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Reported shoes size during GH therapy: is foot overgrowth a myth or reality?

Débora C. F. Lago[1], Cláudia A. Coutinho[1], Cristiane Kochi[1], Carlos A. Longui[1]

ABSTRACT

Objectives: To describe population reference values for shoes size, and to identify possible disproportional foot growth during GH therapy. **Materials and methods:** Construction of percentile chart based on 3,651 controls (male: 1,838; female: 1,813). The GH treated group included 13 children with idiopathic short stature (ISS) and 50 children with normal height, but with height prediction below their target height; male: 26 and female: 37 mean ± SD age 13.3 ± 1.9 and 12.9 ± 1.5 years, respectively. GH (0.05 mg/kg/day) was used for 3.2 ± 1.6 years, ranging from 1.0-10.3 years. Height expressed as SDS, target height (TH) SDS, self-reported shoes size and target shoes size (TSS) SDS were recorded. **Results:** Reference values were established showed as a foot SDS calculator available online at www.clinicalcaselearning.com/v2. Definitive shoes size was attained in controls at mean age of 13y in girls and 14y in boys (average values 37 and 40, respectively). In the study group, shoes size was -0.15 ± 0.9 and -0.02 ± 1.3 SDS, with target feet of 0.08 ± 0.8 and -0.27 ± 0.7 SDS in males and females, respectively. There was a significant positive correlation between shoes size and familial TSS, between shoes size and height and between TSS and TH. There was no correlation between duration of GH treatment and shoes size. Our data suggest that during long-term treatment with GH, patients maintain proportional growth in shoes size and height, and the expected correlation with the familial target. **Conclusions:** We conclude that there is no excessive increase in the size of foot as estimated by the size of shoes in individuals under long term GH therapy.

Keywords
Growth hormone; growth; foot

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INTRODUCTION

The recombinant human growth hormone (GH) has been used since the 80s in children with GH deficiency (1). During treatment, it is observed an initial growth of feet and hands, eventually determining the recovery of normal size expected for age. GH has also been employed in other non GH deficient conditions presenting short stature, such as Turner syndrome and Prader-Willi syndrome (PWS), chronic renal failure, children born small for gestational age (SGA) and idiopathic short stature (ISS) (2-5). Recovery of feet and hands size also occurs in SGA and PWS patients (3), known diseases presenting reduced extremities before therapy.

Previous reports, describing body proportions in hypocondroplasia and in Turner syndrome patients (2), suggest that a disproportional growth of the extremities occurs during GH therapy. This is consistent with the underlying mechanism of osteodysplasia observed in the pathogenesis of short stature in these conditions. In patients with chronic renal disease, a proportional growth was identified during GH treatment (4). In Turner syndrome, the use of GH in higher than the replacement dose, represents an additional risk for excessive growth of the extremities (2).

Despite of initial increase in hands and feet during GH therapy it remains uncertain whether long-term treatment and/or higher than replacement doses of GH can induce disproportional enlargement of extremities. One complicating factor preventing the recognition of the actual impact of GH on foot size is the lack of population based reference data.

The aims of the present study were: (i) to describe population reference values for the shoes size, according to the age and gender. (ii) to describe shoes size of ISS patients, as well in patients with stature into the normal range but with reduced height in relation to the expected for target height (RH/TH) non-GH deficient patients under treatment with GH, identifying the impact of treatment on its size.

MATERIALS AND METHODS

This is a cross-sectional study, which employed a questionnaire, recording all personal and anthropometric data including the self-reported number of shoes, in control subjects and in ISS patients under GH treatment for at least one year. The control population consisted of students and family members who never received GH therapy. Patients receiving GH were followed longitudinally by the same physician. All individuals, children or their parents in case of very young, were asked to record the shoes size number. In a similar way of French shoes number, Brazilian shoes size is defined as the foot size length corrected by the factor 0.66 cm. As a consequence of different Brazilian feet shape, the correspondent shoes size is decreased by 2 points in relation to French standards. Therefore, Brazilian shoes number is calculated by employing the following formula: shoes size number = [(feet length/0.66)-2].

If the shoes size was uncertain, the midpoint between the two reported numbers was assigned as reported value. The shoes number of each individual was also compared to the shoes number of their respective parents. All patients and parents provided previous written consent approved by the institutional human research ethics committee (process # 076/11).

Control population group

The reference population data was previously described (6), and presented in this study including 3,651 school students from five government and private schools and family members (Male: 1,838; Female: 1,813), height SDS (mean ± SD) of 0.33 ± 1.1 and 0.21 ± 0.93 was observed in female and male controls, respectively. Height and target height were grouped by chronological age from 2 to 18 years, and ≥ 19 years in boys, and from 2 to 15 years, and ≥ 16 years in girls (Table 1). For descriptive analysis of the values, we used the software SigmaStat for Windows version 3.5 (SPSS, San Jose, CA, USA). To draw the percentile chart according to age and gender, we used the software Stata 12.0 for Windows. The final percentile curves were generated by considering these three variables SD scores, corresponding to each percentile employing the formula: M (1 + LSZ). This method corrects for skewness in the data distributions: M stands for mean, S stands for a parameter and L stands for the Box-Cox power scal-

Table 1. Height SDS and target height SDS* of individuals from control population

Age (years)	Female				Male			
	n	Height (SDS)	n	TH (SDS)	n	Height (SDS)	n	TH (SDS)
2	17	-0.11(1.8)	14	-0.28 (0.9)	27	0.53 (1.8)	23	-0.59 (0.9)
3	21	1.05 (1.6)	19	-0.02 (0.9)	27	0.8 (1.5)	21	-0.51 (0.6)
4	17	1.02 (1.2)	15	-0.3 (0.8)	26	1.01 (1.5)	25	-0.29 (0.9)
5	34	0.98 (1.3)	32	-0.7 (0.9)	32	0.1 (1.7)	24	-0.28 (1.0)
6	108	0.49 (1.1)	96	-0.37 (0.9)	115	0.41 (1.2)	107	-0.36 (0.8)
7	153	0.34 (1.1)	125	-0.35 (0.9)	133	0.28 (1.0)	113	-0.39 (0.9)
8	143	0.15 (1.0)	112	-0.41 (0.9)	130	0.08 (1.0)	134	-0.42 (0.9)
9	178	0.42 (1.1)	144	-0.52 (0.8)	134	0.19 (1.0)	121	-0.44 (0.8)
10	183	0.4 (1.1)	138	-0.45 (0.9)	149	0.27 (1.2)	137	-0.39 (0.9)
11	183	0.38 (1.1)	141	-0.35 (0.9)	135	0.26 (1.0)	107	-0.4 (0.7)
12	153	0.09 (1.1)	116	-0.48 (0.8)	124	0.31 (1.2)	99	-0.57 (0.8)
13	105	0.18 (1.0)	80	-0.44 (0.9)	126	0.3 (1.2)	103	-0.42 (0.8)
14	121	-0.27 (1.0)	80	-0.64 (0.9)	135	0.22 (1.2)	100	-0.5 (0.8)
15	112	-0.12 (1.2)	60	-0.56 (0.9)	75	-0.02 (1.1)	43	-0.24 (0.9)
≥ 16	285	-0.09 (1.1)	211	-0.51 (0.7)	78	-0.2 (1.1)	47	-0.48 (0.9)
17					86	-0.17 (1.1)	45	-0.44 (0.8)
18					61	-0.24 (1.1)	46	-0.48 (0.8)
≥ 19					245	-0.28 (1.2)	214	-0.48 (0.8)

* Height of both mother and father was not available in all cases. and brothers and sisters were also included as control individuals. Therefore. Target Height (TH) was possible to calculate in around 70% of control individuals.

ing (7,8). That is required to transform the skewed data to normality, now employed by many modern growth references.

GH treated patient group

GH treated group included 50 children with height within normal range, but height adjusted to bone age ≤ 1 SDS below the target height of non-recognized causes. This group represents a non-classical indication for GH treatment and was included as part of research protocol. We also included in this GH treated group 13 children with idiopathic short stature (ISS) being 7 with familial short stature and 6 with constitutional delay of growth and puberty, both with reduced final height prediction. Reported shoes number was obtained from the 63 GH treated patients, 26 boys (mean age ± SD: 13.3 ± 1.9 years) and 37 girls (mean age ± SD: 12.9 ± 1.5 years).

GH was used at a dose of 0.05 mg/kg/day for a mean ± SD period of 3.1 ± 1.6 years in females, ranging from 1.0 to 7.5 years; and in males for 3.4 ± 2.5, ranging from 1.0 to 10.3 years. The age at GH therapy was started was 10.0 ± 1.8 years in girls and 9.8 ± 2.6 years in boys. At the beginning of treatment, height SDS was -1.2 ± 0.9 and -1.5 ± 1.1 in girls and boys, respectively.

At the last visit after 3 years of treatment, height SD score was -0.3 ± 0.7 in girls and -0.5 (± 0.9 in boys, corresponding to an increment in height of 0.9 SDS, both in girls as in boys. Target height of GH treated group was 160 ± 4.0 cm in girls and 172 ± 4.0 cm in boys; target height SDS was -0.4 ± 0.6 and -0.6 ± 0.6, in female and male, respectively, showing that TH was attained in the majority of treated patients.

Similar to what was done to obtain target height, after recognizing that (i) shoes size of individuals from control population was correlated with the shoes size of parents (ii) mean difference of female to male shoes number is around #3, we were able to calculate the familial determinant of shoes size (Target Shoes Size, TSS) by using the formula: TSS = (number of the father shoes plus number of the mother shoes ± 3) / 2. Both the familial correlation in shoes size and the factor three of correction between genders were established based on 471 individuals and their parents from the control population (male: 238; female: 233), with age above 19 years, who already reached the final shoes size.

In order to identify the impact of GH therapy among children in different ages and in both genders, the statistical analyses were performed by expressing the shoes size in SD scores in comparison to the reference data generated from control population.

RESULTS

The representative growth curve of shoes size of Brazilian individuals is shown in figure 1. The final shoes number was attained in the reference population at a mean age of 13 years in girls and 14 years in boys soon after growth spurt ends. The descriptive size of shoes according to the age and gender is shown in table 2. The corresponding sizes for the European and American populations were calculated by using the sites: http://www.abravest.org.br/arquivos/006.pdf and http://www.humanitarian.com.br/Ajuda/TabelaTamanhos.

In the reference group, the median (p25-75) shoes size was 37.0 (36.0 - 37.5) in females and 40.0 (39.0 - 42.0) in males. In this group, target shoes size was positively correlated to target height, both in girls (r: 0.51; $p < 0.001$) as in boys (r: 0.54; p: < 0.001). However, as the coefficient of correlation was around 0.5 no individual correction of shoes size by height was performed.

In the study group, the calculated SD score for shoes size was -0.15 ± 0.9 in females and -0.02 ± 1.3 in males. The target shoes size of females treated with GH was 36 ± 1.0 with SDS scores of 0.08 ± 0.8, and 39.5 ± 0.7 in males) with SDS of -0.27 ± 0.7.

Figure 2 shows the correlation between the SDS score of shoes size and its respective familial target shoes size. There was a significant correlation between these two variables in females (p: 0.004).

In girls as in boys, there is no correlation between duration of GH treatment and the SD scores for shoes size, suggesting that no significant increase in shoes size has been induced during prolonged treatment with growth hormone (Figure 3). There are significant positive correlation between shoes size and height (upper panel) and also significant correlation between target shoes size and target height in GH treated patients. The maintenance of correlations between these variables suggests that during long-term treatment, GH treated patients keep proportional growth of shoes and height, and the expected correlation with the familial targets (Figure 4).

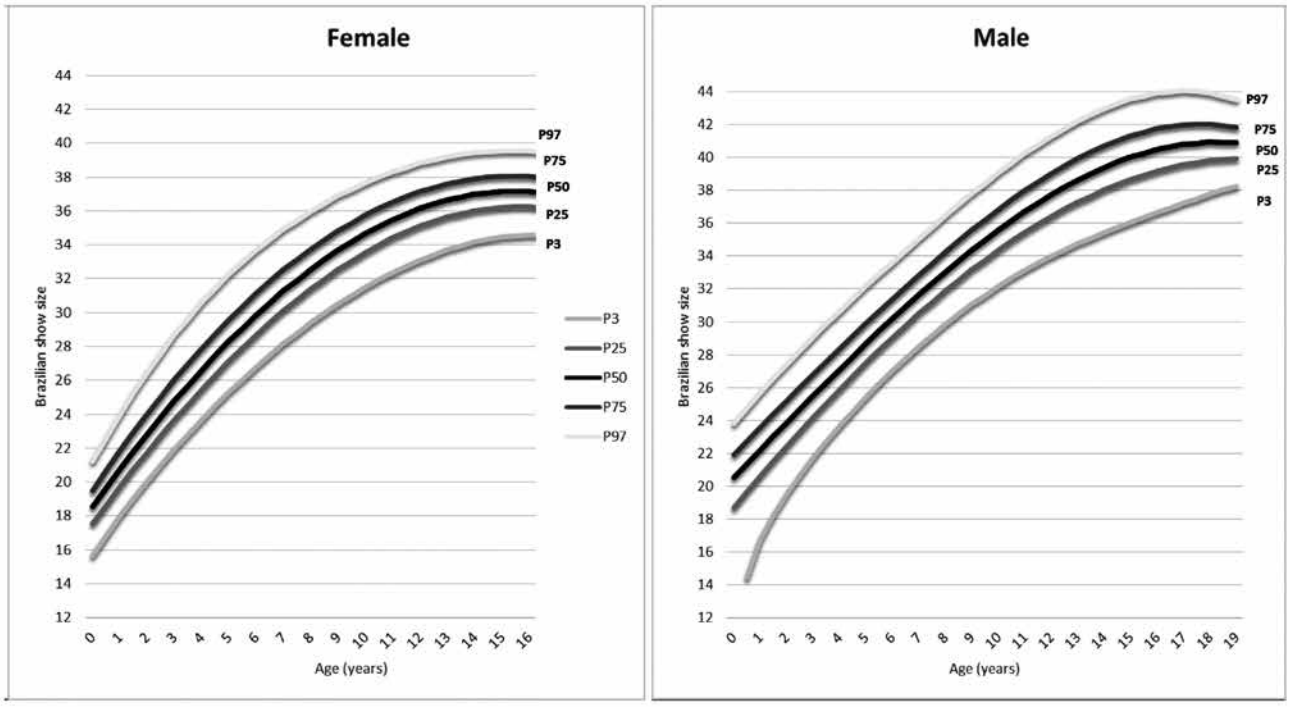

Figure 1. Representative chart showing the shoes size according to gender and age.

Table 2. Descriptive shoes size of the Brazilian population showed as a mean. SD, median and interquartile interval (p25-p75), according to age and gender

Age (years)	Female					Male				
	n	Median (p25- 75)	Mean (SDS)	Mean Europe	Mean USA	n	Median (p25-p 75)	Mean (SDS)	Mean Europe	Mean USA
2	32	23.0 (22.0-23.5)	23 (1.4)	25.5	8.5	37	23.5 (22.7-24.0)	23 (2.3)	25.5	8.5
3	40	25.0 (23.7-25.0)	24 (2.4)	26	9	39	26.0 (25.0-27.0)	26 (1.9)	27	10
4	32	26.0 (25.0-27.0)	26 (2.92)	27	10	41	27.0 (26.0-28.0)	27 (1.6)	28	11
5	46	28.0 (26.0-29.5)	28 (2.3)	29	11.5	41	29.0 (27.0-30.0)	29 (1.9)	30	12.5
6	114	30.0 (29.0-31.0)	30 (1.8)	31	13	124	30.0 (29.0-31.0)	30 (2.2)	31	13
7	138	31.0 (29.5-32.0)	31 (2.1)	32	1	139	32.0 (30.0-33.0)	32 (1.9)	33	1.5
8	130	32.0 (31.0-34.0)	32 (2.1)	33	1.5	148	32.5 (31.5-34.0)	32.5 (2.1)	33	1.5
9	168	34.0 (32.5-35.0)	34 (2.0)	36	5.5	140	34.0 (33.0-35.0)	34 (1.9)	36	5.5
10	161	35.0 (33.5-36.0)	34.5 (1.7)	36	6.0	158	35.5 (34.5-37.0)	35 (1.9)	37	6.5
11	168	36.0 (34.2-37.0)	35.5 (1.7)	37	7.0	134	36.0 (35.0-37.5)	36 (1.9)	38	7.5
12	135	36.0 (35.5-37.0)	36 (1.3)	38	7.5	115	37.0 (36.0-39.0)	37 (2.4)	39	8
13	95	37.0 (35.6-37.5)	36.5 (1.8)	38	7.5	119	39.0 (37.0-40.0)	39 (2.0)	41	9.5
14	91	37.0 (36.0-37.9)	37 (1.2)	39	8	113	40.0 (38.4-41.0)	40 (1.9)	42	10.5
15	75	37.0 (36.0-38.0)	37 (1.4)	39	8	52	40.0 (38.0-40.5)	39 (1.7)	41	9.5
≥ 16	348	37.0 (36.0-37.1)	37 (1.2)	39	8	54	40.0 (39.0-42.0)	40 (1.8)	42	10.5
17						58	41.0 (40.0-42.0)	41 (1.4)	43	11.5
18						49	40.5 (39.4-42.0)	41 (2.0)	43	11.5
≥ 19						233	40.0 (39.0-42.0)	40 (1.7)	42	10.5

n: number of children by age.

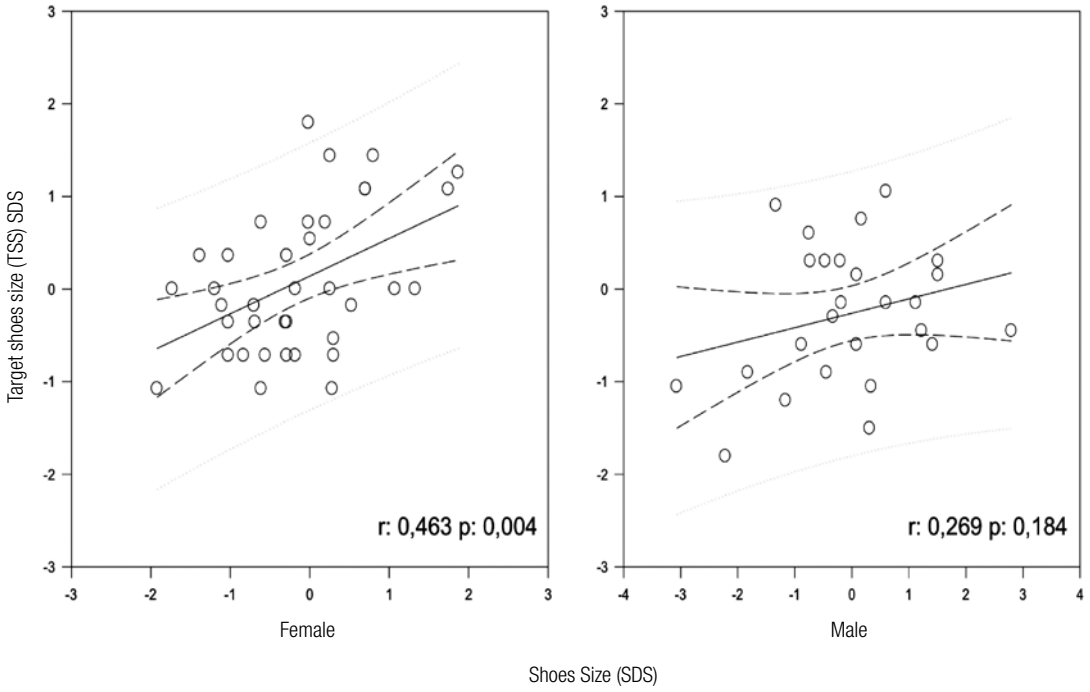

Figure 2. Correlation between the SDS score for shoes size and its respective familial target shoes size (TSS) in idiopathic short stature (ISS) patients as well in patients with reduced height to target height under GH therapy. TSS was calculated by using the formula: TSS = (number of the father shoes plus number of the mother shoes ± 3) / 2.

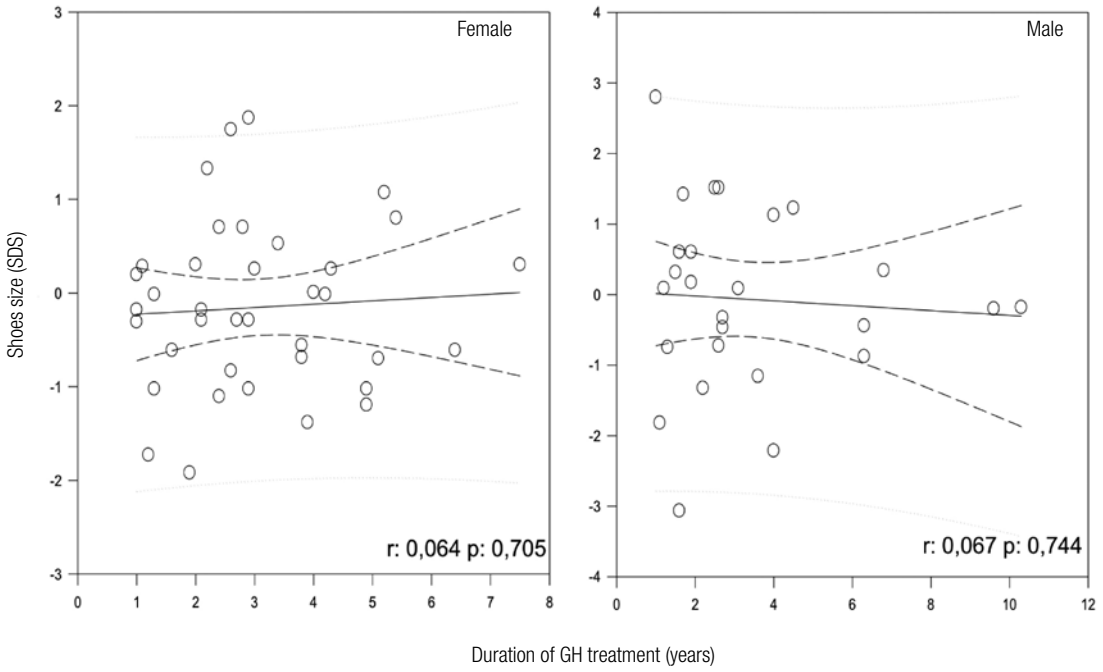

Figure 3. Correlation between shoes size SDS and the duration of GH treatment in patients with idiopathic short stature (ISS) and patients with reduced height to target height.

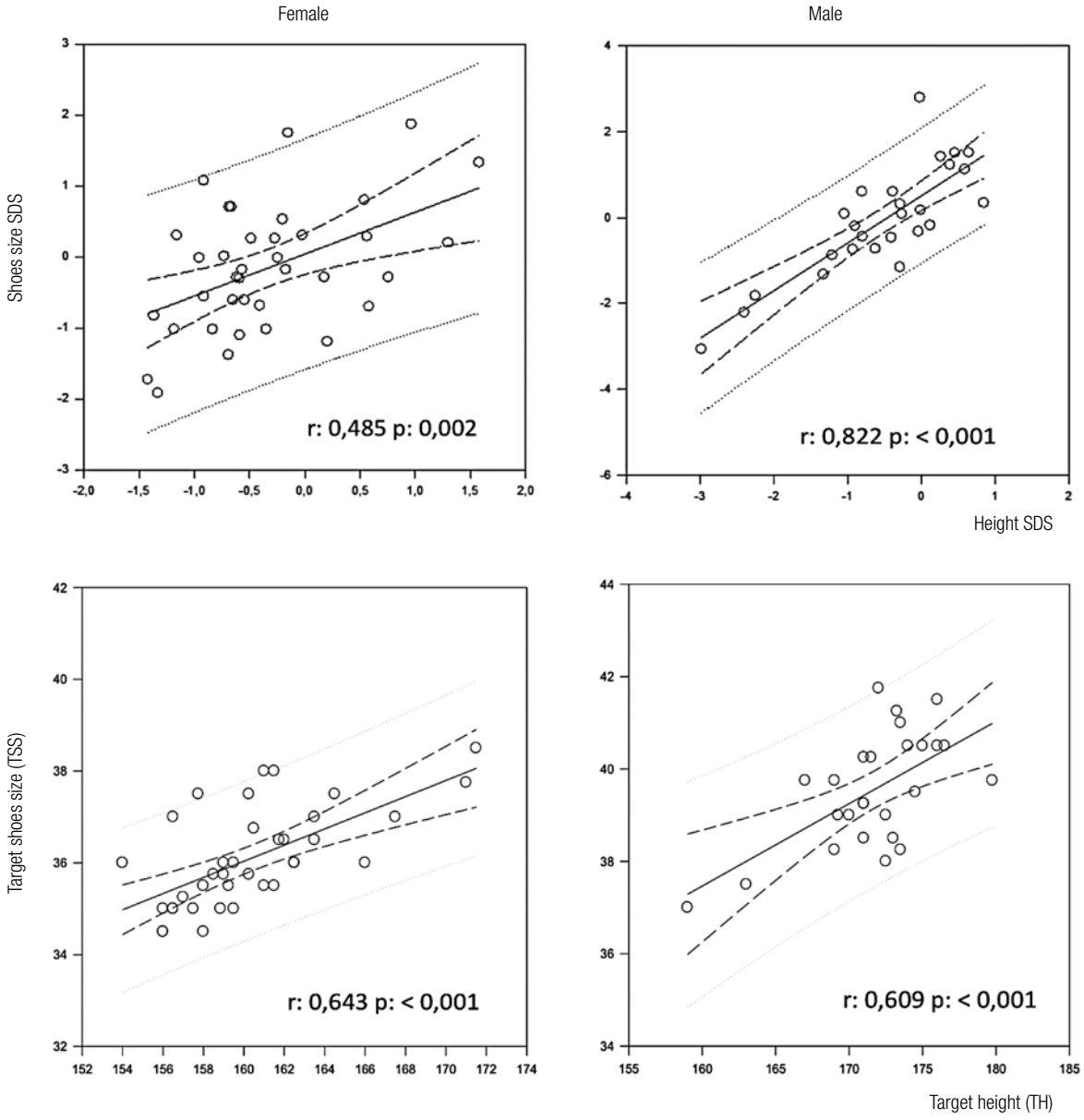

Figure 4. Correlation between shoes size and height (upper panel) and correlation between target shoes size (TSS) and target height (TH) in idiopathic short stature (ISS) and patients with reduced height to target height under GH therapy.

DISCUSSION

Growth hormone is an essential drug in the treatment of poor growth, but we have few and still controversial reports on induction or aggravation of disproportional extremities. This study evaluated the hypothesis that the use of GH could determine an excessive increase of feet estimated by the size of shoes in patients treated with GH at a higher than substitutive doses (0.05 mg/kg/d) for a period longer than one year.

Other reports already evaluated the effect of GH in the extremities of GHD patients treated with substitutive doses (0.033 mg/kg/d) and observed an increase in foot size for height > p97 in 20% of patients. This increase was not directly related to the duration of treatment, and the prominent increase was observed during the first year of GH (9). Segal and cols. evaluated 52 GH deficient patients treated also with substitutive doses; size of hand and feet were compared with first-degree relatives, and observed that hands and feet grew proportionally to height (10). On the other hand, Faria and cols. reported that in 21 GHD patients (17 patients with combined hormone deficiency) treated

with substitutive GH dose, excessive growth of feet and jaw was observed during long-term GH therapy, especially in girls (11). Those previous reports show that depending on the population subset studied, anthropometric background and duration of treatment, different impact of GH on the extremities can be achieved.

In PWS children the foot size and growth of the extremities seems to be dependent on factors other than GH, such as genetic factors, skeletal muscle mass gain and physical activity. In this group of patients it was identified the persistence of small feet even after long--term treatment with GH (3).

In TS patients the disproportional extremities seems to be present before therapy, increasing during GH therapy and remaining higher than normal thereafter. However, it is also suggested that this disproportion is similar to that observed in TS patients not treated with GH (12).

SGA infants have small hands and feet as compared to controls, presenting partial recovery during GH therapy (13).

If an excessive production of GH starts after puberty, a characteristic disproportional increase of the extremities is observed, especially in cases of GH-secreting pituitary adenoma were high GH concentration and prolonged exposition are usually present. The same risk could be expected if GH therapy in maintained after closure of growth plates, with potential compressive effect on the peripheral distal nerves (14).

The analyses of shoes size performed in the study group were only possible after establishment of reference values from general population control individuals. We describe for the first time in our population a representative growth curve of shoes size, according to the age and gender. Adequate adjustment in curves is necessary, because of the presence of extreme values that influence the homogeneity of the sample. The curve adjustment employed a very useful and robust method (LMS), providing reference tables and charts for clinical applications. The observed curve is in agreement to the previously reported by Dimeglio (15) which reported that the foot growth stops about 3 years before the end of skeletal maturation.

The study group treated with GH maintained the SDS for shoes size and its proportion with patient height and familial shoes size. There was no correlation between the SDS for shoes size and the duration of GH treatment, suggesting that no significant impact is observed during therapy of GH treated patients, even under prolonged use of recommended doses of GH. In our sample of patients with idiopathic causes treated with GH for an average period of three years, we did not observe any subsequent increase in foot size during GH treatment.

CONCLUSION

Based on our results in the Brazilian general population and in GH treated patients we concluded that: (i) the establishment of the first representative curve of shoes size in Brazilian population allowed the identification of normal reference, and the development of shoes SDS calculator now available online at www.clinicalcaselearning.com/v2. (ii) As a group, GH treated patients who received adequate GH dose (0.05 mg/kg/day) did not present excessive increase in shoes size when compared with the control population or with the familial target.

Although excessive growth of the feet estimated by the shoes size during GH treatment do not seems to be a reality, we should follow those patients to the end of shoes size to be sure that final foot increase during GH is only a myth.

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