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ORIGINAL ARTICLE

Growth hormone effect on body composition in Turner syndrome

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Abstract This study analyzes the body composition of young adult women with Turner syndrome (TS) either treated or not treated with recombinant human growth hormone (rhGH) and compares them with a group of healthy women. Fifty-two non-treated TS patients (23.0 ± 5.8 years), 30 treated with rhGH (21.5 ± 1.5 years), and 133 healthy young adult women (22.9 ± 3.2 years) were evaluated regarding height (*H*) and weight, body mass index (BMI), brachial perimeter and tricipital cutaneous fold (fat and lean areas at the arm), sitting height (SRH = sitting height/*H* × 100), leg length (leg/*H*), waist and hip circumferences (waist/hip), and bioimpedance (percentages of water, lean mass, and fat mass). Age at start of rhGH therapy varied from 7.8 to 15.1 years (10.0 ± 1.3 years), duration of treatment from 2.8 to 8.2 years (3.7 ± 1.5 years), and the mean dose was 0.42 mg/kg/w (from 0.32 to 0.50 mg/kg/w). Body composition (except height) did not differ between TS groups, but there were differences when compared to the control group: weight and sitting height were lower in TS patients; and BMI, SHR, and leg/*H* were higher. There was an association between all groups with regards to BMI, waist, SHR, and leg/*H*, but not in percentage of fat mass. SHR was positively correlated with BMI, waist, hip, and percentage of fat mass. This sample of TS patients (with and without rhGH therapy) did not differ in BMI or body composition. However, there were differences between patients with TS patients and normal healthy women. Regardless of rhGH therapy, TS patients should be monitored, particularly for sitting height, SHR, leg length, leg/*H*, and waist/hip.

Keywords Hypogonadism · Body weight · Human adipose tissue · Obesity · Waist circumference · Growth hormone

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Introduction

Turner syndrome (TS) is a well-known sex chromosome disorder that affects one in every 2,000 live born females [1]. In about 50% of cases, karyotype analysis of peripheral lymphocytes reveals the complete loss of one of the sex chromosomes (45, X), whereas the remaining patients display mosaicism and/or structural aberrations of sex chromosomes. TS is characterized by short stature, gonadal dysgenesis, webbed neck, high arched palate, cubitus valgus, short metacarpals, Madelung deformity, low-set ears, and other somatic stigmata [2, 3]. Short stature remains one of the most investigated characteristic of TS and is a feature that may be present during fetal development, as well as after birth [3]. Adult women with TS usually achieve a height 12–20 cm shorter than their control partners [4]. Gonadal dysgenesis is the main cause of absence of puberty, and the majority of patients need estrogen replacement therapy [5].

Obesity is a condition that may aggravate or lead to the development of diabetes mellitus (DM) or arterial hypertension, conditions that are frequently seen in patients with TS [6–8]. In TS patients, lean mass is decreased, while fat

mass and abdominal fat are increased [9, 10]. Elsheikh and Conway [11] studied 91 women with TS and concluded that they had an increased risk of developing cardiovascular disease due to the high prevalence of obesity and arterial hypertension. Body mass index (BMI) is increased with TS compared to a control groups, and increases with age, particularly after 9 years of age and even when recombinant human growth hormone (rhGH) therapy is used [12].

Some studies in different populations have reported that treatment with rhGH, depending on the dose and age at initiation of therapy [8–20], lead to an improved final height, as well as decreased total and visceral fat, and increased lean mass and bone mineral density, while glucose and insulin levels remain within the normal range [13, 14].

According to Delgado et al. [15], and Isojima et al. [16], weight, height, and BMI reference charts for normal healthy populations are inadequate for women with TS due to their significant height loss.

Thus, the aim of this study was to evaluate body composition variables in women with TS untreated or treated with rhGH, as well as to compare them with a group of adult healthy women.

Methods

Study population

Eighty-two female patients with a diagnosis of TS confirmed by lymphocyte chromosomal analysis were enrolled in this study. All patients were routinely followed at pediatric endocrinology clinics at Hospital of Clinics at State University of Campinas (UNICAMP), Campinas (SP, Brazil) and Hospital Sao Paulo at Federal University of Sao Paulo (UNIFESP/EPM), Sao Paulo (SP, Brazil). Inclusion criteria were final height attainment (growth velocity less than 0.5 cm/year), regular menses for at least 2 years, and normal thyroid function. Patients were assigned to one of three groups, as follows: Group A: non-treated TS patients ($n = 52$), Group B: TS patients treated with rhGH for at least 2 years ($n = 30$), and Group C: young adult healthy women ($n = 133$). Patients in Group C were recruited medical students, without a past medical history that would possibly interfere with growth. No patients had a history of medication use other than estrogens, rhGH, or thyroid hormone. The study protocol was approved by the Ethics Committee of the Faculty of Medical Sciences—UNICAMP, and registered under the number 166/2002. Written informed consent was obtained from all participants.

Ten of 52 (19%) TS patients with no rhGH use (Group A) underwent spontaneous puberty, and the remaining 42 (81%) received estrogen therapy for development of secondary sexual characters. Among TS patients treated with rhGH (Group B), 2 (7%) presented spontaneous puberty, and 28 (93%) required estrogen replacement therapy. At the time of evaluation, all 215 women had regular menses: 76 (47 from Group A and 29 from Group B) with estrogen and progesterone replacement therapy, and 139 (5 from Group A, 1 from Group B, and 133 from Group C) with no hormonal replacement therapy (Table 1).

Clinical evaluation

This was a cross-sectional study, with all clinical and anthropometric data being collected by a single evaluator. Karyotyping of TS patients was performed in peripheral blood lymphocytes with a minimal count of 50 methaphases. Regarding karyotype analysis, in Group A, chromosomal constitution showed: 25 (48%) patients with karyotype 45, X; 11 (21%) with structural aberration; 16 (31%) with mosaicism with no structural aberration; and in group B, 13 (40%) with 45, X; 12 (40%) with structural aberration; and 5 (17%) with mosaicism with no structural aberration.

The following clinical variables were analyzed: chronologic age (years); need for estrogen replacement therapy; positive history of hypothyroidism, and current thyroid function; and age at start of therapy, dose and, duration of rhGH administration.

All patients underwent anthropometric and body composition assessment, comprising weight (kg), standing height (cm), sitting height (cm), leg length (cm), brachial

Table 1 Puberty outcome and thyroid profile in 215 adult women: 82 with Turner syndrome (Group A = no treatment; Group B = rhGH therapy) and 133 healthy

	Group A $n = 52$ (%)	Group B $n = 30$ (%)	Group C $n = 133$ (%)
Spontaneous puberty	10 (19)	2 (7)	133 (100)
Estrogen therapy for puberty induction	42 (81)	28 (93)	0 (0)
Estrogen + progesterone for induction or normalization of menses	47 (90)	29 (97)	0 (0)
Hypothyroidism under therapy	25 (48)	5 (17)	0 (0)

perimeter (cm), and tricipital skinfold (in mm, with calculation of fat and lean areas at the arm in mm^2, according to Frisancho [17]); waist and hip circumferences (in cm), and the ratios leg length/standing height (Leg/*H*) (SHR = sitting height/standing height × 100) and waist/hip. Impedance measurements (for percentages of water, lean mass, and fat mass) were conducted by the same operator using an impedance plethysmograph that emitted an 800-μA, 50-kHz alternating current (BIA-101, RJL/Akern Systems, Clinton Township, MI, USA). Standard, pregelled surface electrodes were placed on the right hand and foot, and measurements were made with patients in the supine position according to the standard tetrapolar method [18]. Before each testing session, the external calibration of the analyzer was checked with a calibration circuit of known impedance value ($r = 470\ \Omega$, $X_c = 90\ \Omega$, 1% error). BMI was calculated as weight divided by height in meters squared (kg/m^2), and was analyzed in absolute values.

The following variables were considered for comparisons between TS patients: karyotype, requirement for estrogen replacement therapy, positive history of hypothyroidism, and age at start of treatment, duration, and dose of rhGH therapy.

Statistical analysis

Data were stored and analyzed in SPSS program for Windows (version 11.0). Initially, a descriptive analysis of data was performed, with calculation of means, standard deviation score (SDS) and 95% confidence interval. Chi-square, Mann–Whitney, and Pearson correlation tests were employed. The results were considered statistically significant if $P < 0.05$.

Results

There were no difference in anthropometric and body composition variables between non-treated TS patients (Group A) and TS patients who received rhGH replacement therapy (Group B), except for a higher standing height ($P = 0.05$) in Group B (Table 2). When non-treated TS patients were compared to the control group, there were differences in the following variables: weight ($P = 0.0001$); standing height ($P = 0.0001$), BMI ($P = 0.04$), sitting height ($P = 0.0001$), SHR ($P = 0.0001$); leg length ($P = 0.0001$), leg/*H* ($P = 0.0001$), waist ($P = 0.02$), hip ($P = 0.0001$), waist/hip ($P = 0.0001$), and lean mass/fat mass ($P = 0.05$) (Table 2).

Table 2 Anthropometric and body composition variables (mean ± SDS/[95% confidence interval]) of a sample of 215 adult women: 82 with Turner syndrome (Group A = no treatment; Group B = rhGH therapy) and 133 healthy

	Group A $n = 52$ Mean ± SDS [95% CI]	Group B $n = 30$ Mean ± SDS [95% CI]	Group C $n = 133$ Mean ± SDS [95% CI]	*P**		
				A vs. B	A vs. C	B vs. C
Weight (kg)	48.4 ± 10.4 [45.5–51.3]	49.7 ± 10.6 [44.7–54.6]	59.2 ± 9.2 [57.6–60.8]	0.06	**0.0001**	**0.0001**
Standing height (cm)	143.9 ± 5.0 [142.5–145.5]	146.2 ± 4.1 [144.7–147.8]	165.0 ± 5.7 [164.1–166.1]	**0.05**	**0.0001**	**0.0001**
BMI (kg/m^2)	23.2 ± 4.7 [21.9–24.6]	24.3 ± 4.6 [22.2–26.4]	21.6 ± 2.9 [21.1–22.2]	0.92	**0.03**	**0.04**
Sitting height (cm)	78.3 ± 3.6 [77.3–79.3]	78.3 ± 4.1 [76.3–80.2]	87.5 ± 4.0 [86.9–88.2]	0.50	**0.0001**	**0.0001**
SHR	54.3 ± 1.5 [53.9–54.7]	54.0 ± 1.5 [53.3–54.6]	53.3 ± 1.8 [53.0–53.6]	0.30	**0.0001**	**0.05**
Leg length (cm)	65.6 ± 3.9 [64.5–66.7]	65.3 ± 2.8 [64.3–66.4]	77.5 ± 4.8 [76.7–78.4]	0.60	**0.0001**	**0.0001**
Leg/*H*	0.46 ± 0.02 [0.45–0.46]	0.46 ± 0.02 [0.45–0.46]	0.47 ± 0.02 [0.46–0.47]	0.33	**0.0001**	**0.0001**
Brachial perimeter (cm)	25.6 ± 3.9 [24.5–26.7]	25.2 ± 2.9 [23.9–26.6]	25.8 ± 2.7 [25.4–26.3]	0.54	0.74	0.42
Tricipital skinfold (mm)	23.4 ± 6.5 [21.6–25.1]	23.0 ± 7.7 [19.5–26.6]	22.7 ± 6.6 [21.6–23.9]	0.86	0.25	0.37
Arm lean area (mm^2)	27.5 ± 6.7 [25.7–29.4]	25.8 ± 5.1 [23.4–28.2]	28.0 ± 5.6 [27.0–29.0]	0.39	0.45	0.13
Arm fat area (mm^2)	26.6 ± 0.0 [23.8–29.4]	25.2 ± 9.7 [20.7–29.8]	25.6 ± 9.2 [24.0–27.1]	0.89	0.44	0.68
Waist (cm)	77.8 ± 11.3 [74.7–80.9]	75.2 ± 8.9 [71.0–79.4]	73.4 ± 8.4 [72.0–79.4]	0.42	**0.02**	0.39
Hip (cm)	88.9 ± 8.8 [86.5–91.4]	87.9 ± 8.6 [83.9–92.0]	97.1 ± 6.4 [96.0–98.2]	0.57	**0.0001**	**0.0001**
Waist/hip	0.87 ± 0.08 [0.9–0.9]	0.86 ± 0.06 [0.8–0.9]	0.75 ± 0.07 [0.7–0.8]	0.41	**0.0001**	**0.0001**
Total water (%)	50.9 ± 7.2 [48.9–52.9]	51.4 ± 5.7 [48.7–54.1]	52.3 ± 4.8 [51.5–53.1]	0.72	0.07	0.26
Lean mass (%)	70.0 ± 9.3 [67.4–72.5]	70.5 ± 7.9 [66.8–74.2]	71.1 ± 6.4 [69.9–72.1]	0.77	0.15	0.40
Fat mass (%)	27.9 ± 9.3 [27.0–32.2]	29.4 ± 7.9 [25.7–33.1]	28.7 ± 6.3 [28.0–30.1]	0.91	0.22	0.35
Lean mass/fat mass	2.8 ± 2.7 [2.1–3.6]	2.7 ± 1.5 [2.0–3.4]	2.7 ± 1.5 [2.5–2.9]	0.55	**0.05**	0.34

BMI Body mass index, *SHR* (sitting height/standing height) × 100, *Leg/H* Leg length/standing height

* Mann–Whitney test

The significance of bold is $P < 0.05$

TS patients treated with rhGH (Group B) showed differences in the same variables observed in non-treated TS patients, except for waist and lean mass/fat mass, when compared to the control group (Table 2). These variables showed lower values in TS patients, despite rhGH treatment, except for BMI, SHR, leg/*H*, and waist/hip, all of which were increased in TS patients, when compared to the control group (Table 2).

In Group B, the age at start of rhGH treatment varied from 7.8 to 15.1 years (10.0 ± 1.3 years), and duration of therapy from 2.8 to 8.2 years (3.7 ± 1.5 years), with a mean dose of 0.42 mg/kg/w (range 0.32–0.50 mg/kg/w).

Within Group B, patients were divided according to age at the start of rhGH replacement therapy from less than 10 years, 10–12 years, and over 12 years of age; according to duration of rhGH replacement as less than or more than 60 months; and according to the daily dose of rhGH as less than or more than 0.33 mg/kg/w. There were no differences in body composition variables (BMI, arm lean and fat areas, waist, hip, waist/hip, total water, lean mass, fat mass, and lean mass/fat mass) in Group B patients based on age at the start of rhGH, duration of rhGH replacement, and the daily dose of rhGH.

Patients with TS with or without rhGH treatment and healthy women were divided according to BMI (≤25, 25–30, and ≥30 kg/m^2), percentage of fat mass (≤ or >30%), waist (≤ or >88 cm), SHR (≤ or >53), and leg/*H* (≤ or >0.46). There were no differences between TS patients (Group A vs. Group B) for these parameters, except for SHR. When TS patients in Groups A and B were compared to the control group (Group C), significant differences were found regarding all variables, except for percentage of fat mass (Table 3).

Among all TS patients ($n = 82$), leg/*H* was not correlated with BMI, arm fat area, waist, hip, waist/hip, or percentage of fat mass. However, SHR was positively correlated with BMI ($r = 0.37$; $P = 0.001$); waist ($r = 0.31$; $P = 0.009$); hip ($r = 0.41$; $P = 0.0001$); and percentage of fat mass ($r = 0.28$; $P = 0.02$).

Discussion

This study analyzed the body composition of 82 adult women with TS, including 52 non-treated and 30 treated with rhGH, and observed that there were no differences between the two groups, despite the use of rhGH, except in standing height.

Differences in age at start of rhGH therapy, the duration of rhGH use, or mean dose of rhGH did not modify the body composition of treated patients with TS.

However, when both TS groups were compared to a control group without TS, weight, standing height, BMI, sitting height, SHR, leg length, leg/*H*, hip, and waist/hip did differ. Weight, standing height, sitting height, leg/*H*, and hip were decreased in TS patients; while increases were seen in BMI, SHR, leg/*H*, and waist/hip as compared to controls. BMI was increased in patients with TS compared to controls, in accordance with data described by Corrigan et al. [19], who analyzed 131 women with TS and found increased BMI values both in TS and control groups. However, BMI was higher in TS patients when compared

Table 3 Body mass index, fat mass, and waist circumference distribution in a sample of 215 adult women: 82 with Turner syndrome (Group A = no treatment; Group B = rhGH therapy) and 133 healthy

	Group A	Group B	Group C	*P**	
	n (%)	*n* (%)	*n* (%)	A vs. B	A vs. B vs. C
BMI (kg/m^2)					
<25	39 (75)	20 (66.7)	117 (87.9)	0.60	0.008
≥25 and <30	9 (17.3)	8 (26.7)	15 (11.3)		
>30	4 (7.7)	2 (6.6)	1 (0.8)		
Fat mass (%)					
<30	24 (46.1)	18 (60)	78 (58.6)	0.23	0.27
≥30	28 (53.9)	12 (40)	55 (41.4)		
Waist (cm)					
<88	41 (78.8)	24 (80)	124 (93.2)	0.90	0.009
≥88	11 (21.2)	6 (20)	9 (6.8)		
SHR					
<53	8 (15.4)	11 (36.7)	60 (45.1)	0.03	0.0008
≥53	44 (84.6)	19 (62.3)	73 (54.9)		
Leg/*H*					
≤0.46	36 (69.2)	23 (76.7)	49 (36.8)	0.47	0.000003
> 0.46	16 (30.8)	7 (23.3)	84 (63.2)		

BMI Body mass index, *SHR* (sitting height/standing height) × 100, *Leg/H* Leg length/standing height

* Chi-square test

to controls (27.8 ± 7.0 vs. 26.6 ± 4.0). In 2007, Darendeliler et al. [20] analyzed a group of 24 patients with TS, mean age 9.4 ± 2.6 years, treated with rhGH 50 μg/kg/day for 1 year, but did not observe differences in BMI. Blackett et al. [12] showed that BMI did not change during rhGH treatment in TS patients; however, this variable may increase after 9 years of age.

This study did not find abnormalities in arm fat and lean areas, or body composition by impedance in TS patients when compared with the control group. Gravholt et al. [8] compared 54 women with TS (aged 42.5 ± 9.7 years), and 55 healthy age-matched women by means of dual-energy X-ray absorptiometry, and found that BMI and percentage of fat mass were increased in TS patients, even though percentage of lean mass was decreased, when compared to controls. Wooten et al. [13] stated that those modifications are seen particularly in non-treated patients, compared to those treated with rhGH. Ari et al. [14] observed the same differences, and also stated that percentage of lean mass is increased in patients treated with rhGH, compared to those not treated. Gravholt and Naeraa [21] showed patients not treated with rhGH to be overweight when compared to control group, but with normal total body water; however, there was an increased in fat mass and a decrease in lean mass.

Patients with TS are 15–20 cm shorter than healthy adult women [4]. The treatment for short stature in TS patients is rhGH [5]; indeed, this study showed improved stature in the group of TS patients treated with rhGH [22]. The short stature of these patients is now considered a consequence of short stature homeobox-containing gene (*SHOX*) haploinsufficiency [23]. *SHOX* is located on the short arm of both sex chromosomes, X and Y, inside the telomeric part of pseudoautosomal region 1 (PAR1). This region contains genes that escape X inactivation, and *SHOX* is expressed on both sex chromosomes [23]. In *SHOX* deficiency, as occurs in TS patients, short stature is accompanied by shortening of the extremities [24].

In this study, we observed that the use of rhGH in TS patients did not modify their body proportions, including sitting height, leg length, leg/*H*, and SHR. All female patients with TS (treated or not with rhGH) showed lower values of sitting height, leg length, and leg/*H*, and higher values of SHR when compared to healthy adult women. These results were also observed by Bannink et al. [25] and Menke et al. [26], both of whom showed that rhGH treatment alone or with oxandrolone did not significantly affect leg growth in TS patients. Hagenäs and Hertel [27] showed that body proportion in TS patients was not modified by as much as 4 years of rhGH treatment. These authors compared data with that observed from rhGH treatment for achondroplasia, hypochondroplasia, and dyschondrosteosis, confirming that body proportion does not seen to correlated with growth hormone status of short individuals and, in particular, GH deficiency does not typically confer short legs [25–27].

Recent studies have demonstrated that analyzing stature by its major components (leg length, sitting height and their ratios, leg/*H*, and SHR) is a useful strategy to assess the association with disease, morbidity, and death in adulthood. Relatively shorter legs and shorter stature (due to relatively shorter legs) may increase the risk of obesity, coronary heart disease, diabetes, and liver dysfunction [28]. Our results are in accordance with these observations; there is a higher risk of all of these diseases in TS patients [5], and SHR had positive correlation with BMI, waist, hip and percentage of fat mass, none of which were modified by rhGH treatment.

This sample of female patients with TS did not show any differences in body composition, regardless of rhGH therapy. Nonetheless, there were differences between female patients with TS and age-matched healthy adult women. Treatment with rhGH did not modify body composition of women with TS, regardless of the dose, duration of use, or age at start of therapy. However, all TS patients with or without rhGH therapy should be monitored, regarding body proportions such as sitting height, SHR, leg length, leg/*H*, and waist/hip.

Keeping in mind that the high frequency of obesity, dyslipidemia, essential arterial hypertension, and subsequent risk for cardiovascular disease in TS patients is not fully understood, we suggest future studies to analyze the association between these morbidities and body proportions in TS patients.

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