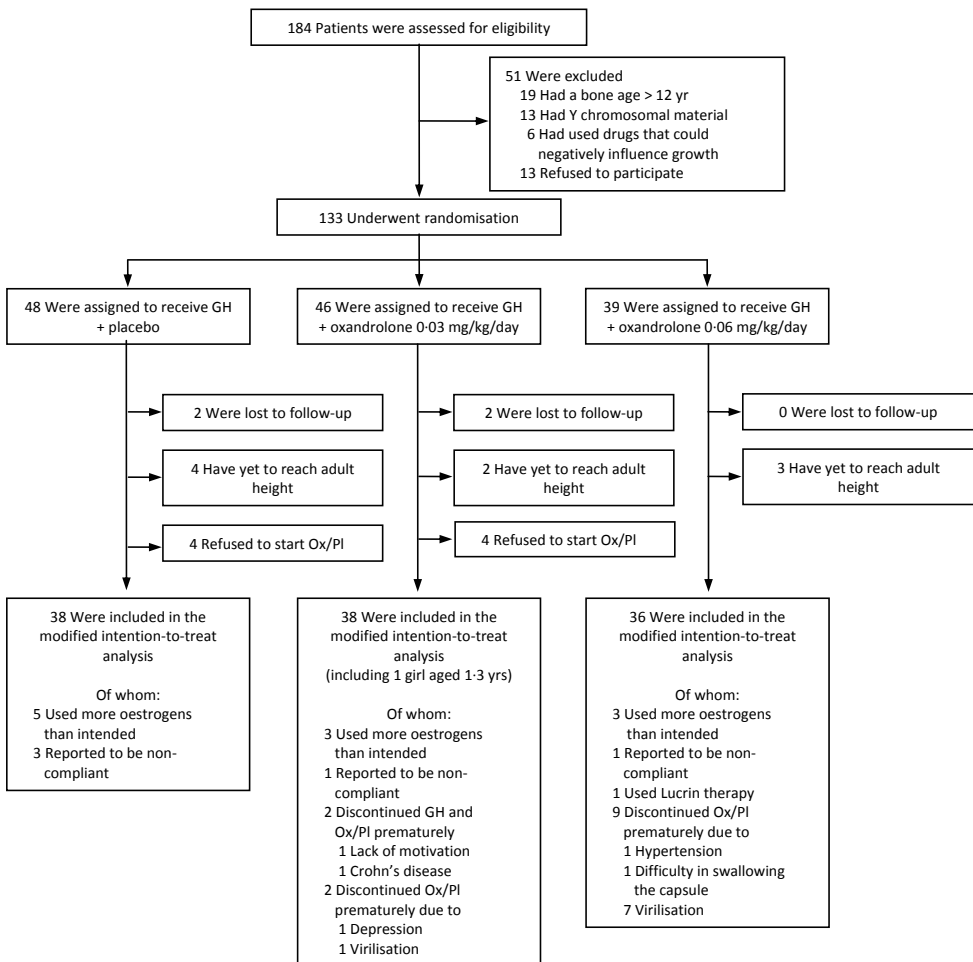


Figure 1. Enrollment, randomisation and analysis of the patients.

GH, growth hormone; Ox/PI, oxandrolone/placebo; IGT, impaired glucose tolerance.

Table 1. Characteristics and treatment per dosage group.*

Characteristic	GH+PI (n =38)	GH+Ox 0.03 (n =38)	GH+Ox 0.06 (n =36)
Age at starting GH – yr	9.7±3.8	9.0±3.8	9.1±3.5
Height at starting GH – SDS [†]	-2.9±0.7	-2.9±0.6	-2.9±0.7
Age at starting Ox/PI – yr¶	10.9±2.3	10.2±2.5	10.2±2.2
Karyotype, 45,X – no. (%)	21 (55)	14 (37)	16 (44)
Karyotype, other – no. (%)	17 (45)	24 (63)	20 (56)
Puberty developed spontaneously – no. (%)	9 (24)	8 (21)	9 (25)
Duration of GH therapy – yrs	6.1±3.1	6.2±2.9	5.8±2.8
Duration of Ox/PI therapy – yrs	5.0±1.5	4.8±1.6	4.2±1.7
Age at discontinuation of GH+Ox/PI – yr	15.8±1.2	15.2±1.5	14.9±1.3
Age at last visit – yr	17.8±1.4	17.0±1.5	17.0±1.2

* Values are expressed as means ±SD, unless otherwise indicated.

† Height SDS was calculated using Dutch references.

¶ 'At starting Ox/PI' denotes at baseline for age group 2 and 3, and a full number of years after starting GH therapy for age group 1 (between the ages of 8 and 9).

Body proportions

Fig. 2 shows body proportion SDS, and Fig. 3 shows body proportion shape values before, during, and after therapy. At baseline, height SDS, sitting height SDS, and biacromial and biliacal distance SDS were significantly lower than zero ($P<0.001$ for all comparisons) (Fig. 2), whereas the body proportion shape values (i.e. values compared with height) were significantly higher than zero ($P<0.001$ for all comparisons) (Fig. 3).

Sitting height shape values decreased significantly during Ox/PI therapy ($P<0.001$) (Fig. 3) and became comparable with adult values in untreated women with TS. Compared with GH+PI, and corrected for values at starting Ox/PI, mean adult values were higher on GH+Ox 0.06 ($P=0.02$), but comparable on Ox 0.03 ($P=0.2$) (Fig.3). Mean adult leg length SDS was similar between the dosage groups (PI, $-2.2±0.7$; Ox 0.03, $-2.1±1.0$, $P=1.0$; Ox 0.06, $-2.2±0.7$, $P=0.5$).

The mean biacromial shape value did not change significantly during GH+Ox/PI ($P=0.4$) (Fig. 3). The mean adult value, however, tended to be higher on GH+Ox 0.06 than on GH+PI (corrected for values at starting Ox/PI: Ox 0.03, $P=0.2$; Ox 0.06, $P=0.07$) (Fig. 3). Biliacal distance shape values increased between starting Ox/PI therapy

and the last measurement ($P<0.001$) (Fig 3). Compared with GH+PI, the mean adult biliacal distance shape value was significantly lower on GH+Ox 0.03, and tended to be lower on GH+Ox 0.06 (corrected for values at starting Ox/PI, $P=0.004$ and $P=0.08$, respectively) (Fig. 3).

During Ox/PI therapy, a broadening of the shoulders and/or thorax was reported in one, three, and one patient on GH+PI, GH+Ox 0.03, GH+Ox 0.06, respectively. One patient on Ox 0.03 and one on Ox 0.06 mentioned this complaint as one of the virilizing side effects because of which she discontinued Ox.

Among the three age groups, no differences were found in the effect of GH+Ox vs. GH+PI on the shape values.

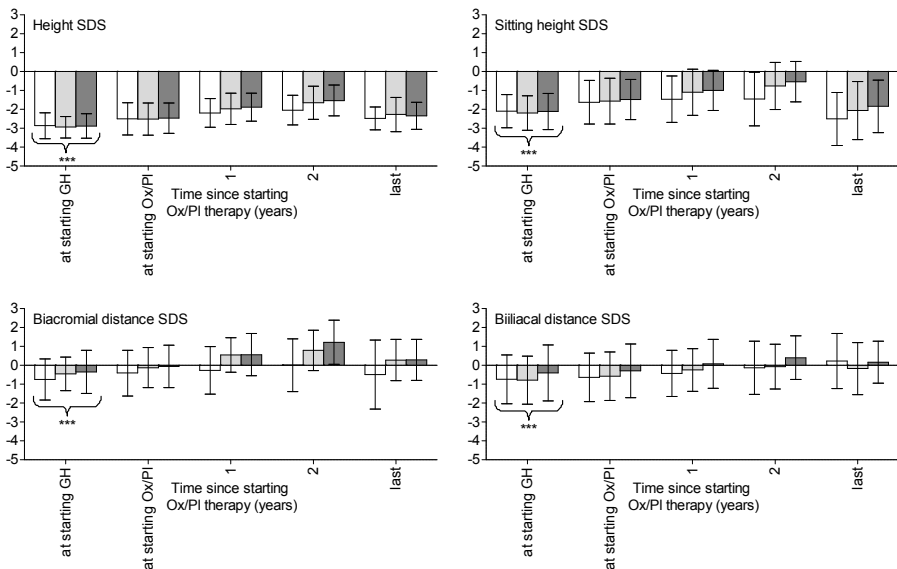


Figure 2. Mean±SD body proportions during the study on GH+PI (white bars), GH+Ox 0.03 (light grey bars), and GH+Ox 0.06 (dark grey bars).

Note that reference values for 18 year old girls were used to calculate the SDS of the last measurements. 'At starting Ox/PI' denotes at baseline for age group 2 and 3, and a full number of years after starting GH therapy for age group 1 (between the ages of 8 and 9) ; 'at starting GH', at baseline for age group 1, 2, and 3; ***, $P<0.001$, compared with 0 SDS.

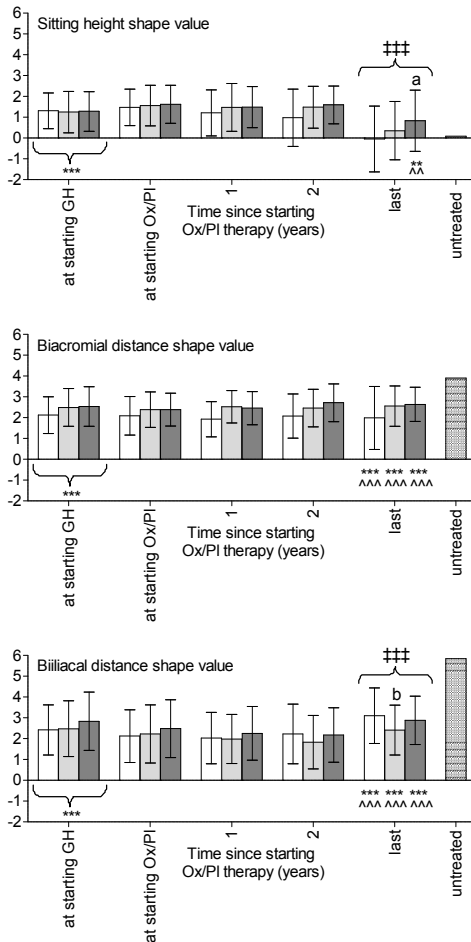


Figure 3. Mean±SD shape values on GH+PI (white bars), GH+Ox 0.03 (light grey bars), GH+Ox 0.06 (dark grey bars), and untreated women with TS (striped bars).

Note that reference values for 18 year old girls were used to calculate the SDS of the last measurements. 'At starting GH' denotes at baseline for age group 1, 2, and 3; 'at starting Ox/PI', at baseline for age group 2 and 3, and a full number of years after starting GH therapy for age group 1; **, P<0.01, ***, P<0.001, compared with 0 SDS; ###, P<0.001, compared with values at starting Ox/PI therapy; ^^, P<0.01, ^^, P< 0.001, compared with untreated adult patients with TS; a, P<0.05, b, P<0.01, compared with GH+PI (corrected for values at baseline).

Body composition

Fig. 4 shows body composition SDS before, during, and after therapy. At baseline, mean BMI SDS was significantly higher than zero ($P=0.004$), while mean waist circumference SDS was significantly lower than zero ($P=0.001$). During Ox/PI therapy, both measures increased ($P<0.001$ for both comparisons), without any significant differences between the three dosage groups (Fig. 4). At discontinuing GH+Ox/PI, mean BMI SDS and waist circumference SDS were higher than zero in each dosage group ($P<0.002$ for all comparisons) (Fig.4). After discontinuing GH+Ox/PI, both measures did not change significantly.

At baseline, mean sum4skin SDS was significantly higher than zero ($P<0.001$) (Fig. 4). The decrease during Ox/PI therapy was greater on GH+Ox than on GH+PI (GH+Ox 0.03, $P=0.2$; GH+Ox 0.06, $P=0.005$), leading to a mean value at discontinuing therapy that was significantly lower than zero on GH+Ox 0.06 ($P=0.001$) (Fig. 4). After discontinuing GH+Ox/PI, mean sum4skin SDS increased ($P<0.001$), and differences between the dosage groups were not significant anymore.

Baseline mean upper arm muscle area (UAMA) SDS was lower than zero ($P<0.001$), but values increased significantly during GH+Ox/PI therapy ($P<0.001$) (Fig. 4). The increase was greater on GH+Ox than on GH+PI (Ox 0.03, $P=0.002$; Ox 0.06, $P=0.009$), resulting in mean values that were higher than on GH+PI ($P=0.006$ and $P<0.001$, respectively) and higher than zero ($P<0.001$ for both comparisons) at discontinuing therapy (Fig. 4). During Ox/PI therapy, an increase in muscularity was reported by 1, 5, and 6 patients on GH+PI, GH+Ox 0.03, GH+Ox 0.06, respectively. After discontinuing GH+Ox/PI, mean UAMA SDS decreased ($P=0.009$), and differences between the dosage groups were not significant anymore.

The greater decrease of sum4skinSDS on GH+Ox 0.06 vs. GH+PI was smaller in age group 3 than in age groups 1 and 2 ($P<0.001$). For the other body composition measures, no differences were found in the effect of GH+Ox vs. GH+PI among the three age groups.

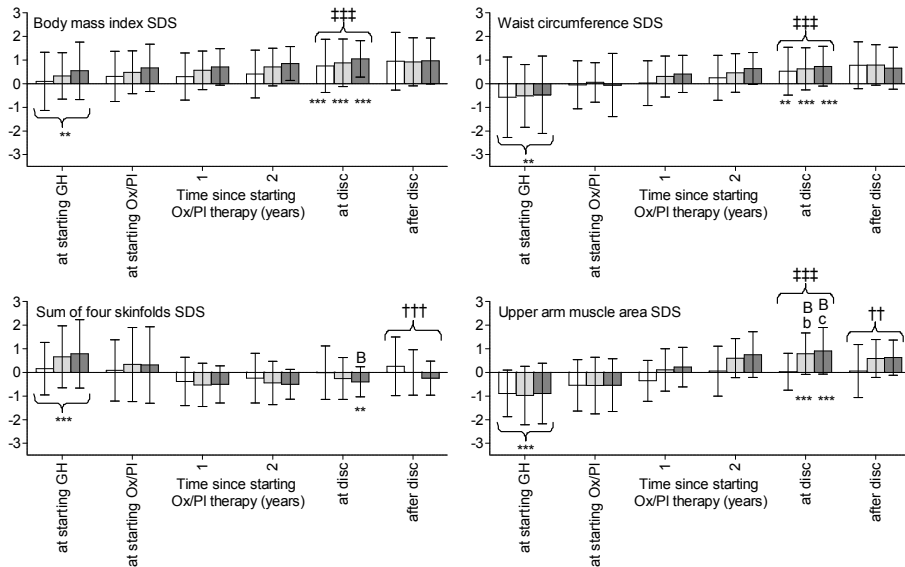


Figure 4. Mean±SD body composition on GH+PI (white bars), GH+Ox 0.03 (light grey bars), and GH+Ox 0.06 (dark grey bars).

Body composition measures were taken until 6 months after discontinuing GH+Ox/PI. 'At starting GH', at baseline for age group 1, 2, and 3; 'at starting Ox/PI', at baseline for age group 2 and 3, and a full number of years after starting GH therapy for age group 1; **, $P < 0.01$, ***, $P < 0.001$, compared with 0 SDS; ###, $P < 0.001$, compared with values at starting Ox/PI therapy; B, $P < 0.01$, mean change during Ox/PI therapy compared with that on GH+PI; b, $P < 0.01$, c, $P < 0.001$, mean value at last measurement compared with that on GH+PI; ††, $P < 0.01$, †††, $P < 0.001$, change after discontinuing GH+Ox/PI.

Discussion

This randomised, placebo-controlled, double-blind study shows that Ox at a low (0.03 mg/kg/day) and previously conventional (0.06 mg/kg/day) dosage influences body proportions and composition in GH-treated girls with TS. Ox 0.06 increases sitting height and Ox 0.03 decreases biliacal distance compared with height. In addition, Ox 0.06 reduces subcutaneous fat mass, and both Ox dosages increase muscle mass. BMI and waist circumference are not influenced by the addition of Ox.

At baseline, height, sitting height, and biacromial and biliacal distances were significantly smaller than in healthy girls, reflecting the stunted growth in both the linear and the horizontal body axis in untreated girls with TS.^{1,2} Height SDS was lower than sitting height SDS, and lower than biliacal and biacromial SDS, which is in line with the impression that untreated patients have a relatively stocky figure, with short lower extremities and a relatively broad thorax.^{1,2} Haploinsufficiency of the Short stature Homeobox-containing (SHOX) gene, regarded as the main cause of the short stature in TS,²⁰ may also partly explain some of these disproportions.²¹ Previous reports have shown that GH therapy increases height in girls with TS, and moderately decreases the disproportion between sitting height and height. GH did not seem to affect shoulder and biliacal distances, but higher GH dosages may increase the size of the feet compared with the height.^{1,22} Present data show that the addition of Ox to GH therapy further influences the body proportions. We showed that Ox 0.06 increased adult sitting height compared with height, while it did not significantly influence adult subischial leg length. This may indicate that the addition of Ox to GH does not so much affect growth in the legs, but increases growth especially in the trunk. Oxandrolone 0.03 had no significant effect on sitting height shape value.

Whereas mean biacromial distance shape value somewhat decreased on GH+PI, it somewhat increased on GH+Ox 0.03 and 0.06, resulting in adult values that tended to be greater on GH+Ox 0.06 than on GH+PI. Adult shape values however remained much lower than in untreated adult patients. In contrast, the adult biliacal distance shape value was lower on GH+Ox 0.03, and tended to be lower on GH+Ox 0.06 than on GH+PI. These findings indicate that Ox therapy may increase biacromial distance and reduce biliacal distance shape value. This observation is in line with the changes in body shape in male adolescence (broadening of the shoulders, whereas the pelvis remains relatively small compared with height), which are ascribed to increased androgen secretion.²³ One should however bear in mind that the effect of Ox on biliacal distance may have been somewhat influenced by the decrease in subcutaneous fat on GH+Ox (see below). Because biliacal distances are increasingly difficult to measure with increasing subcutaneous fat mass,²² greater widths may have been incorrectly measured in some of the patients on GH+PI.

At baseline, subcutaneous fat mass was greater, while upper arm muscle area (UAMA) was smaller than in healthy girls. These data support previous findings that patients with TS have a profoundly altered body composition, with a high fat mass and a low skeletal muscle mass.³ GH was described to lower abdominal fat mass and increase muscle mass,⁴ and our data demonstrates that the addition of Ox to GH further alters body composition. We showed that during Ox/PI therapy subcutaneous fat mass decreased to a value that was even lower than those of healthy girls. The finding that the decrease was greater on GH+Ox 0.06 than on GH+PI confirms a previous suggestion that GH+Ox (0.1 mg/kg/day) decreased subcutaneous fat mass more than GH alone.²⁴

The addition of either Ox 0.03 or Ox 0.06 to GH strongly increased UAMA, resulting in mean values that were significantly higher than in healthy girls. These data are in line with a previous comment that 'almost all patients became more muscular' on Ox (0.07-0.26 mg/kg/day),²⁵ and with similar findings in other patient groups.⁵⁻⁷ Ox therapy is thought to promote muscle anabolism by increasing skeletal muscle protein synthesis, as well as by blocking glucocorticoid signalling.²⁶

Even though subcutaneous fat mass decreased during the study, BMI and waist circumference increased. We suggest that the increase in BMI was mainly caused by the increase in muscle mass, and that no differences between the dosage groups were found because the Ox-induced decrease in fat mass was compensated for by the increase in muscle mass.⁶ The mean waist circumference probably increased due to the increase in height, and shoulder and biiliacal distances during the study. Therefore, in our view, it is an inappropriate indicator for visceral adiposity in TS, and could not be used to detect the effect of Ox on visceral adiposity. Although in other patient groups, Ox reduced visceral adiposity, we can not draw conclusions at this point.²⁷

The finding that an increase in muscularity was noted by 12 patients implies that the change in UAMA was clinically noticeable. The increased muscularity was however never mentioned as one of the reasons to discontinue Ox, suggesting that these changes were not so inconvenient that patients decided to give up possible extra centimetres of height gain. In contrast, two out of five patients mentioned the increase in shoulder and/or thorax width as one of the reasons to discontinue

Ox prematurely. Whereas muscle mass decreases after discontinuing GH+Ox, the increase in biacromial distance compared with height is, of course, irreversible.

Since in GH-treated girls with TS Ox 0.06 increases sitting height and tends to increase biacromial distance compared with height, while it does not significantly increase adult height gain and does lead to virilisation,⁸ we believe that Ox 0.06 should not be used in GH-treated girls with TS, in spite of the theoretically favourable consequences of a decrease in subcutaneous fat mass. In contrast, because of the acceptable effects of the addition of Ox 0.03 on body proportions and body composition, in addition to the significant adult height gain and fairly good safety-profile (except for a small deceleration in breast development),⁸ we believe that in patients considering breast deceleration less important than the increment in height gain, Ox 0.03 mg/kg/day may be added to GH to increase height.

A limitation of the present study was that body composition was assessed by indirect measurements of fat and muscle mass instead of DEXA, CT-slice or MR scan. One should furthermore bear in mind that the algorithm to measure UAMA has been derived from studies of healthy girls and women, and has therefore not been validated for TS. In addition, lymphoedema (which may be present in TS) may have resulted in an overestimation of the skinfold measurements. We however think that any of these effects would be similar in the three dosage groups, and therefore would not influence our findings on the effect of GH+Ox vs. GH+Pl. Another limitation is that we did not assess lengths and breadths of the hands and feet. A previous study covering data on the first two years of Ox therapy, showed that Ox (at a dose of 0.1 mg/kg/day) increased hand and foot breadths, whereas it did not significantly increase hand and foot length compared with height.²⁷ Whether Ox 0.06 and 0.03 may have a similar (though smaller) effect on hand and foot breadths is, as far as we are aware, unknown.

We conclude that in GH-treated girls with TS, Ox 0.06 increases sitting height and tends to increase biacromial distance and decrease biiliacal distance, while Ox 0.03 significantly decreases biiliacal distance compared with height. Furthermore, Ox 0.06 reduces subcutaneous fat mass, and both Ox dosages increase muscle mass, resulting in a fat mass that is lower and muscle masses that are higher than in healthy girls, respectively. Whereas we consider the effects of Ox 0.03 on body proportions

and composition acceptable, we think that the effects of Ox 0.06 confirm that this dosage should not be prescribed in TS.

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Declaration of interest

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