Impact of Growth Hormone Therapy on Quality of Life in Adults with Turner Syndrome

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Context: GH and/or oxandrolone are used to promote growth in Turner syndrome (TS).

Objective: The aim of this study was to compare quality of life (QoL) in TS women with controls and determine the impact of growth promoting therapy on QoL in TS women.

Design: This was a cross-sectional, case-control study.

Setting: The study was conducted at an outpatient clinic at Sahlgrenska University Hospital, Göteborg, Sweden.

Patients: Patients included 111 TS women (age range 18–59 yr) and 111 randomly selected, age-matched women (25–54 yr) from the World Health Organization Monitoring Trends and Determinants for Cardiovascular Disease project (Göteborg, Sweden) served as controls.

Main Outcome Measures: QoL was estimated by the Psychological General Well-Being scale (anxiety, depressed mood, positive well-being, self-control, general health and vitality) and the Nottingham Health Profile (physical mobility, pain, sleep, energy, social isolation, and emotional reactions).

Results: TS women reported more social isolation than controls ($P < 0.001$). After age adjustment, significantly less pain (<0.05) was reported attributable to GH treatment within TS. No significant difference in any other subscales used could be shown. In TS, QoL was negatively affected by higher current age and age at diagnosis and positively affected by better body balance, fine motor function, and higher bone mineral density.

Conclusions: Social isolation was more commonly reported in the whole TS cohort than in the population. Except for less pain, no significant impact on QoL attributable to GH treatment could be found, despite the mean +5.1 cm final height. **(*J Clin Endocrinol Metab* 95: 1355–1359, 2010)**

Turner Syndrome 45,X (TS) occurs in approximately one in 2500 female births and is characterized by sex hormone deficiency leading to incomplete pubertal development and infertility. TS is also characterized by external physical features (stigmata), *i.e.* short stature, webbed neck, cubitus valgus, shield thorax, and micrognathia (1, 2). Women with TS suffer from congenital heart malformations, hypertension (3), hypothyroidism (4), hearing loss (5, 6), impaired body balance (7), osteoporosis, and fractures (8). In Sweden, GH treatment has been used for short stature in TS since 1988. Apart from an effect on height, its effect on health-related quality of life (QoL) is still not known. Psychological and social problems in TS women have been reported (9) but vary considerably and far from all women with TS have these problems (10). The aim of this case-control study was to compare QoL in TS

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Abbreviations: BMI, Body mass index; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being Index; QoL, quality of life; TS, Turner syndrome.

women with controls and study the impact of GH and/or oxandrolone treatment on QoL in TS women.

Subjects and Methods

Subjects

Between 1995 and 2008, 114 TS patients, who underwent their regular hospital visit at the Turner Clinic at Sahlgrenska University Hospital (Göteborg, Sweden) were asked to fill in two QoL questionnaires. Three women did not want to participate, resulting in a study sample of 111 TS women (mean age 30.3 ± 11.4 yr; range 18–59 yr). GH (0.1 IU/kg · d) and oxandrolone (0.05 mg/kg · d; mean 12 ± 2, range 10–14 months) treatment were given to 45 (40%), GH only to 13 (12%), oxandrolone only to 19 (17%), and neither GH nor oxandrolone had been given to 35 (31%) TS women. Continuous estrogen hormone replacement therapy (HRT) was given to 94%, mainly 2 mg 17β-estradiol, due to ovarian dysfunction. The remaining 6% had spontaneous menarche.

An age-matched population sample randomly selected from the city census from the same area as the patients of 111 women (mean age 32.1 ± 6.3 yr; range 25–54), from the World Health Organization MONItoring trends and determinants for CArdiovascular disease study (11) served as controls. Oral contraceptives and HRT (2 mg 17ß-estradiol) were used by 17% (HRT = 4%) of the controls.

Methods

Each subject completed the self-rating questionnaires Psychological General Well-Being index (PGWB) and the Nottingham Health Profile (NHP).

The PGWB is a self-rating scale constructed to measure personal affective or emotional states reflecting a sense of well-being (12) or QoL. This scale is made up of 22 questions with a six-grade response format, which are divided into six subscales: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. All the questions are summarized into an overall well-being score (total PGWB score), which is used in this study as a measure of QoL (the higher the score, the better the patient's QoL, with a maximum score of 132).

The NHP scale is a standardized way of evaluating quality of life using a two-part questionnaire. In this study only part I was used. Part I comprises 38 statements covering six elements concerning limitations of activity or aspects of distress: physical mobility, pain, sleep, energy, social isolation, and emotional reactions. Yes/no answers are given. Scores range from 0 to 100 and each statement is weighted to show the level of severity the statement represents (the higher the score, the greater the limitations/distress the patient experiences, *i.e.* the lower QoL) (13).

Anthropometry, bone density measurements, blood pressure, and echocardiography

Body weight was measured to the nearest 0.1 kg in the fasting state with the subjects in their underwear and barefoot. Body

TABLE 1. Unadjusted anthropometric background data, blood pressure, blood lipids, occupational and degree of physical activity, smoking habits, number of subjects with hypertension, hypothyroidism, and child-bearing (including adopted) in TS women and randomly selected controls from the World Health Organization MONItoring trends and determinants for CArdiovascular disease study

Anthropometric data	TS GH+ (n = 58)	TS GH− (n = 53)	All TS (n = 111)	Controls (n = 111)	*P* value, all TS *vs.* controls
Age (yr)	22.4 ± 4.1	38.9 ± 10.5	30.3 ± 11.4	32.1 ± 6.3	ns
Height (cm)	154.7 ± 5.0	149.6 ± 6.1	152.3 ± 6.2	167.7 ± 6.4	<0.001
Weight (kg)	60.9 ± 12.1	56.2 ± 10.9	58.8 ± 11.8	65.5 ± 10.0	<0.001
BMI (kg/m^2)	25.6 ± 4.6	25.1 ± 4.2	25.4 ± 4.5	23.3 ± 3.5	<0.001
Waist to hip ratio	0.80 ± 0.09	0.84 ± 0.07	0.81 ± 0.08	0.76 ± 0.05	<0.001
Systolic blood pressure (mm Hg)	116.6 ± 11.3	125.1 ± 14.8	120.7 ± 13.7	120.7 ± 12.1	ns
Diastolic blood pressure (mm Hg)	73.2 ± 10.2	77.7 ± 9.2	75.3 ± 10.0	77.4 ± 9.1	ns
Pulse (beats/min)	65.5 ± 6.3	67.3 ± 7.7	67 ± 7	73 ± 10	<0.01
Serum total cholesterol (mmol/liter)	4.8 ± 0.8	5.4 ± 1.3	5.1 ± 1.2	5.2 ± 1.1	ns
HDL (mmol/liter)	1.7 ± 0.5	1.8 ± 0.5	1.7 ± 0.5	1.6 ± 0.4	ns
LDL (mmol/liter)	2.5 ± 0.8	2.7 ± 1.2	2.6 ± 1.2	3.3 ± 0.9	<0.05
Triglycerides (mmol/liter)	1.13 ± 0.5	1.40 ± 1.1	1.30 ± 0.8	1.04 ± 0.4	<0.001
Antihypertensive treatment (%)	10	28	19	1	<0.001
Hypothyroidism (%)	36	17	27	1	<0.001
HRT treatment (%)	95	92	94	17[a]	<0.001
Physical exercise					
Sedentary (%)	29	35	33	11	<0.001
Moderate (%)	30	35	31	59	<0.01
Regular (%)	41	30	36	30	ns
Smokers (%)	3	3	3	32	<0.01
Married/cohabiting (%)	31	26	31	39	ns
Fully employed/students (%)	93	76	86	77	ns
Sick leave or disability pension (%)	3	14	9	7	ns
Child-bearing women (%)	4	15	9	74	<0.001

Means ± SD. *P* values are given for comparison between all TS (n = 111) and age-matched controls (n = 111). GH+, GH treated; GH−, untreated; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant.

[a] Oral contraceptives and HRT (HRT = 4%).

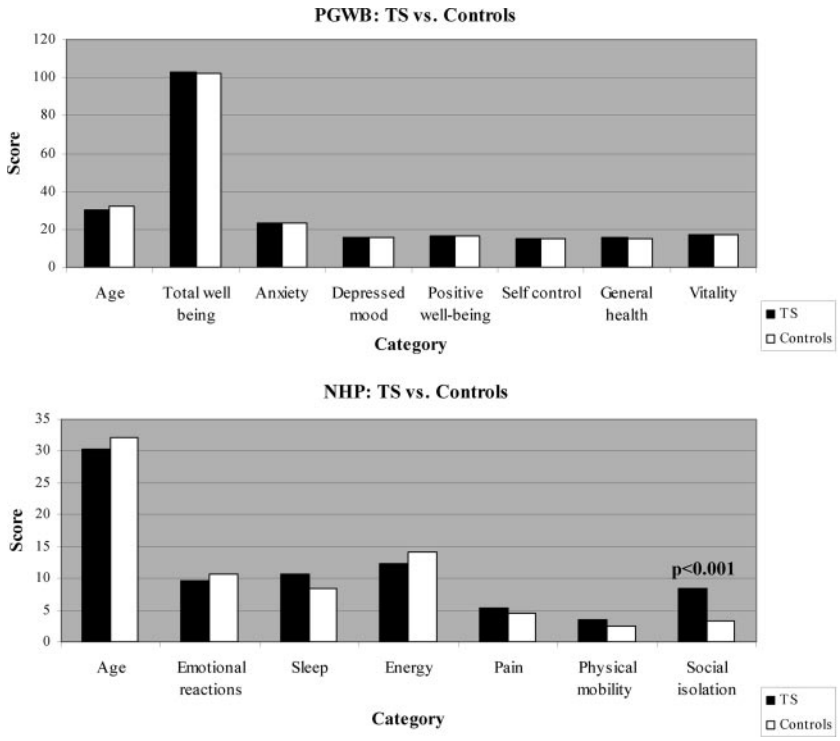

FIG. 1. PGWB scales and NHP scales in the whole TS cohort (n = 111) and the age-matched, randomly selected controls (n = 111). A value of $P < 0.001$ was reported for social isolation between TS and controls.

height was measured barefoot to the nearest 1 cm. Body mass index (BMI) was calculated as body weight divided by height squared (kilograms per square meter). Waist circumference was measured with a soft tape midway between the lowest rib margin and the iliac crest in the standing position. Hip circumference was measured over the widest part of the gluteal region, and the waist to hip ratio was calculated. In TS bone mineral density and body composition (body fat and lean body mass) were estimated with dual-energy x-ray absorptiometry (Lunar, Madison, WI); total, femur neck, and lumbar spine (L2-L4) bone density and t-score at the lumbar spine were measured. Blood pressure was measured to the nearest 2 mm Hg, and hypertension was defined as greater than 140/90 mm Hg and/or if treatment for hypertension was present. Echocardiography was performed in all TS patients according to international guidelines (14). Cardiac left ventricular ejection fraction was estimated. A medical history was taken and physical examination was performed by the same specialist in all patients. Degree of physical activity, low to high 1–5, and smoking habits were asked for in similar ways in patients and controls.

Biochemical analyses

Blood samples were drawn in fasting state and analyzed at the accredited Laboratory for Clinical Chemistry, Sahlgrenska University Hospital. Hypothyroidism was defined as TSH 4 μU/ml or greater (milliunits per liter) or as being on T_4 substitution. The chromosome status in the TS women was based on both karyotyping and fluorescence *in situ* hybridization (2).

Fine motor function and balance test

The modified Bruininks-Oseretsky test for fine motor function and body balance has been described elsewhere (7).

Ethical considerations

This study was approved by the Ethics Committee at the University of Gothenburg and all participants gave their informed consent. Human rights were also respected in accordance with the Helsinki Declaration.

Statistics

Means and SD values were calculated with conventional methods. Odds ratio and χ^2 tests were used to compare differences between groups regarding noncontinuous data. Data in groups regarding continuous variables were tested with Student's *t* test. Simple correlations were calculated using Pearson's method. Age adjustment and logistic regression models were used to test interactions between factors. $P < 0.05$ (two sided test) was considered statistically significant.

Results

Background data

Background data for TS women and controls are given in Table 1. TS women were shorter and had higher BMI and waist to hip ratio than the age-matched controls. TS women smoked less, had lower pulse rates, lower low-density lipoprotein cholesterol levels, a lower degree of physical activity, but higher triglycerides. Hypertension and hypothyroidism were more prevalent among TS than controls.

QoL in TS *vs.* controls

TS women reported more social isolation than controls ($P < 0.001$). No other differences in the PGWB and NHP subscales could be found when comparing the whole TS cohort with age-matched controls (Fig. 1).

QoL in relation to growth-promoting therapy

TS women who had received GH treatment, irrespective of oxandrolone, were taller and younger than those who had not received GH (Table 2). TS women treated with GH, with or without oxandrolone, had consistently higher PGWB and consistently lower NHP scores than untreated TS women. After age adjustment with a logistic regression analysis with GH as the dependent variable, only pain (NHP) remained significant and attributable to GH treatment.

TS women without GH or oxandrolone reported more sleeping problems and social isolation compared with controls when age was taken into account.

TABLE 2. Age-adjusted QoL data and PGWB and NHP scales in TS women compared with controls

Treatment	GH+O+	GH+O−	GH−O+	GH−O−	*P* value GH+ *vs.* GH−	Controls
Height (cm)	154.5 ± 4.7	155.3 ± 6.3	149.5 ± 4.8	149.6 ± 6.7	<0.001	167.7 ± 6.4
Age (yr)	22.8 ± 3.9	21.4 ± 4.6	33.9 ± 7.2	41.5 ± 11.1	<0.001	32.1 ± 6.3
PGWB scale						
n	45	13	18	35		111
Total well-being	105.5 ± 17.0	111.4 ± 8.7	104.0 ± 15.1	95.4 ± 17.3	n.s.	102.5 ± 18.5
Anxiety	23.9 ± 5.0	25.8 ± 2.5	23.5 ± 4.1	21.6 ± 4.8	n.s.	23.6 ± 5.1
Depressed mood	15.8 ± 2.6	16.5 ± 1.6	16.3 ± 1.6	14.4 ± 3.0	n.s.	15.6 ± 3.0
Positive well-being	17.2 ± 3.4	18.0 ± 1.8	17.1 ± 3.3	15.1 ± 3.3	n.s.	16.4 ± 3.9
Self-control	15.3 ± 2.8	15.6 ± 1.2	14.7 ± 2.6	14.4 ± 2.4	n.s.	15.0 ± 2.6
General health	15.8 ± 2.3	16.6 ± 1.7	15.3 ± 2.5	14.7 ± 2.9	n.s.	14.8 ± 2.8
Vitality	17.9 ± 3.5	18.8 ± 3.2	17.1 ± 3.1	15.8 ± 3.3	n.s.	17.0 ± 4.1
NHP scale						
n	43	13	16	34		111
Emotional reactions	6.6 ± 14.7	1.3 ± 3.1	8.6 ± 15.6	17.7 ± 27.2	n.s.	10.7 ± 18.4
Sleep	5.8 ± 11.7	4.9 ± 6.8	10.2 ± 20.3	20.6 ± 29.3[a]	n.s.	8.3 ± 15.0
Energy	11.0 ± 23.2	8.5 ± 27.6	8.0 ± 18.1	17.0 ± 26.6	n.s.	14.2 ± 25.5
Pain	1.7 ± 7.1	0.0 ± 0.0	5.0 ± 13.7	12.3 ± 26.2	<0.05	4.5 ± 15.3
Physical mobility	2.5 ± 7.1	2.6 ± 7.0	2.4 ± 5.0	5.7 ± 11.5	n.s.	2.4 ± 9.0
Social isolation	8.9 ± 17.9	1.4 ± 5.0	3.3 ± 10.4	12.6 ± 23.1[a]	n.s.	3.3 ± 9.3

The lower the PGWB score, the greater the distress; the higher the NHP score, the greater the distress. Means ± SD *P* value (column) reported for comparison between GH+ and GH−, irrespective of oxandrolone treatment. GH+, GH treated; GH−, GH untreated; O+, oxandrolone treated; O−, oxandrolone untreated.

[a] $P < 0.01$ is also given for comparison with controls.

QoL in relation to HRT

Calculations on the importance of HRT could not be performed due to the small number in the group who had not received this treatment (n = 7).

QoL with regard to medical variables

In TS, QoL (PGWB and NHP scales) correlated negatively with current age ($P < 0.001$) and age at diagnosis and positively with body balance, fine motor function, and bone mineral density. QoL decreased with increasing age also in controls. There were no correlations between QoL and height, BMI, the number of TS stigmata, left ventricle ejection fraction, thyroid hormones, or blood lipids. TS women with and without hypothyroidism, hypertension, and cardiac malformations exhibited similar PGWB and NHP scale scores (not shown).

Discussion

GH-treated TS women reported less pain than those without such treatment. It would be speculative to attribute this to GH therapy alone and requires further investigation. No other significant impact attributable to GH was seen on QoL despite the mean +5.1 cm final height. This is in line with earlier studies (15, 16), and the QoL perspective should be considered when discussing the treatment effects and cost-effectiveness of GH treatment in TS (15–18). Furthermore, this study confirms that social isolation is still a major concern for the whole TS cohort when compared with age-matched controls (9, 10).

TS women who had received GH averaged almost half the age of those who had never received GH. Age alone had a strong negative influence on QoL in both TS women and controls. It will be interesting to evaluate the new generation of TS women (here < 30 yr) who have received modern therapy when they enter their 40th year of life. The question will then be whether the GH-treated TS women score similarly to the present TS group without GH treatment or to the control group at that age. Further studies with a longer perspective are warranted for a more detailed evaluation of the effects of GH treatment (18).

TS is often considered a syndrome of early aging, and TS patients can be regarded as young postmenopausal women due to their estrogen deficiency and because the syndrome includes a number of age-related disorders such as cardiovascular disease, metabolic syndrome, osteoporosis, and sensorineural hearing loss. This is also true for this TS cohort, which has been followed longitudinally for 13 yr by the same physicians with a detailed protocol on function, morbidity, and medical treatment. Of all the age-related symptoms investigated in this study, only dysfunctions related to the musculoskeletal system had a negative impact on QoL in TS. It could well be that this applies even to the non-TS population because osteoporosis and impaired balance limit activity of daily life with increasing age (7). Surprisingly, factors related to TS such as geno-

type, adult height, heart or thyroid dysfunction, blood pressure, and body size had no impact on QoL. This may be due to the close monitoring program at the Sahlgrenska University Hospital, which ensures early detection and treatment of some of these preventable factors.

A limitation was that this was not a clinical trial. For ethical reasons it was not possible to perform placebo-controlled studies regarding GH treatment in TS. Therefore, only case-control studies like this one are possible, yielding a short report of the present treatment status in relation to controls. Naturally the GH-treated TS women were younger (GH treatment has been available in Sweden for only 20 yr) than the nontreated TS women. There are also limitations inherent to measuring QoL with questionnaires in a complex disorder such as TS, and therefore, conclusions must be drawn with caution. However, the scales used in this study are validated in other chronic diseases (12, 13).

Strengths of this study were the randomly selected, age-matched controls from the general population and, to our knowledge, the longest follow-up of GH treatment in adult TS. Furthermore, two different QoL scales were used with similar outcome, increasing the reliability.

In conclusion, social isolation was more commonly reported in the whole TS cohort than in the population. Except for less pain, no significant impact on QoL in TS, attributable to GH treatment, could be found, despite the mean +5.1 cm final height.

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