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Resistance exercise alone improves muscle strength in growth hormone deficient males in the transition phase

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Abstract

Background: During the transition phase (TP), patients with growth hormone deficiency (GHD) exhibit decreased muscle strength. Studies assessing the effects of resistance exercise alone on muscle strength in these individuals are scarce. The objective of this study was to evaluate the effects of a program of resistance exercise (PRE) on parameters of muscle strength in subjects in the TP and with childhood-onset GHD treated with recombinant GH (rGH).

Methods: Sixteen male patients were enrolled and divided into two groups: GHD (n = 9) and GH sufficiency (GHS, n = 7). Patients with GHD underwent a 12-week PRE followed by another 12-week PRE plus rGH, while GHS patients underwent a 12-week PRE alone. Dynamic knee muscle strength was evaluated using an isokinetic dynamometer.

Results: Before PRE, there were significant differences between the groups regarding the results of flexor peak torque (FPT) normalized to body weight (BW-FPT) in the dominant (DO, $p = 0.008$) and non-dominant (ND, $p = 0.01$) limbs, and in the agonist/antagonist (A/A) ratio in the DO ($p = 0.02$) and ND ($p = 0.006$) limbs. After PRE in the GHD group, values of FPT and BW-FPT in both limbs increased significantly ($p < 0.001$) and independently of rGH, while the A/A ratio value improved significantly ($p < 0.001$) in the ND limb.

Conclusions: A short period of PRE alone was sufficient to improve parameters of muscle strength in young male adults with childhood-onset GHD.

Keywords: growth hormone; muscle strength; resistance exercise.

Introduction

Growth hormone (GH) is fundamental for the acquisition and stability of muscle mass and strength. Once adolescents achieve their final height, GH continues to participate in muscle maturation and maintenance [1–3]. This is further supported by the observation that adolescents with childhood-onset growth hormone deficiency (GHD) who interrupt GH treatment upon achievement of final height present compromised muscle and skeletal peak mass acquisition [4, 5], reduced isometric muscle strength [6], increased body fat and impaired lipid profile, cardiac morphology and performance [7, 8].

The effects of GH on muscle include an increased number of myocytes and muscle expression of insulin-like growth factor 1 (IGF-1) [9]. *In vitro* studies have shown that IGF-1 stimulates the expression of myogenin by satellite myoblasts, leading to differentiation of the latter in myotubes and mature myocytes [10, 11].

Resistance exercise is critical for muscle development [12–14] and improves the efficiency of both agonist and antagonist muscle groups [15]. In adults with GHD, the best approach to improve muscle function is GH replacement in association with exercise. The combination of both improves neural activation and increases IGF-1 muscle stimulation [16–18]. However, studies analyzing the impact of resistance exercise in individuals with GHD are scarce.

This study was conducted to evaluate the impact of a program of resistance exercise (PRE) on muscle strength in two groups of individuals in the transition phase (TP): one

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with GHD and the other with GH sufficiency (GHS), both treated with recombinant GH (rGH) throughout childhood and adolescence with the aim of improving final height.

Materials and methods

Subjects

The study included male patients with idiopathic GHD followed-up at the Pediatric Endocrinology Unit at the Clinics Hospital of Federal University of Paraná (HC-UFPR). Eligibility criteria included male gender, chronological age (CA) 18–31 years, bone age (BA) ≥ 17 years [19], regular treatment with rGH to achieve final height, adequate replacement of other hormone deficiencies and normal cardiac tests. Of 66 individuals who fulfilled the inclusion criteria, 31 were successfully contacted. Of those, 18 agreed to participate in the study, but two did not perform the entire protocol and were excluded from the analysis.

Retrospective data were collected from the patients' files and included date of birth, CA at diagnosis of GHD, type of GHD (isolated or multiple deficiency), CA at the start of treatment, duration (decimal years) of rGH therapy (DT), CA at the end of treatment, height Z-scores at the start of treatment (Z-ST), at the final height (Z-FH) and of the target height (Z-TH) and peak GH both on insulin tolerance test (ITT) and clonidine tests for the diagnosis of GHD and on ITT upon completion of treatment and attainment of final height. Because IGF-1 measurement was not available for many patients at diagnosis of GHD, it was not considered for the statistical analysis in the retrospective part of the study.

Based on the peak GH values on ITT at the end of treatment, the patients were grouped as GHD and GHS.

Inclusion criteria, GHD group

(a) Idiopathic GHD diagnosed during childhood; (b) peak GH ≤ 3.0 ng/mL [20], and IGF-1 ≤ 2 standard deviations (SD) [21]; (c) CA in the range of 18–31 years; (d) BA ≥ 17 years [19]; (e) good adherence to GH treatment until final height was achieved; (f) adequate treatment of other concomitant hormonal deficiencies; (g) normal heart function tests.

Inclusion criteria, GHS group

(a) Idiopathic isolated GHD diagnosed during childhood; (b) peak GH > 3.0 ng/mL [20], and IGF-1 values within the normal range [21]; (c) CA in the range of 18–31 years; (d) BA ≥ 17 years; (e) good adherence to GH treatment until final height is achieved; (f) normal heart function tests.

Exclusion criteria, GHD group

(a) rGH use over the last 6 months; (b) regular/irregular use of drugs with the potential to affect muscle strength or to interfere with the biochemical and/or hormonal profile, such as anabolic steroids or supraphysiological doses of glucocorticoids; (c) presence of anemia, psychiatric disturbances and chronic diseases such as cardiac or renal insufficiency, musculoskeletal disease or other conditions with the potential to interfere with the parameters of body composition and/or muscle strength; (d) active, regular practice of physical exercise and/or sports in the last 6 months; (e) inadequate treatment of another pituitary insufficiency; (f) incomplete investigation; (g) adult GHD (AGHD).

Exclusion criteria, GHS group

(a) Chronic use of any medication with the potential to interfere with the biochemical/hormonal profile and muscle strength parameters; (b) active, regular practice of physical exercise and/or sports in the past 6 months; (c) incomplete investigation.

Physical examination

All individuals were examined by one of the authors (LDL). Height was measured using a stadiometer with measuring accuracy of 0.1 cm (Stadiometer Model S100, Ayrton Corporation®, Prior Lake, MN, USA). Weight was assessed using a platform scale (Filizola®, Sao Paulo, SP, Brazil) with a measuring accuracy of 100 g. The patients' heights at the beginning of GH treatment and on study enrollment were calculated according to the Tanner's criteria [22] and are expressed in Z-scores. Target height was calculated according to the formula ([mother's height + 13 cm] + father's height)/2. Body mass index (BMI) was calculated using the Quetelet index (kg/m^2). Body composition was assessed using dual-energy X-ray (DXA) absorptiometry (Lunar Prodigy Primo, GE Health care Lunar Corp; Madison, WI, USA) at the Center for Research of Innovative Therapies (CETI, Curitiba, Paraná, Brazil). CA and treatment duration with rGH are expressed in decimal years. All participants gave informed consent, and the study was approved by the Ethics Committee in Research on Human Beings of HC-UFPR.

Laboratory tests

Blood was drawn between 7:30 and 8:30 AM after 12 h of fasting and collected in tubes containing sodium fluoride and ethylenediaminetetraacetic acid (EDTA) for a plasma glucose test and in BD Vacutainer tubes (BD, Plymouth, UK) without anticoagulant for biochemistry and hormone tests. After centrifugation, plasma was divided into 0.1 mL aliquots and stored at –20 °C for analysis.

The assessments included a complete blood count, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, glycosylated hemoglobin, inorganic phosphorus, total calcium, potassium, sodium, creatinine, cortisol, thyroid-stimulating hormone (TSH), total thyroxine (T4), free T4, IGF-1, luteinizing hormone (LH), follicle-stimulating hormone (FSH), 25-OH-vitamin D, total testosterone and antiendomysial antibodies.

GH levels were determined at baseline and at 20, 30, 40 and 60 min after intravenous administration of 0.1 IU/kg regular insulin bolus (Novolin®). Capillary blood glucose was monitored to confirm the occurrence of hypoglycemia using a glucose meter. Plasma GH

levels <3 ng/mL were considered diagnostic of GHD [20]. Biochemical and hormone measurements were performed using commercial kits (Abbott Laboratories). Plasma IGF-1 levels were determined by chemiluminescence (Immulite, Diagnostic Products Corp.) and the results are expressed as Z-scores [21]. All subjects were evaluated using an electrocardiogram (ECG) and cardiac Doppler to exclude heart conditions contraindicating the assessment of dynamic muscle strength tests and the admission to the PRE.

Assessment of dynamic muscle strength

Dynamic muscle strength was assessed using an isokinetic dynamometer (Biodex®, Biodex Medical Systems, Shirley, NY, USA). The test was conducted first on the dominant (DO) leg and consisted of three repetitions of maximal flexion and extension of the knee in the concentric mode at a speed of 60°/s. We chose this angular speed because the muscle strength assessed at lower speeds recruits a higher number of motor units and allows better representation of the maximal work performed by the muscle groups being assessed [23]. Before the test, all subjects performed a 5-min warm-up exercise on a stationary bicycle (Precor®, Workout Samter Commercial Cycle C846, USA), followed by two submaximal repetitions for acquaintance with the equipment and the procedure.

Results of extensor peak torque (EPT) and flexor peak torque (FPT) in the DO and non-dominant (ND) legs are expressed in Newton/meter (Nm), according to the International System of Units. EPT and FPT values were normalized to body weight (BW-EPT and BW-FPT) and are expressed in percentiles. The agonist/antagonist (A/A) ratio at a speed of 60°/s is expressed in percentiles.

PRE protocol

The PRE protocol lasted 24 weeks in the GHD group and 12 weeks in the GHS group. GHD patients received rGH (0.66 mg/kg) during the second period of 12 weeks. The training consisted of three sessions per week on alternate days. During the first 2 weeks, the subjects received instructions regarding all procedures and techniques related to each piece of equipment and regarding the speed of execution of the exercises, both in the concentric and eccentric phases [24]. Some strategies were adopted: (a) a 10-min warm-up followed shortly by stretching exercises; (b) the load used for the execution of the exercise was estimated by the perceived exertion of the individual as being moderate to perform each movement; (c) an interval of 60–90 s between each repetition and each series and an interval of 2–3 min between each machine were adopted; (d) subjects were instructed to inform their trainers when a series was carried out with ease for two sessions in a row and, considering their subjective perception of effort, the trainer responsible for the session increased the load of the equipment.

Nine exercise machines were used: five for the lower limbs (leg extension bench press, leg curl bench press, adductor bench press, abductor bench press and leg press) and four for the upper limbs (chest bench press, Larry Scott bench and back and triceps pulley), alternating the use of an upper limb machine with a lower limb one. After the resistance training, the patients performed abdominal exercises (with or without equipment), aerobic exercise (exercise bike or treadmill) for no longer than 30 min and stretching exercises at the end of each training session.

Statistical analysis

Mean, median, minimum and maximum and SD values are used to describe quantitative variables. For comparison of two independent groups and their evaluations carried out twice, Student's t-test for independent samples and the nonparametric Mann-Whitney test were applied. For comparisons between three distinct time points, the model of analysis of variance for repeated measurements was applied. In the case of rejection of an equality hypothesis, all time points evaluated were compared two-by-two using Fisher's least-significant difference (LSD) test. The Jarque-Bera test was applied to assess the condition of normality of the quantitative variables. All analyses adopted a significance level of 0.05.

Results

In the GHD group (n = 9), six patients had isolated GHD, and three had multiple hormonal deficiencies (two had hypogonadism, hypothyroidism and hypoadrenalism, and one had hypogonadism and hypothyroidism). A patient in the GHD group completed only the first PRE period and refused to participate in the PRE plus rGH period. In the GHS group (n = 7), all subjects had a normal pituitary function. As far as pubertal status is concerned, patients with hypogonadism were regularly treated with depot testosterone, while the others had complete sexual maturation. Hypothyroidism and hypoadrenalism were adequately managed with L-thyroxine and glucocorticoid. No patient in both groups had received rGH in the last 6 months before entering this study.

In the GHD and GHS groups, no significant differences were observed in levels of total testosterone (570.7 ± 210.0 ng/dL and 538.1 ± 245.7 ng/dL, respectively), free T4 (1.13 ± 0.23 ng/dL and 1.24 ± 0.14 ng/dL, respectively), TSH (2.66 ± 1.99 mIU/mL and 1.26 ± 0.31 mIU/mL, respectively), LH (2.33 ± 1.41 mIU/mL and 3.81 ± 2.01 mIU/mL, respectively), FSH (2.32 ± 2.09 mIU/mL and 3.83 ± 1.12 mIU/mL, respectively), cortisol (10.22 ± 4.35 μg/dL and 11.97 ± 3.99 μg/dL, respectively) and 25-OH-vitamin D (25.5 ± 11.0 ng/mL and 24.6 ± 5.2 ng/mL, respectively). Values of fasting glucose, calcium, creatinine, sodium, potassium, hemoglobin, hematocrit, glycosylated hemoglobin, total cholesterol (159.3 ± 25.2 and 138.8 ± 13.7, respectively), HDL-C (41.2 ± 10.6 and 41.6 ± 7.0, respectively), LDL-C (98.9 ± 23.3 and 81.1 ± 17.6, respectively) and triglycerides (89.2 ± 65.7 and 81.0 ± 19.4, respectively) were not significantly different between the groups. Glucose nadir in the ITT test of the GHD group (20.5 ± 5.8) was significantly lower than that of the GHS group (28.0 ± 4.8, p = 0.02). Antiendomysial antibodies were negative in all patients.

Weight, BMI and total lean mass and total fat mass did not differ among the groups before the PRE. However, total lean mass of the GHD group significantly increased ($p < 0.001$) at the end of the 12 weeks of PRE plus rGH.

Table 1 shows the values of CA at diagnosis, DT, CA at PRE, Z-ST, Z-TH, Z-FH, peak GH before and at final height and IGF-1 before PRE and after PRE plus rGH. A difference was observed in GH peak values during stimulation tests (ITT and/or clonidine) before ($p = 0.02$) and after final height attainment ($p < 0.01$), and in CA at PRE ($p = 0.02$). Levels of IGF-1 before PRE were lower in the GHD group when compared with the GHS group ($p < 0.01$). At the end of the PRE plus rGH, the level of IGF-1 significantly increased in the GHD group (92.0 ± 54.5 ng/mL vs. 259.2 ± 103.8 ng/mL; $p < 0.01$).

Muscle strength: GHD vs. GHS

The mean EPT and BW-EPT values of the DO and ND limbs before and after PRE did not differ significantly between groups. On the other hand, the FPT values of both limbs were significantly lower in the GHD group in the pre-PRE period, while in the post-PRE period the values were no longer significantly different (DO, $p = 0.172$; ND, $p = 0.065$, respectively; Figures 1 and 2). The BW-FPT values in the DO ($p = 0.008$) and ND ($p = 0.011$) limbs were significantly lower in the GHD group in the pre-PRE period. This difference was no longer present in the post-PRE period (Figures 3 and 4). The A/A ratio value of the DO and ND limbs at pre-PRE were significantly lower in the GHD group (49.5 ± 8.7 vs. 61.0 ± 9.2, $p = 0.02$ and 44.0 ± 9.2 vs. 62.2 ± 13.2, $p = 0.006$, respectively). This difference was no longer present in the post-PRE period.

Muscle strength: GHD group

In the GHD group, no differences were observed between the EPT and BW-EPT values of the DO and ND limbs in the three periods. However, the FPT and BW-FPT values in the DO and ND limbs were significantly greater in the post-PRE and post-PRE plus rGH periods ($p < 0.001$; Table 2).

Discussion

After attainment of final height, a large number of patients with childhood-onset GHD retested at the end of treatment presented a normal serum GH response to the insulin hypoglycemia stimulation test [20, 25, 26]. Despite reaching the final height (as determined by the target height), subjects with persisting GHD presented decreased total lean mass, decreased bone mineral content, decreased muscle strength and increased total fat mass [4, 27, 28].

Almost all studies evaluating muscle strength in adults with GHD include individuals with both childhood-onset and adult-onset GHD. Studies on the effects of resistance exercise on muscle strength parameters involving only individuals with childhood-onset GHD are rare.

In the present study, the groups GHD and GHS showed no differences with regard to CA, height, weight, BMI, final and target height and duration of treatment with rGH.

In the pre-PRE period, FPT and BW-FPT values in the DO and ND limbs were significantly lower in the GHD group when compared with those in the GHS group, but after 12 weeks of PRE, the difference between the groups was no longer significant. In contrast, the pre- and post-PRE EPT and BW-EPT values in the DO and ND limbs were not significantly different between the groups. Muscles that are used more in daily tasks and sports practices become stronger and tighter, while the antagonist muscles (flexors) are subject to weakening and stretching [29]. A low A/A ratio indicates a predominance of extensor musculature or a deficit of flexor musculature [30]. The previous A/A ratio difference between the groups disappeared after the post-PRE period. The increase in muscle strength occurs more steeply during the first few weeks of training, which is attributed by many researchers to neural adaptations, increased recruitment of motor units and synchronization of motor units' discharge [31, 32] or even to a reduction of antagonist muscle coactivation during exercise [33].

In the GHD group, the FPT and BW-FPT values in the DO and ND limbs significantly increased at the end of the 12-week PRE and 12-week PRE plus rGH. Although the DO limb A/A ratio in the GHD group increased from 50.5 ± 8.8% to 63.1 ± 16.8%, this difference was not significant ($p = 0.13$). However, the change was significant in the ND limb, which featured a sharp muscle imbalance (A/A < 50%), with a greater contribution from the isolated resistance exercise (from 44.2 ± 9.8% to 58.3 ± 5.6%, $p < 0.001$) than that provided by resistance exercise plus rGH (58.3%–61.8%, $p = 0.33$). According to Bittencourt et al. [30], the A/A ratio is the most appropriate parameter to evaluate muscle proportion and, consequently, muscle balance. At the lowest speed (60°/s), as employed in this study, the ratio must be around 60%, and values below 50% indicate a severe degree of muscle imbalance, as observed in the GHD group, but not in the GHS group

Table 1: Clinical characteristics of the GHD (#1–9) and GHS (#10–16) groups.

	CA at diagnosis	DT	CA at PRE	Z-ST	Z-TH	Z-FH	Peak GH before rGH, ng/mL	Peak GH at final height, ng/mL	IGF-1 before PRE, ng/mL	IGF-1 upon PRE+rGH, ng/mL
#1	15.6	4.2	24.3	−2.21	−0.9	−0.95	0.6	2.2	136.0	452.9
#2	14.4	6.7	30.5	−5.27	−1.92	−1.48	0.5	0.0	43.5	177.0
#3	8.3	7.5	28.0	−5.16	−1.6	−0.95	1.3	0.8	25.0	175.0
#4	6.0	8.0	19.1	−3.06	−1.74	−1.12	1.7	1.4	391.0	310.7
#5	12.5	4.1	25.0	−3.95	−1.69	−1.62	0.1	0.2	103.0	308.0
#6	8.9	5.0	19.3	−4.1	−2.67	−1.3	1.0	1.3	177.0	235.7
#7	13.9	5.5	28.9	−3.61	−0.97	0.13	3.0	0.1	95.0	335.0
#8	7.7	5.0	20.2	−2.8	−0.88	−1.48	1.3	1.3	32.1	108.4
#9	8.1	9.1	24.0	−4.56	−0.65	−0.24	1.7	1.7	73.1	ND
Mean ± SD	10.6 ± 3.5[a]	6.1 ± 1.8[a]	24.4 ± 4.2[b]	−3.12 ± 1.70[c]	−1.44 ± 0.66[a]	−1.00 ± 0.59[a]	1.2 ± 0.8[b]	1.0 ± 0.8[d]	92.0 ± 54.5[e]	259.3 ± 103.8
#10	10.8	4.0	18.1	−1.99	−1.49	−1.35	7.5	28.7	387.0	
#11	9.9	5.0	20.0	−2.29	−2.23	−1.27	5.6	14.9	600.0	
#12	13.4	4.7	21.9	−4.86	−2.3	−2.7	4.3	19.2	186.0	
#13	12.9	6.0	20.0	−2.16	−0.98	−1.4	5.8	6.1	260.0	
#14	12.8	4.0	18.3	−0.75	−0.74	0.05	2.8	17.0	403.0	
#15	12.1	3.11	20.1	−1.96	−0.87	−1.12	4.1	28.3	255.0	
#16	11.8	4.7	22.9	−1.77	−0.89	−0.27	2.6	61.0	262.0	
Mean ± SD	12.0 ± 1.3[a]	4.6 ± 0.8[a]	20.2 ± 1.7[b]	−2.25 ± 1.26[c]	−1.36 ± 0.66[a]	−1.15 ± 0.89[a]	4.7 ± 1.7[b]	25.0 ± 17.7[d]	336.1 ± 139.7[e]	

GHD, growth hormone deficiency; GHS, growth hormone sufficiency; CA, chronological age; DT, duration (decimal years) of rGH therapy; PRE, program of resistance exercise; Z-ST, height Z-score at the start of treatment; Z-TH, target height Z-score; Z-FH, final height Z-score; rGH, recombinant human growth hormone. [a]Student's t-test for independent samples, $p > 0.05$; [b]Student's t-test for independent samples $p = 0.02$; [c]nonparametric Mann-Whitney test, $p > 0.05$; [d]Student's t-test for independent samples $p < 0.01$; [e]Student's t-test for independent samples $p < 0.01$.

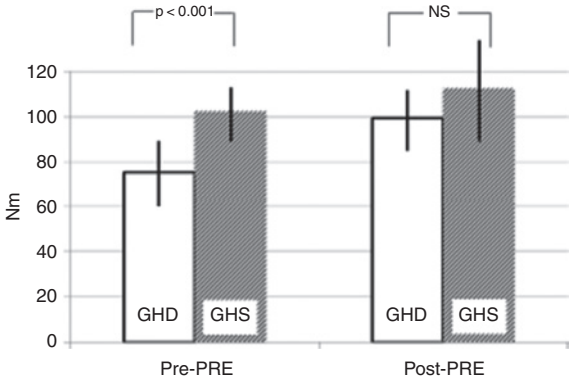

Figure 1: Mean (±SD) flexor peak torque (FPT) values in the dominant (DO) limb before and after the program of resistance exercise (PRE).
GHD, growth hormone deficiency; GHS, growth hormone sufficiency; NS, nonsignificant.

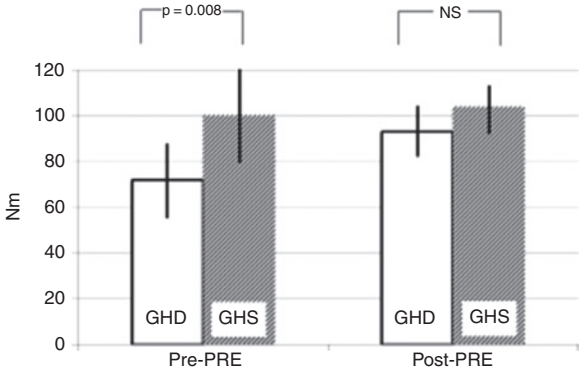

Figure 2: Mean (±SD) flexor peak torque (FPT) values in the nondominant (ND) limb before and after the program of resistance exercise (PRE).
GHD, growth hormone deficiency; GHS, growth hormone sufficiency; NS, nonsignificant.

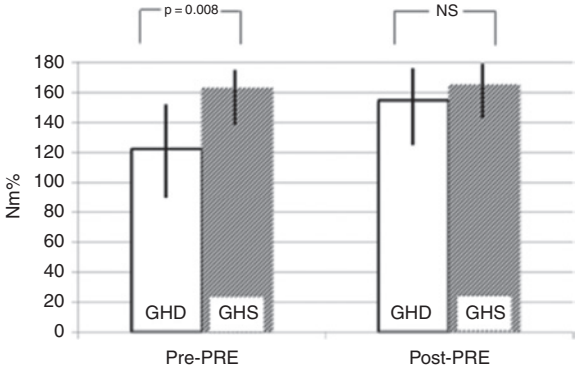

Figure 3: Mean (±SD) flexor peak torque (FPT) values in the dominant (DO) limb normalized to body weight (BW-FPT) before and after the program of resistance exercise (PRE).
GHD, growth hormone deficiency; GHS, growth hormone sufficiency; NS, nonsignificant.

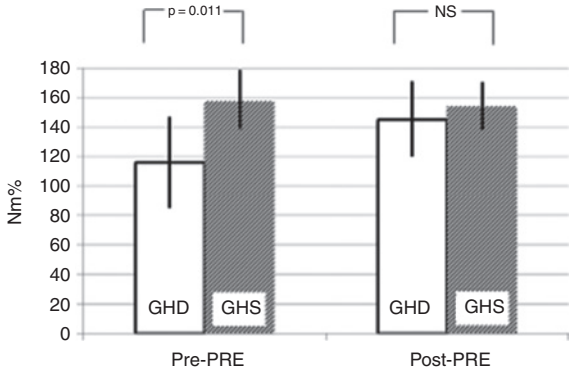

Figure 4: Mean (±SD) flexor peak torque (FPT) values in the nondominant (ND) limb normalized to body weight (BW-FPT) before and after the program of resistance exercise (PRE).
GHD, growth hormone deficiency; GHS, growth hormone sufficiency; NS, nonsignificant.

Table 2: Values (mean ± SD) of FPT, BW-FPT in the GHD group in the different periods.

Periods	LIMB	FPT, Nm	BW-FPT, Nm%
Pre-PRE	DO	74.6 ± 15.6[a]	119.7 ± 32.2[a]
Post-PRE	DO	100.6 ± 13.8[b]	155.5 ± 26.9[b]
Post-PRE+rGH	DO	103.6 ± 15.3[c]	156.8 ± 17.9[c]
Pre-PRE	ND	69.6 ± 16.0[a]	117.7 ± 31.2[a]
Post-PRE	ND	92.7 ± 11.7[b]	144.0 ± 27.4[b]
Post-PRE+rGH	ND	101.8 ± 16.7[c]	154.2 ± 22.6[c]

FPT, flexor peak torque; BW-FPT, flexor peak torque normalized to body weight. FPT of DO limb: a vs. b and c $p < 0.001$; b vs. c $p = 0.56$; FPT of ND limb: a vs. b and c $p < 0.001$; b vs. c $p = 0.23$. BW-FPT DO limb: a vs. b and c $p < 0.001$; b vs. c $p = 0.84$; BW-FPT of ND limb: a vs. b and c $p < 0.001$; b vs. c $p = 0.3$.

(61.0 ± 9.2% and 62.2 ± 13.2% for DO and ND limbs, respectively), in the pre-PRE period.

Most studies evaluating parameters of muscle strength during rGH treatment have enrolled patients with AGHD [34–36], and have not evaluated the effects of resistance exercise alone, as performed in the first period of this study. Janssen et al. [37] observed no significant difference in muscle strength indexes in patients with GHDA vs. a control group after 52 weeks of daily rGH. Götherström et al. [38], in a study in which participants received rGH replacement for 10 years, observed an increase in muscle strength in the first 5 years. In the following 5 years, the treatment partially prevented the decline related to aging. The practice of resistance exercise during rGH treatment can change the profile of body composition and muscle strength in individuals with AGHD [39].

There seems to be a temporal relationship between GHD in childhood and its deleterious effects on muscle tissue. In

patients with GHD, the IGF-1 paracrine/autocrine effect and the neuromuscular activity are important factors affecting the muscle function and volume [17]. Unlike serum IGF-1, local production of muscle IGF-1 is significantly increased after a short period of resistance exercise [40]. One interesting aspect of this study is the fact that compared with the GHD group, the GHS group presented a different pattern in muscle strength parameters during the 12 weeks of PRE.

While increments of muscle strength values were significant in the GHD group, only 10% and 4% increases in FPT were observed in the DO and ND limbs, respectively, in the GHS group. In the case of individuals with normal GH secretion and without muscle imbalance (A/A ratio > 60%), it can be assumed that a PRE for 12 weeks was insufficient to promote significant changes in the GHS group. This finding may be explained by the differences in values of muscle strength before the PRE between the two groups, i.e. the GHS group presenting higher baseline muscle strength. Notably, in the study by Johannsson et al. [18], 2 years of rGH treatment in adults with GHD increased isometric and isokinetic muscle strength more markedly in younger patients and in those with initial lower muscle strength. According to Woodhouse et al. [41], the optimum regimen of GH treatment for adult patients with GHD, aiming to increase muscle function, in combination with physical exercise to improve neural activation, remains an unresolved issue. GH replacement is recommended for patients in the TP with GH deficiency confirmed and that resisted exercise could be recommended in addition to GH replacement.

Possibly, if resisted exercise was added early on to the treatment of patients with GHD, and maintained during the TP with the continuation of rGH, the acquisition of normal peak muscle mass and peak bone mass would be more feasible.

In conclusion, despite the small sample of individuals and the duration of the exercise period in this study, resistance exercise by itself was able to improve muscle strength parameters in adults with childhood-onset GHD.

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