ORIGINAL ARTICLE

WILEY

Skeletal disproportion in girls with Turner syndrome and longitudinal change with growth-promoting therapy

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Abstract

Objective: Short stature in Turner syndrome (TS) may be accompanied by skeletal disproportion. This retrospective study investigates growth and disproportion from early childhood to adult height.

Study design: Data were collected from 59 girls prior to growth hormone (rhGH) treatment and in 30 girls followed up longitudinally. Standard deviation scores (SDS) for height (Ht), sitting height (SH) and sub-ischial leg length (LL) were compared and a disproportion score (SH SDS – LL SDS) calculated.

Results: In 59 girls, mean (SD) age 6.6 (2.1) years prior to rhGH treatment, LL SDS of −3.4 (1.1) was significantly lower than SH SDS of −1.2 (0.8) [$p < .001$]. In girls with Ht SDS < −2.0, disproportion score was > +2.0 in 27 (63%), cf eight (50%) with Ht SDS ≥ −2.0. For the longitudinal analysis, skeletal disproportion prior to rhGH was +2.4 (1.1) and +1.7 (1.0) on rhGH but prior to introduction of oestrogen [$p < .001$]. Disproportion at adult height was +1.1 (0.8), which was less marked than at the earlier time points [$p < .001$ for both comparisons]. Change in disproportion SDS over the first two years of rhGH predicted overall change in disproportion from baseline to adult height [R^2 51.7%, $p < .001$].

Conclusion: TS is associated with skeletal disproportion, which is more severe in the shortest girls and present in only half of those with milder degrees of short stature. Growth-promoting therapy may improve disproportion during both the childhood and pubertal phases of growth. Change in disproportion status two years after starting rhGH helps predict disproportion at adult height.

KEYWORDS
anthropometry, growth disorders, human growth hormone, longitudinal studies, methods, oestrogens, skeletal disproportion, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is a chromosomal disorder caused by an abnormal or missing second X chromosome in a phenotypic female.

Cardinal features of TS are short stature and primary ovarian insufficiency leading to failure in onset and progression of secondary sexual characteristics. At adult height, untreated women are an average of 21 cm shorter than their peers,[1] while girls receiving recombinant

human growth hormone (rhGH) can expect at least 5 cm of height gain.[2]

A proportion of girls with TS continue to be diagnosed beyond early childhood, with significant numbers presenting in adolescence. Previous studies have reported delays in diagnosis, with up to 22% of cases identified beyond the age of 12 years.[3,4] Girls presenting late often have the largest height deficit, while an earlier start of rhGH may lead to a greater gain in height.[2,5] Earlier diagnosis allows screening for other health problems associated with TS, for appropriate timing of pubertal induction and for counselling of future issues with fertility, while late diagnosis is associated with poorer psychosocial adjustment.[6]

Short stature in girls with TS is partly explained by haploinsufficiency in the short stature homeobox-containing gene (*SHOX*), which is critical to growth promotion. The *SHOX* gene is located on the short arm of the X chromosome and is spared from X-inactivation in the normal female embryo. Cohorts of children with *SHOX* deletions have been studied, and phenotypic similarities with TS have been identified.[7] Children with *SHOX* deletions are disproportionate as well as short, with short limbs but a near-normal sitting height.[8] Similar skeletal disproportion may exist in TS and could perhaps aid in achieving an earlier diagnosis in those with a milder degree of short stature. The effect of growth, rhGH and oestrogen therapy on skeletal disproportion in TS is unclear.

The aim of this study was to describe skeletal proportions in girls with TS prior to any growth-promoting therapies and evaluate the change in proportions over time in relation to growth, rhGH therapy and pubertal induction with oestrogen.

2 | SUBJECTS AND METHODS

2.1 | Subjects

This retrospective study involved analysis of routinely collected data as part of a clinical evaluation of the TS clinic. Case notes of 157 girls born from 1976, who attended a designated TS clinic at the Royal Hospital for Children, Glasgow, between 1990 and 2015 were reviewed. All girls had genetically confirmed TS karyotype by cytogenetic analysis of lymphocyte culture, with at least 20 cells counted. Girls were excluded if they had any other secondary chronic medical condition that may affect growth by last clinic visit (including hypothyroidism and coeliac disease) and if they did not require rhGH or oestrogen therapy for pubertal induction or hormone replacement.

2.2 | Methods

Out of the 157 girls, 59 girls had height (Ht) and sitting height (SH) measured at a routine outpatient clinic visit prior to any growth-promoting therapy and were at least four years of age prior to

treatment with rhGH. Sub-ischial leg length (LL) was obtained from measured Ht minus measured SH. Out of the 59 girls, 30 had serial measurements up to the attainment of final height to evaluate the impact of rhGH and oestrogen therapy. For these 30 girls, the last visit prior to introduction of oestrogen therapy or prior to signs of spontaneous puberty after 10 years of age was taken as the pre-pubertal measurement. Subjects were deemed to have reached adult height when height velocity was less than 1 cm per year (or 2 cm over two years where data were incomplete due to missed outpatient appointments).

Standard deviation scores (SDS) for Ht, SH and LL were calculated using the LMSgrowth application and the British 1990 reference population.[9] Skeletal disproportion was quantified using a disproportion score: sitting height SDS minus leg length SDS (SH SDS − LL SDS).[10] A subject with a relatively lower sitting height will have a lower, negative SH SDS − LL SDS, whereas a subject with a relatively lower leg length will have a higher, positive SH SDS − LL SDS. For example, an individual with SH SDS of −3.0 and LL SDS of −2.0 will have SH SDS − LL SDS of −1.0, indicating a relatively short back, while SH SDS of −2.0 and LL SDS of −3.0 gives SH SDS − LL SDS of +1.0, indicating relatively short legs. This difference can be considered a standard deviation score in its own right (the standard deviation of the SDS difference is close to one[11]), allowing it to be viewed in context with the standard deviation scores for Ht, SH and LL.

Recombinant human growth hormone (rhGH) via daily injections was administered at a dose of 0.3 mg/kg/week. Oestrogen in the form of ethinyloestradiol was used for pubertal induction, commencing at 2 micrograms (mcg) daily and building up to adult doses. Detailed descriptions of our method of pubertal induction and hormone replacement have previously been published.[12] In some girls, oxandrolone therapy was commenced at a dose of 0.05 mg/kg/day (maximum dose 2.5 mg daily) from the age of nine years, in conjunction with the use of rhGH.[12]

The association between change in height SDS following the first two years of rhGH and change in height SDS from the baseline measurement to adult height was analysed in the 26 girls in whom these data were available. In this group, the association between change in disproportion SDS over the first two years on rhGH and overall change in disproportion SDS was also analysed. IGF-1 data were not analysed since this hormone had not been measured systematically during the study period.

2.3 | Statistical analysis

Auxological parameters were normally distributed, and so descriptive data were expressed as mean (standard deviation). Differences were analysed using one-sample, two-sample and paired *t* tests where appropriate, and using chi-square analysis for categorical data, with statistical significance set at less than 0.05. The impact of various factors on skeletal disproportions at adult height was assessed by linear regression analysis. The Bonferroni method was used to adjust for multiple

TABLE 1 Univariate regression analysis for predictors of skeletal disproportion at final height, as measured by the disproportion score: difference in sitting height and sub-ischial leg length standard deviation scores (SH SDS – LL SDS)

	SH SDS–LL SDS			
	R^2	p	β	99% CI
Age at starting rhGH	2.6	0.4	+0.06	-0.14, +0.26
Age at starting synthetic oestrogen	3.1	0.4	-0.09	-0.38, +0.19
Change in height SDS following two years of rhGH	<0.1	0.9	+0.01	-1.01, +1.04
Length of rhGH therapy prior to synthetic oestrogen	4.1	0.3	-0.05	-0.20, +0.09
Karyotype	2.8	0.4	+0.28	-0.62, +1.18
Disproportion prior to rhGH	37.4	<0.001	+0.48	+0.14, +0.82
Final height	10.0	0.09	-0.05	-0.13, +0.03

Abbreviation: rhGH, recombinant human growth hormone.

comparisons, giving a 99% adjusted confidence interval for the serial measurements and for the regression analysis displayed in Table 1.

2.4 | Ethical approval

This study did not require ethical approval or informed consent as it was conducted as part of healthcare evaluation of routine clinical practice and according to national guidance.

3 | RESULTS

3.1 | Baseline measurements, prior to rhGH

Mean age at first sitting height measurement was 6.6 (2.1) years. Out of the 59 subjects, a specific karyotype was recorded for 57 girls: 45,X (19); 45,X/46,XiXq (15); 45,X/46,XY (4); 45,X/47,XXX (4), 45,X/46,XX (3); and others (including structural anomalies) (12). The two remaining subjects had a karyotype confirming TS but we were unable to attain records of the specific karyotype. These subjects are known not to have undergone gonadectomy and therefore can be assumed to have had no Y material detected. Mean Ht SDS at first measurement was −2.6 (0.9), while LL SDS of −3.4 (1.1) was lower than mean SH SDS of −1.2 (0.8) [$p < .001$; Figure 1A]. Mean SH SDS – LL SDS was + 2.2 (1.1), which was significantly greater than zero [$p < .001$; Figure 1B]. Out of the 59 girls, 35 (59%) had a disproportion score greater than +2.0. There was no difference in disproportion in those girls with 45,X karyotype, +2.5 (1.1), compared with other karyotypes, +2.0 (1.0) [$p = .10$], or between those with a Y chromosome, +1.6 (1.2), compared with the rest of our subjects, +2.2 (1.1) [$p = .37$]. No orthopaedic problems, including progressive varus deformity of the proximal tibia, were recorded in the study patients.

In a multiple regression analysis, with Ht SDS and age as independent factors, only Ht SDS was significantly associated with skeletal disproportion [$p = .01$, 95% confidence interval (CI): −0.68 to −0.10].

This indicates that disproportion is greater in shorter girls and that variability in stature is driven more by differences in leg length than in trunk length. In those girls with a Ht SDS of less than −2.0, 27 (63%) had a disproportion score greater than +2.0, compared with eight (50%) of those with a Ht SDS of −2.0 or greater [$p = .37$].

3.2 | Longitudinal changes in growth with rhGH, oxandrolone and oestrogen treatment

In 30 girls, measurements were available at each time point of interest—prior to rhGH treatment, pre-pubertal prior to introduction
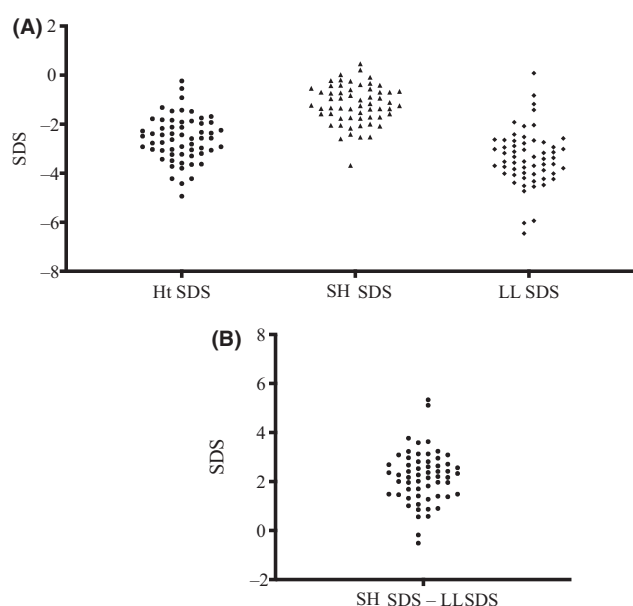

FIGURE 1 (A, B) Body proportions in 59 girls with Turner syndrome prior to recombinant human growth hormone therapy, showing height (Ht), sitting height (SH) and sub-ischial leg length (LL) standard deviation score (SDS) (A); and the disproportion score – SH SDS minus LL SDS (B)

of oestrogen and at final height (Figure 2A,B). For this longitudinal analysis, mean age was 6.5 (2.1) years prior to rhGH treatment, 12.5 (1.5) years pre-pubertal prior to introduction of oestrogen and 18.0 (1.0) years at attainment of final height. Of the 30 girls, 18 (60%) were treated with oxandrolone, commencing at 12.6 (2.2) years. Mean duration of oxandrolone therapy was 3.0 (1.4) years. Of the 18 treated with oxandrolone, 12 (67%) received oxandrolone prior to introduction of oestrogen.

Mean Ht SDS prior to rhGH was −2.7 (0.8). After 5.8 (3.2) years of rhGH treatment, mean Ht SDS was −2.2 (0.8) at the pre-pubertal measurement, prior to introduction of oestrogen therapy [$p = .001$]. Mean adult height SDS was −1.9 (0.9), which was greater than both of the other timepoints [$p < .001$ vs. baseline, $p = .009$ vs. pre-pubertal].

Figure 2A,B shows differences in SH SDS and LL SDS with follow-up. Mean SH SDS was not different between baseline and the assessment prior to commencement of oestrogen therapy at −1.1 (0.6) and −1.3 (0.6), respectively [$p = .23$]. At attainment of adult height, mean SH SDS was −1.0 (0.7), which was also not different from baseline [$p = .37$]. However, there was significant difference between the measurement prior to oestrogen therapy and adult height [$p = .002$]. Mean LL SDS prior to rhGH was −3.6 (1.1), and this was −3.0 (1.0) after rhGH treatment but prior to introduction of oestrogen [$p < .001$]. Mean LL SDS at adult height was −2.1 (1.0), which was significantly different compared with the two other timepoints [$p < .001$ for both comparisons].

3.3 | Changes in disproportion score with follow-up

Prior to rhGH, mean disproportion score was +2.4 (1.0), decreasing to +1.7 (1.0) after rhGH treatment but prior to introduction of oestrogen [$p < .001$] (Figure 3). Disproportion at adult height was +1.1 (0.8) which was significantly lower compared with the other two timepoints [$p < .001$ for both comparisons]. Out of the 30 girls, three (10%) had a disproportion score of +2.0 or greater at adult height.

3.4 | Factors associated with adult height and disproportion

To evaluate factors associated with skeletal proportions at adult height, univariate linear regression was performed. Table 1 shows regression analysis with SH SDS – LL SDS as the dependent factor. Disproportion at adult height was not associated with age of starting rhGH, age of starting oestrogen, improvement in height SDS following the first two years of rhGH, pre-pubertal duration of rhGH, karyotype (45,X vs others) or adult height. However, disproportion at adult height was associated with disproportion prior to rhGH [$p < .001$]. Change in height SDS from the initial measurement to final adult height was associated with change in height SDS during the first two years of rhGH therapy [R^2 26.1%, $p = .008$, β 0.77, 95% CI (+0.23, +1.32)]. Similarly, change in skeletal disproportion SDS from the baseline measurement to adult height was associated with the change in disproportion measured over the first two years of treatment with rhGH [R^2 51.7%, $p < .001$, β 0.56, 95% CI (+0.34, +0.77)].

4 | DISCUSSION

This study confirms the finding of abnormal body proportions in children with TS, with disproportionately shorter legs compared with trunks,[13-15] and adds detail to our knowledge of change in proportions during rhGH-promoted growth. Our analysis is important in that we studied a unique cohort of patients who were followed up in one tertiary centre clinic dedicated for TS patients, and also that our subjects had no other underlying co-morbidities that may impact on growth. We have clearly separated the phases of growth and have shown for the first time using longitudinal data that skeletal disproportion (SH SDS – LL SDS) was less marked by the end of childhood growth and largely resolved at adult height with rhGH therapy and puberty. Our results support published data on less marked disproportion in adults with TS but also provide more detail on longitudinal changes in growth with rhGH, and oestrogen therapy.[14,16] While improvement in height during the first two years of rhGH therapy did not predict
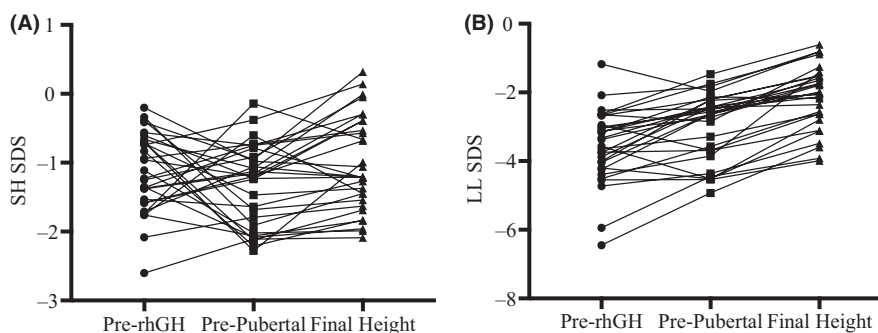
FIGURE 2 (A, B) Differences in sitting height (SH) and sub-ischial leg length (LL) standard deviation scores (SDS) in 30 girls with Turner syndrome treated with recombinant human growth hormone (rhGH) and oestrogen therapy. SH SDS and LL SDS were assessed at three time points: prior to rhGH therapy (pre-rhGH), prior to oestrogen therapy (pre-pubertal stage) and at final height
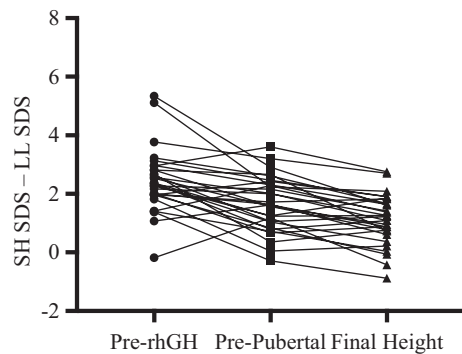
FIGURE 3 Differences in disproportion score in 30 girls with Turner syndrome receiving recombinant human growth hormone (rhGH) and oestrogen therapy. Disproportion score (sitting height standard deviation score (SH SDS) minus sub-ischial leg length standard deviation score (LL SDS)) was assessed at three time points: prior to rhGH therapy (pre-rhGH), prior to oestrogen therapy (pre-pubertal stage) and at final height

adult disproportion in the individual patient, we found that changes in height and disproportion over this time period were highly predictive of the overall change in height and disproportion from commencement of rhGH to final adult height. Apart from its retrospective design, our study findings are limited by the absence of an untreated group of girls with Turner syndrome, against whom changes in growth and disproportion attributable to growth-promoting therapy could be evaluated. In practice, however, it would have been difficult to justify denying rhGH treatment to short girls with TS during the study period, and this ethical constraint would apply to any future prospective study.

In our cohort, in early childhood, approximately 60% of girls with TS had SH SDS – LL SDS > +2.0, an indicator of skeletal disproportion. This is consistent with published literature in TS, but our prevalence is lower than the almost 90% disproportion seen with *SHOX* deficiency.[13] While disproportion in TS has been previously reported,[13-15] it is unclear if these studies excluded those with other underlying chronic conditions that may affect growth. In TS, *SHOX* haploinsufficiency is thought to be largely responsible for short stature and skeletal abnormalities. *SHOX* is highly expressed in multiple tissues, and studies in the human foetal growth plate and in adolescents have shown that it is identified predominantly in the hypertrophic zone.[17,18] It is mainly confined to the distal ends of the humerus, radius, ulna and lower limb bones, as well as the maxilla, mandible, first and second pharyngeal arches.[19] It is therefore logical that *SHOX* insufficiency should have a greater impact on the growth of the limbs rather than on the axial skeleton, leading to skeletal disproportion, as our results illustrate. We were unable, in this retrospective study, to investigate a correlation between features of skeletal dysplasia consistent with *SHOX* haploinsufficiency and the severity of skeletal disproportion. This possible association should inform the design of a future prospective study.

Late diagnosis of TS still occurs, with approximately 20% diagnosed in adolescence and adulthood.[3,4,20] It is clinical convention

that a screening karyotype should be performed in all short girls.[21] However, interpreting height in the parental context may be more specific for the diagnosis of TS, especially with a girl who is relatively tall.[22] We hypothesized that skeletal disproportion in a girl with a milder degree of short stature may be an additional clue to raise clinical suspicion of TS. Our results, however, showed that only about 50% of girls with milder degrees of short stature had evidence of skeletal disproportion defined by SH SDS – LL SDS > +2.0, meaning that this skeletal disproportion index (SH SDS – LL SDS) is unlikely to be a helpful diagnostic clue based on the threshold we used in our analysis. We found no difference in disproportion between the subgroups of karyotype we assessed, although patient numbers in this sub-analysis were small. It would be interesting to further evaluate the effect of karyotype on disproportion in a larger cohort of patients.

Our longitudinal analysis showed that there was some improvement in skeletal disproportion following an average of six years of rhGH therapy prior to pubertal induction with oestrogen, and disproportion resolved by adult height. On the other hand, in a dose-response trial of rhGH in 68 girls with TS, where subjects were randomized to three groups, receiving varied doses of rhGH (ranging from 4 to 8 IU/m^2 of rhGH), skeletal disproportion did not improve after the first seven years of rhGH. Changes in disproportion did not appear to be related to the dose of rhGH.[14] In another study of 73 girls and 120 women with TS, where around one third had received rhGH, disproportion was less frequent at adult height but did not differ regardless of whether rhGH therapy was administered.[13] However, both of these studies used measures of disproportion based on the relationship between sitting height and height, which could impact on the interpretation of their results. The ratio between sitting height and height will be inherently greater in shortest girls due to the statistical concept of regression to the mean. Thus, when a girl has one very extreme measurement, for example extreme short stature, then by the law of averages, other measurements are likely to be less extreme and closer to the population mean (causing sitting height to be proportionately greater). This strong inverse relationship between height and the sitting height-to-height ratio could then skew results. The disproportion score used in our study avoids the confounding factor of height and focusses solely on disproportion itself, leading to more reliable results.

In addition to our other analysis, we studied various factors that might help predict skeletal proportions at final adult height, following a course of rhGH and synthetic oestrogen. Our data show that while childhood disproportion predicts adult disproportion, improvement in height SDS during the first two years of rhGH does not predict disproportion at adult height. By contrast, height SDS increase over the first two years of rhGH was predictive of overall increase in height SDS on rhGH, in keeping with findings from previous trials.[23] Additionally, we have shown for the first time that change in skeletal disproportion over the first two years of rhGH is predictive of overall change in disproportion from commencement

of rhGH to final height. Thus, two years after starting rhGH appears a valuable time point for assessing growth status and predicting the changes in growth and disproportion that an individual patient is likely to experience on treatment. Others have found no association between final adult height and factors such as age at commencing rhGH, duration of therapy or age at commencing synthetic oestrogen,[24] and similarly, we have found no association between these factors and disproportion at final height.

We found that skeletal disproportion was less marked at adult height following rhGH therapy and pubertal induction. While some of our subjects with TS were commenced on oxandrolone prior to oestrogen therapy, a previous study from a randomized trial of oxandrolone in TS did not show any effect on body proportions.[16]

The majority of patients with TS require synthetic oestrogen for induction of puberty, including all of the subjects included in our study.[12] Previous evidence on the effect of synthetic oestrogen on skeletal disproportion is limited. In a UK study, disproportion was not different between 16 girls with TS who did not receive oestrogen and six girls who have received oestrogen when evaluated at a median age of 13.8 years (range 9 to 19.5 years).[25] A cohort of Danish adult women with TS who had not received rhGH but were treated with oestrogen did not exhibit disproportion at adult height.[26] Our longitudinal analysis identified ongoing improvement in disproportion score following oestrogen therapy. The average reduction in disproportion score following rhGH therapy (−0.7 SD) and oestrogen therapy (−0.6 SD) was relatively similar in our analysis. Our results and those of published evidence do not allow us to draw conclusions on factors which contribute to the less marked disproportion at adult height in TS. It is of course possible that this is the natural evolution in untreated people with TS. However, taken together, our results and those of published data provide reassurance that the current treatment regimen of promoting growth and managing hypogonadism in these girls does not enhance disproportion and may indeed help to lessen it.

5 | CONCLUSION

Skeletal disproportion is prominent in untreated young girls with TS, with reduced leg length. This is more severe in the shortest girls and is present in only half of those with milder degrees of short stature. Our data provide reassurance that growth-promoting therapy has no adverse effect on, and may improve, this disproportion. Change in height and disproportion status two years after starting rhGH helps predict adult height and degree of disproportion, indicating that this is a useful time point to gauge treatment responsiveness.

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REFERENCES

1. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. *Arch Dis Child*. 1985;60:932-935.
2. Betts PR, Butler GE, Donaldson MDC, et al. A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child*. 1999;80:221-225.
3. Savendahl L, Davenport ML. Delayed diagnoses of Turner's syndrome: proposed guidelines for change. *The Journal of pediatrics*. 2000;137(4):455-459.
4. Massa G, Verlinde F, De Schepper J, et al. Trends in age at diagnosis of Turner syndrome. *Arch Dis Child*. 2005;90(3):267-268.
5. Davenport ML, Crowe BJ, Travers SH, et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab*. 2007;92(9):3406-3416.
6. Reimann GE, Bernad Perman MM, Ho PS, Parks RA, Comis LE. Psychosocial characteristics of women with a delayed diagnosis of Turner syndrome. *J Pediatr*. 2018;3476(18):206-211.
7. Ross JL, Scott C, Marttila P, et al. Phenotypes associated with SHOX deficiency. *J Clin Endocrinol Metab*. 2001;86(12):5674-5680.
8. Binder G, Ranke MB, Martin DD. Auxology is a valuable instrument for the clinical diagnosis of SHOX haploinsufficiency in school-age children with unexplained short stature. *J Clin Endocrinol Metab*. 2003;88(10):4891-4896.
9. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med*. 1998;17(4):407-429.
10. Qayyum N, Alcocer L, Maxwell H, et al. Skeletal disproportion in children with chronic renal disease. *Horm Res*. 2003;60:221-226.
11. Dangour AD, Schilg S, Hulse JA, Cole TJ. Sitting height and sub-ischial leg length centile curves for boys and girls from Southeast England. *Ann Hum Biol*. 2002;29:290-305.
12. Donaldson MD, Gault EJ, Tan KW, Dunger DB. Optimising management in Turner syndrome: from infancy to adult transfer. *Arch Dis Child*. 2006;91(6):513-520.
13. Malaquias AC, Scalco RC, Fontenele EG, et al. The sitting height/height ratio for age in healthy and short individuals and its potential role in selecting short children for SHOX analysis. *Horm Research Paediatr*. 2013;80(6):449-456.
14. Sas TC, Gerver WJ, de Bruin R, et al. Body proportions during long-term growth hormone treatment in girls with Turner syndrome

participating in a randomized dose-response trial. *J Clin Endocrinol Metab*. 1999;84(12):4622-4628.

15. Rongen-Westerlaken C, Rikken B, Vastrick P, et al. Body proportions in individuals with Turner syndrome. The Dutch Growth Hormone Working Group. *Eur J Pediatr*. 1993;152(10):813-817.

16. Menke LA, Sas TC, Zandwijken GR, et al. The effect of oxandrolone on body proportions and body composition in growth hormone-treated girls with Turner syndrome. *Clin Endocrinol*. 2010;73(2):212-219.

17. Marchini A, Marttila T, Winter A, et al. The short stature homeodomain protein SHOX induces cellular growth arrest and apoptosis and is expressed in human growth plate chondrocytes. *J Biolo Chem*. 2004;279(35):37103-37114.

18. Munns CJ, Haase HR, Crowther LM, et al. Expression of SHOX in human fetal and childhood growth plate. *The Journal of clinical endocrinology and metabolism*. 2004;89(8):4130-4135.

19. Clement-Jones M, Schiller S, Rao E, et al. The short stature homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome. *Hum Mol Genet*. 2000;9(5):695-702.

20. Apperley L, Das U, Ramakrishnan R, et al. Mode of clinical presentation and delayed diagnosis of Turner Syndrome: a single centre UK study. *Int J Pediatr Edocrinol*. 2018;2018(4).

21. Gravholt CH, Andersen NH, Conway GS, et al. International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome. proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177(3):G1-G70.

22. Ouarezki Y, Cizmecioglu FM, Mansour C, et al. Measured parental height in Turner syndrome – a valuable but underused diagnostic tool. *Eur J Pediatr*. 2018;177(2):171-179.

23. Ranke MB, Lindberg A, Chatelaine P, et al. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab*. 2000;85(11):4212-4218.

24. Ahn JM, Suh JH, Kwon AR, et al. Final adult height after growth hormone treatment in patients with Turner syndrome. *Horm Res Paediatr*. 2019;91(6):373-379.

25. Hughes PC, Ribeiro J, Hughes IA. Body proportions in Turner's syndrome. *Arch Dis Child*. 1986;61(5):506-507.

26. Gravholt CH, Naeraa RW. Reference values for body proportions and body composition in adult women with Ullrich-Turner syndrome. *Am J Med Genet Part A*. 1997;72:403-408.