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Quality of Life Determinants in Young Women with Turner's Syndrome after Growth Hormone Treatment: Results of the StaTur Population-Based Cohort Study

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GH is used to increase adult height in children with Turner's syndrome with little knowledge of the impact on quality of life. We carried out a population-based cohort study of quality-of-life determinants in young women with Turner's syndrome, all previously treated with GH. Of 891 eligible women aged over 18 yr and recorded in the French Growth Hormone Register, 818 were available and 568 participated (69%). They were assessed for demographic characteristics, health status, sexual life, treatment expectations, scores for Medical Outcome Study Short Form 36 (SF-36), and General Health Questionnaire 12. Participants were 22.6 ± 2.6 yr old (mean ± SD), measured 150.9 ± 5.6 cm, and had received GH for 4.8 ± 2.2 yr. SF-36 scores were similar in participants and French women of the general population. Cardiac (12% of participants) or otological (26% of participants) involvement or induction of puberty after 15 yr of age was associated with lower scores for at least one of the SF-36 dimensions. Height and estimated height gain from treatment were not associated with quality-of-life scores. Higher expectations from treatment were associated with lower quality of life. We conclude that quality of life is normal and unaffected by height in young adults with Turner's syndrome treated with GH. These data emphasize the need to give appropriate attention to general health and otological care rather than focus on stature in the care of children with Turner's syndrome. (*J Clin Endocrinol Metab* 90: 1992–1997, 2005)

TURNER'S SYNDROME AFFECTS 1 in 2500 females and results from the total or partial absence of one of the X chromosomes (1, 2). The principal features of Turner's syndrome are short stature (adult height about 20 cm below the mean for women of the corresponding ethnic group) and dysfunctional gonads resulting in a lack of, or incomplete, pubertal development and infertility. Other features include cardiac and renal malformations and otological problems leading to hearing impairment and various degrees of dysmorphic features. Females with Turner's syndrome are short at birth and display growth retardation in all phases of growth, particularly late childhood and adolescence, but have no GH deficiency. Several studies have reported increases in adult heights after GH treatment (3–6), although there is some debate as to the magnitude of these increases (7–9). GH is approved for use in children with Turner's syndrome in most industrialized countries and is recommended in recently issued guidelines (9).

Treatments to promote growth in girls with Turner's syndrome aim to reduce the impact of short stature on psychosocial functioning and quality of life. However, these aspects have not been evaluated in young adults after treatment completion. Several small studies have reported changes in psychosocial functioning and quality of life in adolescents and women with Turner's syndrome (reviewed in Refs. 2 and 10). However, the effects on psychosocial functioning of height or height gain from GH treatment remain unclear (11, 12).

In this study, we aimed to evaluate the determinants of quality of life, by means of standardized questionnaires, in all young women with Turner's syndrome who had been treated with GH in France. These women were treated during the 1990s and received GH regimens similar to those currently recommended for Turner's syndrome.

Subjects and Methods

We included all patients with a diagnosis of Turner's syndrome, based on karyotype analysis, who had been treated with GH in France during the study period and who were obligatorily registered in the Association France-Hypophyse database (13). We then selected patients who were over the age of 18 yr on March 1, 2001. Of the 891 eligible patients, 73 were lost to follow-up or unable to answer the questionnaire, and 818 received the questionnaire (Fig. 1). A total of 568 (69%) responded (participants); the remaining 250 did not complete the questionnaire, despite several contacts (nonparticipants). The study was approved by the Departement de la Recherche Clinique et du Développement of Assistance Publique-Hôpitaux de Paris and was considered by their judicial department as requiring no informed consent because on-treatment data had been collected as part of

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Abbreviations: GHQ-12, General Health Questionnaire 12; SDS, SD score; SF-36, Medical Outcome Study Short Form 36.

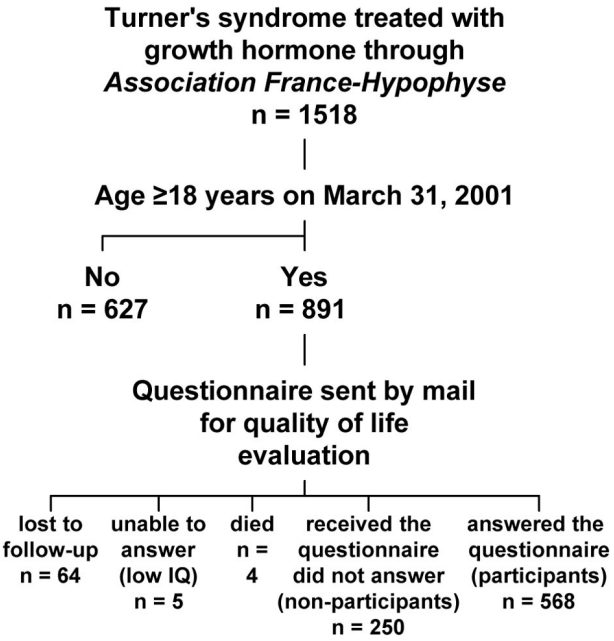

FIG. 1. Distribution of the patients.

a national mandatory program and patients were free to respond to the questionnaire.

Data collection

Data relating to growth and features associated with Turner's syndrome were collected before GH treatment and at follow-up visits (every 3–6 months) by the treating physicians. Karyotype, dysmorphic features, cardiac and renal malformations, associated morbidity, height, weight, age, bone age, pubertal stage, GH dose, frequency of injections, and associated treatments were analyzed (13). Height and weight were expressed as SD scores (SDSs), based on normative general population data (13) and Turner's syndrome data (14). We estimated height gain from GH treatment by comparing attained and projected height, using Turner's syndrome normative data (14).

In 2001 a postal survey was sent to all eligible patients. This survey included the validated French version of Medical Outcome Study Short Form 36 (SF-36) (15) the General Health Questionnaire 12 (GHQ-12) (16) and dealt with demographic characteristics, current health status (morbidity, medication), sexual intercourse experience, and expectations from GH treatment (patients were asked to give the minimum height gain they considered worthwhile for the further use of GH in Turner's syndrome). The SF-36 contains eight subscales: general health (five items), physical functioning (10 items), limitations on usual role-related activities due to physical health problems (four items), bodily pain (two items), energy and fatigue (vitality, four items), limitations on usual role-related activities due to emotional or mental problems (three items), social functioning (two items), and emotional or mental health (five items). Scores for all eight subscales range from 0 to 100, with higher scores indicating better health or function. All items refer to the subject's functioning/status during the past 4 wk, except those for physical functioning and general health, which relate to the time at which the form is completed. We used the 12-item version of the general health questionnaire as a measure of psychological distress. Scores on this questionnaire range from 0 to 12, with a score of 3 or more identifying a probable case of minor psychiatric disorder such as anxiety or depression (16).

GH treatment

Treatment was generally initiated on the diagnosis of Turner's syndrome. However, for the older patients, treatment was initiated when GH became widely available, in the early 1990s. The criteria for treatment discontinuation were a growth rate less than 3 cm/yr or a bone age of 13 yr or more.

Analysis of quality of life and statistical methods

The scores for the SF-36 scales are presented as absolute scores and SDSs, calculated by dividing the difference between the patient's score and the mean of the general population of the same sex and age group by the SD of the general population group. French general population reference values for women aged 18–24 yr were used (17). Pearson correlation coefficient was used to correlate GHQ-12 score (12 point scale) with the eight SF-36 scores (100-point scales).

Multiple regression models were constructed to identify factors associated with SF-36 scale (absolute) scores. These models included paternal socioprofessional class, educational level, and GHQ-12 scores (classified as high if the score was ≥ 3 or lower). Some of the scores for SF-36 scales were skewed, and residual plots from the corresponding regression analyses were checked for departure from normality. The χ^2 test (simple goodness of fit test) was used to compare the proportion of cases with GHQ-12 score of 3 or more with that for the general population. Calculations were performed with SAS software (18).

Results

Characteristics of the subjects and treatments (Table 1)

Eligible patients (participants and nonparticipants) had a mean age of 12 ± 2.5 yr at the start of treatment and used GH for a mean of 4.7 yr, at a mean dose of 0.8 IU/kg·wk (0.27 mg/kg·wk), administered as six or seven injections per week. They stopped treatment at the age of 16.7 ± 1.6 yr and received the questionnaire a mean of 6 yr later, at the age of 22.6 ± 2.6 yr. In the 72% of patients who had no spontaneous pubertal development, estrogen treatment was started at a mean age of 15 yr. Most of the remaining patients required estrogen treatment at a later stage to complete their pubertal development. The mean adult height for the whole group (participants and nonparticipants) was 150 ± 6.1 cm (range 127–167 cm). Participants were a mean of 2.7 cm taller than nonparticipants ($P < 0.005$). Participants and nonparticipants were similar in all other characteristics.

Quality of life and its determinants

SF-36 scores in the 568 women with Turner's syndrome were similar to those of women of the same age from the general population (Fig. 2). If expressed as SDSs, these scores did not differ significantly from zero. The proportion of women with Turner's syndrome who had a high GHQ-12 score (≥ 3) was lower than that for the general population (24 *vs.* 31%, respectively, $P < 0.001$).

We assessed the effect of several of the patients' characteristics on SF-36 scores (Table 2). The father's socioprofessional background (manual *vs.* nonmanual) and the patient's level of education (secondary education completed or not) were associated with several quality-of-life dimensions. GHQ-12 scores were correlated with SF-36 scores, in particular those reflecting psychosocial dimensions with the following correlation coefficients: −0.22 (physical functioning), −0.29 (general health), −0.37 (bodily pain), −0.39 (role limitation, physical), −0.43 (vitality), −0.59 (role limitation, emotional), −0.62 (social functioning), and −0.66 (mental health). Further analyses were performed after adjustment for these three potentially confounding variables (paternal socioprofessional status, participant's educational level, and GHQ-12 score). Adult height was not associated with quality of life, regardless of whether height was treated as a continuous variable or broken down into categories, as in Table 2. Similarly, duration of treatment, age at treatment

TABLE 1. Clinical characteristics of patients with Turner's syndrome included in this study

	Responded to the questionnaire	
	Yes (n = 568)	No (n = 250)
Characteristics at birth		
Birth length (SDS)	−1.9 ± 1.3	−2.0 ± 1.3
Birth weight (SDS)	−1.1 ± 1.1	−1.2 ± 1.1
Midparental height (SDS)	−0.2 ± 1.1	−0.5 ± 1.2
Turner's syndrome		
Karyotype (n, %)		
45,X	299 (53%)	113 (46%)
Other X anomalies or mosaicisms	149 (26%)	71 (29%)
45,X/46XX mosaicism	55 (10%)	34 (14%)
Presence of Y chromosome material	37 (7%)	12 (5%)
Ring X chromosome	28 (5%)	14 (6%)
Presence of Turner's syndrome dysmorphic features (n, %)	280 (49%)	111 (45%)
Before GH		
Age (yr)	11.9 ± 2.6	12.0 ± 2.5
Height (SDS, general population)	−3.3 ± 1.0	−3.7 ± 1.1
Height (SDS, Turner's syndrome reference)	0.4 ± 1.0	0.1 ± 1.1
At the end of GH		
Age (yr)	16.7 ± 1.6	16.7 ± 1.6
Height (SDS, general population)	−2.4 ± 1.0[a]	−2.8 ± 1.1
Height (SDS, Turner's syndrome reference)	2.1 ± 1.1[a]	1.6 ± 1.2
Duration of treatment (yr)	4.8 ± 2.2	4.6 ± 2.3
Mean dose of GH (IU/kg · wk)	0.8 ± 0.2	0.8 ± 0.2
Pubertal development		
Proportion without spontaneous pubertal development (n, %)	406 (71%)	182 (73%)
Age at initiation of estrogen treatment in girls without spontaneous pubertal development (yr)	14.9 ± 1.9	15.3 ± 2.0
Age at initiation of estrogen treatment in girls with spontaneous pubertal development (yr)	15.9 ± 2.1	16.1 ± 1.6
Adult height		
Adult height (cm)	150.9 ± 5.6[b]	148.2 ± 6.7
Adult height (SDS, general population)	−2.2 ± 1.0	−2.7 ± 1.2
Adult height (SDS, Turner's syndrome reference)	2.2 ± 1.1	1.6 ± 1.3
Age when the questionnaire was sent (yr)	22.6 ± 2.6	22.7 ± 2.5

Results are shown as means ± SD or numbers and percentages.
[a] $P < 0.05$; [b] $P < 0.01$ *vs.* those who did not respond to the questionnaire.

initiation, total GH dose, and estimated height gain were not associated with quality of life. The patients who had the highest expectations regarding GH treatment had the lowest quality-of-life scores. Cardiac involvement was strongly associated with low physical scores, whereas kidney and genital malformations associated with the presence of Y chromosome mate-

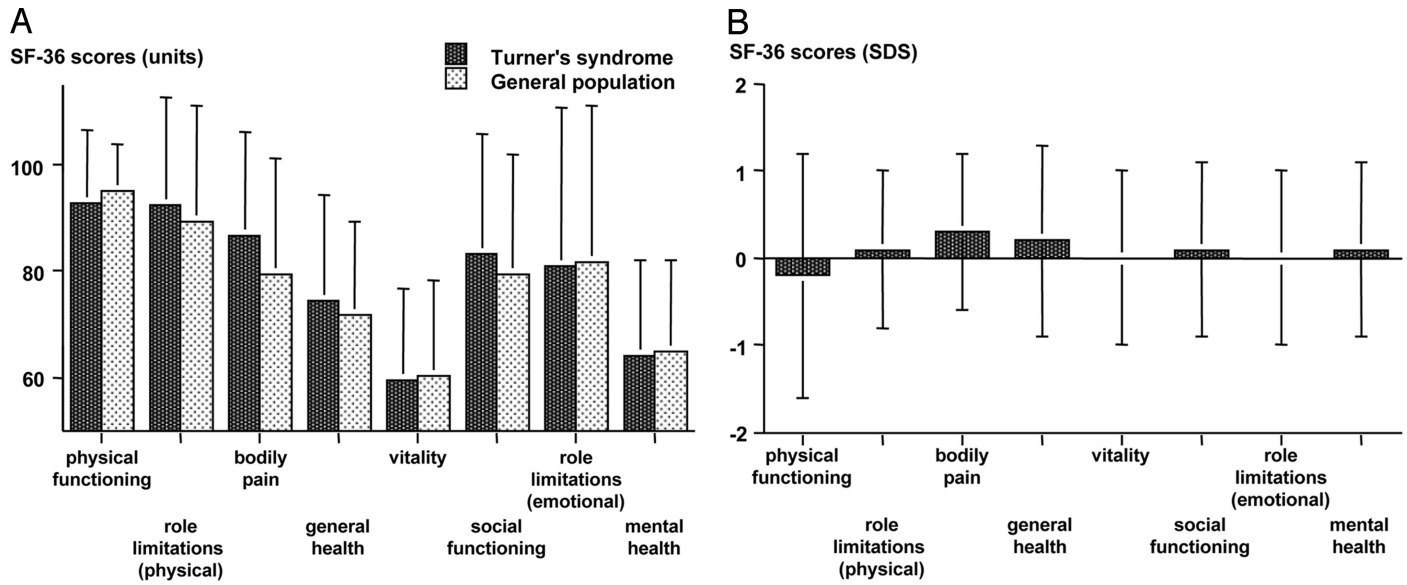

FIG. 2. Quality-of-life measurements in Turner's syndrome patients. Results are shown as absolute scores for patients with Turner's syndrome (*hashed bars*) or for French women from the general population aged 18–24 yr (*dotted bars*) (A) or as SDS using data obtained for French women from the general population aged 18–24 yr (B); means ± SD are shown.

TABLE 2. Determinants of quality of life in patients with Turner's syndrome

	n	Physical functioning	Role limitations (physical)	Bodily pain	General health	Vitality	Social functioning	Role limitations (emotional)	Mental health
Used as adjustment variables in further analyses									
Paternal socioprofessional class		*b*							
Nonmanual workers	305	0	0	0	0	0	0	0	0
Manual worker	130	−5.2	−4.5	−2.5	−1.9	0	−0.7	2.7	−2.8
Retired, inactive	133	−2.5	−1.6	−3.7	−2.5	−0.9	1.1	0.1	−1.4
Participant's educational level		*d*	*c*	*c*	*b*		*a*		
High-school graduation and higher	322	0	0	0	0	0	0	0	0
Did not graduate from high school	246	−5.9	−6.1	−5.9	−5.4	−2.4	−4.7	−0.6	−0.6
GHQ-12 score ≥ 3		*c*	*d*	*d*	*d*	*d*	*d*	*d*	*d*
No	429	0	0	0	0	0	0	0	0
Yes	139	−4.9	−13.3	−13.5	−10.7	−14.3	−28.2	−36.3	−23.5
Height									
Adult height									
>152.1 cm (> −2 SDS general population)	235	0	0	0	0	0	0	0	0
146.5–152.1 cm (−3 to −2 SDS general population)	217	1.4	2.8	1.9	−1.3	0.6	−0.5	−0.4	0.0
<146.5 cm (< −3 SDS general population)	116	0.5	1.1	1.0	−3.1	1.1	1.6	1.8	−0.3
Duration of GH treatment (yr)									
≤3.5	165	0	0	0	0	0	0	0	0
3.5–5.5	216	−0.5	1.2	−0.6	−2.3	−1.1	−1.4	−1.0	1.0
>5.5	187	−0.8	−0.3	−1.4	0.1	−2.3	−1.1	1.4	1.3
Height gain from GH treatment (cm)									
≤7	183	0	0	0	0	0	0	0	0
7–12	187	−1.0	1.6	2.1	0.5	−0.4	−0.2	0.7	2.1
>12	198	−0.8	−0.2	1.6	1.3	−1.3	1.5	0.2	0.6
Minimum gain worthwhile for further use of GH (by patients) (cm)			*a*			*b*			
≤5	132	0	0	0	0	0	0	0	0
5–10	174	−0.8	2.1	0.7	1.2	3.0	−0.6	0.5	0.2
>10	154	−3.1	−3.0	−3.9	−0.4	−2.4	−2.8	−2.8	−3.0
Turner's syndrome characteristics									
Karyotype									
45X	299	0	0	0	0	0	0	0	0
Other	269	0.4	0.9	−0.7	−0.7	−0.3	−1.0	0.4	−0.6
Dysmorphic features									
Absent	291	0	0	0	0	0	0	0	0
Present	277	0.6	−0.9	0.9	−2.9	−1.3	0.7	−2.5	0.5
Any malformation									
Absent	410	0	0	0	0	0	0	0	0
Present	158	−1.9	−1.5	0.8	−2.4	−0.5	2.5	0.9	1.1
Heart malformation		*c*	*a*		*a*				
Absent	497	0	0	0	0	0	0	0	0
Present	71	−5.9	−5.9	−3.3	−6.1	−4.0	−0.8	−4.2	−0.7
Otological condition		*b*	*a*	*a*	*d*	*c*	*b*		*d*
Absent	419	0	0	0	0	0	0	0	0
Present	149	−3.6	−4.1	−4.6	−12.8	−5.5	−5.1	−4.4	−5.6
Puberty and sex life									
Puberty					*a*				
Spontaneous	128	0	0	0	0	0	0	0	0
Induced before the age of 15 yr	222	−1.0	−1.4	1.1	−0.8	−2.5	−1.8	−3.3	0.0
Induced after the age of 15 yr	184	−2.2	−1.7	1.0	−4.9	−2.7	1.9	1.4	−1.4
Sexual intercourse experience									
Yes	202	0	0	0	0	0	0	0	0
No	366	−1.8	−1.4	1.3	−2.2	−1.1	2.0	2.1	0.6

Potential predictors of SF-36 scores were categorized; results are expressed as absolute SF-36 scores relative to a reference category (the most numerous, or the closest to the general population) set to zero, after adjustment for paternal socioprofessional background, level of education, and GHQ-12 score. *P* values below 5% are shown: *a*, $P < 0.05$; *b*, $P < 0.01$; *c*, $P < 0.001$; *d*, $P < 0.0001$.

rial were not. Unexpectedly, otological involvement, present in 26% of the patients and either detected during childhood care or declared by the patients at the time of the survey, was strongly associated with perceived health-related quality of life in all but one dimension. Otological conditions resulted in a loss of 4–13 score points or 0.2–0.7 SDS units. Patients whose puberty had been induced after the age of 15 yr had significantly lower general health perception scores. Other factors were analyzed and found not to be associated with quality of life as assessed by the SF-36 questionnaire: karyotype (either in two

categories as in Table 2 or using subgroups as in Table 1), dysmorphic features of Turner's syndrome, sexual intercourse experience, presence of thyroid dysfunction, or self-reported visual problems.

Discussion

Our main findings, in young women with Turner's syndrome treated with GH who had a mean gain of 8.9 cm, compared with projected height were: 1) perceived health-related quality of life, as measured by the SF-36 questionnaire, was not statistically different from the reference values obtained for young French women of the general population; 2) height and other variables associated with GH treatment did not affect perceived health-related quality of life, with the exception of unrealistic expectations about GH; and 3) other features associated with Turner's syndrome, in particular otological conditions, had a profound impact on perceived health. These findings strongly suggest that priorities should be redefined in the care of these patients during childhood.

This is, to our knowledge, the first study addressing the question of quality of life in patients with Turner's syndrome using standardized questionnaires in a register-based population. The use of a standardized questionnaire made it possible to compare patients' scores with those obtained recently for French women of the same age from the general population (17). Several limitations of our study should be pointed out. First, the 31% of patients who did not participate might have different quality-of-life characteristics from those who did and being on average 2.7 cm shorter might be of greater concern to them than to those who participated. Although this cannot be dismissed, we believe it is unlikely, given the lack of influence of height on quality of life in the rest of the population. Moreover, the response rate of 69% to an unsolicited questionnaire assessing personally intimate information is high and well within acceptable standards for similar surveys. Second, it could be argued that the SF-36 scale used was not sensitive enough to detect small changes in quality of life and that we might have missed important factors, such as height. Although we cannot exclude this possibility, we were able to detect several effects, including those of paternal socioprofessional background, educational level, and the presence of heart malformations or otological conditions. However, the SF-36 scales were not designed to detect the influence of height and the use of syndrome-specific quality-of-life measures addressing the relation between height and ability for daily life activities might have given different results. Altogether, the SF-36 has been used successfully in a variety of similar studies (19, 20). Third, the design of our study, in GH-treated patients, focused on young adults with this condition, and our conclusions may not be applicable to other age groups, in particular adolescents or older adults. It would have been interesting to study untreated women with Turner's syndrome of a similar age. However, since the early 1990s, almost all children diagnosed with Turner's syndrome are treated with GH in accordance with current international recommendations (9). Fourth, all data were obtained from routine examination in daily practice, and their reliability may be questioned. Last, whether our findings are generalizable to cultural contexts other than France remains to be established.

Several studies have assessed quality-of-life or psychosocial parameters in adults or youths with Turner's syndrome (reviewed in Refs. 2 and 10). Most have concluded that self-image or social functioning is low (10, 21). Depression scores were high (22, 23) or low (24). However, the recruitment of these patients from medical clinics or patient support organizations certainly introduced biases. In children and adolescent girls with Turner's syndrome, studies assessing the psychological benefits of increasing height by GH therapy have given inconsistent results (11, 12).

Our results have important implications for the care of children with Turner's syndrome and, more generally, with conditions that limit growth. In Turner's syndrome, height and the use of GH has been a major focus of health providers during the past 15 yr. Indeed, the patients studied here had a mean height of 150 cm, 6–8 cm greater than historical data on French Turner's syndrome patients (14). A long-term untreated contemporary control would have been needed for an optimal assessment of the influence of GH on health-related quality of life. However, the variance of height of our patients (95% between 139 and 161 cm) was three times greater than the estimate of height gain by GH. Another possibility is that the intervention itself (GH treatment) rather than its result (height increment) might have improved perceived health-related quality of life, therefore obscuring the influence of height itself. However, given the limitation indicated above, we found no evidence suggesting that interventions that increase heights by 5–10 cm have an effect on quality of life. In addition, the lower quality of life of patients with higher expectations from GH treatment indicates a long-term negative impact of unduly high expectations, as previously suggested (25). Finally, we found that quality of life was significantly lower in patients with otological disorders. Otological disorders are common in Turner's syndrome, affecting up to 70% of patients, and lead to hearing impairment in up to 90% of adult patients (2, 26, 27). In a placebo-controlled study (6) and in the Canadian long-term randomized, controlled trial (28), GH use was associated with an increase in frequency of otitis media by a factor of two or more. Our results therefore indicate that higher priority should be given to the care of otological problems in childhood and the prevention of their long-term consequences in adulthood.

In young adults with short stature, height has no detectable influence on quality of life (29). GH is increasingly used in GH-sufficient individuals with short stature, but quality of life has not been measured as an end point of these pharmacological interventions. Current estimates indicate adult height gains of 3.7–6 cm (30–32) that are unlikely to influence the quality of life in such individuals with short stature.

We conclude that quality of life, as assessed by SF-36, is normal and unaffected by height in young adults with Turner's syndrome treated with GH. However, in the absence of a contemporaneous group of untreated patients with Turner's syndrome, a beneficial effect of GH treatment irrespective of adult height attained cannot be ruled out. In that regard, our data raise the question as to whether GH treatment is justified in this patient population, given its constraints, costs, and potential side effects (33–35). Moreover, our results clearly indicate that greater attention should be paid to otological care and other specific needs in these patients, given the negative impact of otological problems on

daily life. These findings also call into question the use of GH to treat other conditions involving short stature, associated with a specific diagnosis or idiopathic, for which GH is currently used without evaluation of the psychosocial impact of these demanding and costly treatments. Above all, our findings suggest that for current and future indications for GH treatment, research into the overall impact of pharmacological intervention is necessary.

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