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Physical exercise improves functional capacity and quality of life in patients with acromegaly: a 12-week follow-up study

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Abstract

Objective Although the focus of acromegaly treatment is the hormonal control of the disease, a new perspective must be given to the functional rehabilitation of these patients, especially when considering the recent increase in survival. The aim of this study was to evaluate the effects of therapist-oriented home rehabilitation (TOHR) on patients with acromegaly.
Patients and methods Seventeen adults with acromegaly followed an exercise programme from a booklet with instructions for each exercise prescribed, for 2 months, and were reassessed after 1 month of washout. At each of the 3 timepoints (before and after the intervention and at the 1-month follow-up), the participants were subjected to the following assessments: body composition through bioimpedance, health-related quality of life (HRQoL) using the Acromegaly Quality of Life (AcroQoL) questionnaire, general fatigue through the Functional Assessment of Chronic Illness Therapy-Fatigue scale, handgrip strength, lower extremity functionality using isometric dynamometry and the Lower Extremity Functional Scale (LEFS), body balance through stabilometry, and functional capacity through 6-minute walking distance (6MWD).
Results After performing TOHR, improvements in general fatigue, quadriceps muscle strength, LEFS, 6MWD, balance control and all AcroQoL dimensions were observed (all $P < 0.05$). After 1 month of washout, however, these gains were lost for all parameters, except the LEFS and balance control.
Conclusions In acromegaly, TOHR results in improvements in muscle function, functional capacity, general fatigue, body balance, and HRQoL. Large randomized controlled trials are needed to replicate these benefits and to recommend rehabilitation, especially for those with long-term illness.

Keywords Acromegaly · Muscles · Rehabilitation · Exercise · Quality of life

Introduction

Acromegaly is a chronic debilitating disease characterized by excess growth hormone (GH) and insulin-like growth factor 1 (IGF-1), most frequently caused by a pituitary adenoma. The prevalence and incidence rates vary between 2.8 and 13.7; and between 0.2–1.1 cases per 100,000 people, respectively [1]. The mortality rate has decreased in the past decade, possibly due to the improvement in surgical approaches, greater use of drug therapies, and better control of comorbidities [2, 3]. Acromegaly is characterized by the development of a dysmorphic syndrome with progressive cranial cap and acral growth, accompanied by several comorbidities, such as musculoskeletal disease, heart and respiratory failure, cerebrovascular disease, neurological involvement, diabetes mellitus, hypertension and neoplasms, which usually persist or even appear after hormonal control of the disease [4].

Joint and musculoskeletal pain is described in up to 90% of acromegalic patients and may persist even after

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long-term remission of the disease and compromise the health-related quality of life (HRQoL) [5]. The worsening of osteoarticular and muscular disease can result in worsening HRQoL and a body balance disorder [4]. In addition, the prevalence of visual disorders and cerebrovascular disease (including stroke) is high in patients with acromegaly, especially in those with hypertension or who underwent radiotherapy [3]; these alterations may also impact body imbalance [6, 7]. Cardiac involvement is very frequent in acromegaly, with acromegalic cardiomyopathy being an entity characterized by a hyperdynamic state that can lead to sudden heart failure [3]. Taken together, a multiplicity of mechanisms can then negatively impact the functional capacity of these individuals.

Management objectives in current acromegaly guidelines are focused on achieving the biochemical targets for disease control and the treatment of comorbidities, aiming to reduce their mortality rate [3]. However, as part of the treatment of this condition, emphasis should also be placed on HRQoL, which often remains impaired despite the reduction in serum GH levels. This finding suggests that other therapeutic approaches, in addition to the biochemical control of the disease, are necessary to improve the HRQoL of these individuals. At present, acromegaly treatment is often multimodal, including transsphenoidal surgery, drug therapy, and radiotherapy, which basically aim to suppress the levels of GH/IGF-1. However, due to the chronic and debilitating nature of the disease and the numerous sequelae that result from it, few studies have focused on functional rehabilitation [8, 9].

With progress in acromegaly management, the prognosis of patients has improved, and in most cases, adequate control of the levels of GH/IGF-1 has been achieved, resulting in life expectancy comparable to that of the general population [3, 4]. Therefore, there is an urgent need to reduce the adverse consequences arising mainly from late diagnosis and treatment, improve patient outcomes and reduce the burden on the health system [1]. Because arthropathy, muscle disease, cardiovascular involvement, general fatigue, and balance disorders are conditions that directly affect HRQoL, it becomes imperative to functionally rehabilitate these patients. Thus, the objective of this study was to evaluate the effects of therapist-oriented home rehabilitation (TOHR) on body composition, HRQoL, general fatigue, peripheral muscle performance, body balance, and functional capacity in patients with acromegaly.

Materials and methods

Participants

Between March 2017 and December 2018, a quasi-experimental and longitudinal study was performed with 17 patients with acromegaly aged ≥18 years, who were recruited at the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro, Brazil. The diagnosis of acromegaly was based on clinical characteristics and confirmed by high levels of age-matched IGF-1 and high levels of GH that were not suppressed to levels <1 μg/L in an oral glucose tolerance test [10]; in this condition, the participant was considered to have active disease, unlike if the excessive release of GH/IGF-1 was obtained through pharmacological, surgical or radiotherapy treatment (controlled disease). The following exclusion criteria were applied: presence of comorbidities unrelated to acromegaly; stroke; cognitive alteration; uncontrolled hypertension; use of psychotropic drugs; untreated hypothyroidism or Addison's disease; any significant limitations due to osteoarthropathy; history of any orthopaedic surgery in the previous year; inability to perform functional tests; subjects considered 'very active' by the International Physical Activity Questionnaire (IPAQ) [11]; and treatment abandonment during protocol application. All subjects signed a consent form, and the protocol was approved by the Research Ethics Committee of the Augusto Motta University Center under number CAAE-53384316.6.0000.5235. The trial was registered at ClinicalTrials.gov, reference number NCT03710499.

Intervention

Before starting the protocol, the patients were instructed by the physiotherapist about how to perform the physical exercises. Patients followed an exercise programme from a booklet with instructions for each exercise prescribed for 2 months, 3 times a week, for a total of 24 sessions. With a focus on muscle training, aerobic resistance, and flexibility exercises, each session lasted approximately 60 min and consisted of the following steps: (1) 5 min of warm-up exercises, where the patient was instructed to stretch the muscles (sternocleidomastoid, pectoral, broad dorsal, adductor magnus, biceps femoris, lateral deltoids, trapezius, external oblique, posterior surface of the thighs, hamstrings, calves, quadriceps and lumbar region) to the limit tolerated comfortably while maintaining each elongation for 20 to 30 s; (2) 20 min of muscle strengthening and resistance exercises for the upper and lower limbs, including lateral elevation, frontal elevation, and flexion and extension exercises associated with functional diagonal movements; squatting, dorsiflexion, and plantiflexion exercises were also performed, using objects such as light weights, chairs, steps and the walls of the environment itself; the participants were instructed to perform 20 repetitions of each activity with a 1 min interval between exercises for recovery; (3) 10 min of balance training through proprioceptive exercises on the floor, using objects to overcome and others to be circumvented; (4) 20 min of aerobic training by means of walking and functional circuits, taking into account the muscle groups that are usually used in their daily lives; and (5) 5 min of global stretching and relaxation exercises, using calisthenic exercises for upper and lower limbs [8, 12, 13]. Following the initial physical therapy assessment and inclusion in the protocol, the patients were re-evaluated after 8 weeks, when the TOHR was completed; these patients were reassessed 4 weeks after completing the TOHR. The physiotherapist contacted the patients by phone weekly to monitor treatment progression. The exercise intensity at the household level was monitored using the Borg < 4 perceived exertion scale; if this signal was not within the given range, the patient was instructed to decrease the repetitions [14].

Outcomes

Body composition was measured by bioimpedance (BIA 310e, Biodynamics, Seattle, WA, USA). Patients were instructed to rest for 5 min before the test and remain barefoot, without any metallic object near them, with their feet 15–30 cm apart. Next, two electrodes were placed on the dorsal surface of the right hand, and two electrodes were placed on the dorsal surface of their right foot. Resistance and reactance were calculated and used to estimate fat-free mass (FFM) [15].

HRQoL was assessed using Acromegaly Quality of Life (AcroQoL) questionnaire, which is a disease-specific questionnaire that evaluates specific dimensions affected by acromegaly. This 22-item questionnaire consists of physical ($n = 8$) and psychological ($n = 14$) dimensions subdivided into the dimensions appearance ($n = 7$) and personal relationships ($n = 7$), which can be analysed separately or globally [16]. In the AcroQoL, a lower score is associated with worse HRQoL.

To evaluate general fatigue, we used the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which has 13 questions ranging from 0 to 4, where the higher the score lower the fatigue. Its score ranges from 0 to 52. FACIT-F is a specific scale for fatigue assessment that has a good representation of the individual's condition and is considered an easily applied instrument [17, 18].

Handgrip strength (HGS) was measured using an isometric hydraulic dynamometer (SH5001, Saehan Corporation, Korea) on the dominant side of the body. The tests followed the recommendations of the American Society of Hand Therapists [19]. For standardization, the participants were seated with the elbow flexed at 90° and the forearm in a neutral position. Then, three maximal voluntary contractions were performed with a 60 s interval between tests; the highest value was used for analysis.

Lower limb muscle strength and fatigue resistance were evaluated using a traction dynamometer (DIN-TRO, EMG System do Brasil LTDA, Brazil) and an electromyograph (EMG model 810 C, EMG System do Brasil LTDA, Brazil). For the strength test, the muscle evaluated was the quadriceps, and the maximum load protocol was performed. The dynamometer was positioned at a 90° angle relative to the longitudinal axis of the tibia and was fixed to the ankle joint. The resistance test consisted of a sustained contraction for 60 s using 40% of the greatest maximum voluntary isometric contraction obtained in the strength test. The median frequency and the root mean square slopes (MDF and RMS, respectively) corresponding to the electromyographic signal were recorded as a function of time during the resistance test [20]. In addition, we used the Lower Extremity Functional Scale (LEFS), which is a self-administered questionnaire consisting of 20 questions, each of which has a score ranging from 0 to 4. The sum of all items can generate a maximum total of 80 points. In the LEFS, the higher the value obtained, the higher the level of functionality in the lower limbs [7].

To evaluate body balance, a force plate (AccuSway Plus AMTI, Watertown, MA, USA) was used coupled to a computerized system to capture the signal and subsequent analysis of the results. Patients were instructed to remain in an orthostatic posture, aligned and immobile, fixing their eyes on a target on the wall for 30 s. All participants were evaluated using two tasks: feet apart, eyes open (FAEO, where the heels should be separated by 30 cm) and feet together, eyes closed (FTEC, where the feet were less than 1 cm apart). Block randomization with six participants in each block was used. Considering the three visits of each patient, each block contained the six possible sequences as follows: FAEO-FTEC-FAEO; FAEO-FAEO-FTEC; FAEO-FTEC-FTEC; FTEC-FAEO-FTEC; FTEC-FTEC-FAEO; and FTEC-FAEO-FAEO [21]. We measured the following variables: medial-lateral standard derivation (X SD); anterior-posterior standard derivation (Y SD); medial-lateral range (X range); anterior-posterior range (Y range); length; and average velocity (V avg) [6, 22].

A 30-m hall, marked every 3 m, was used to perform the 6-minute walk test (6MWT). Patients were instructed to walk as fast as possible, and peripheral oxygen saturation, heart rate, blood pressure, and degree of dyspnoea were checked at rest and at the end of the test using the modified Borg scale. Two tests were performed with a 30-min interval between them. The selected 6-min walking distance (6MWD) was that with the best performance. Subsequently, data were calculated according to the predicted values for the 6MWD published by Britto et al. [23].

For each of the study moments (baseline, after 2 months of exercises and after 1 month of washout), all assessments were made within two days. The days on which the evaluations were carried out, as well as the sequences of methods used are show in Fig. 1.

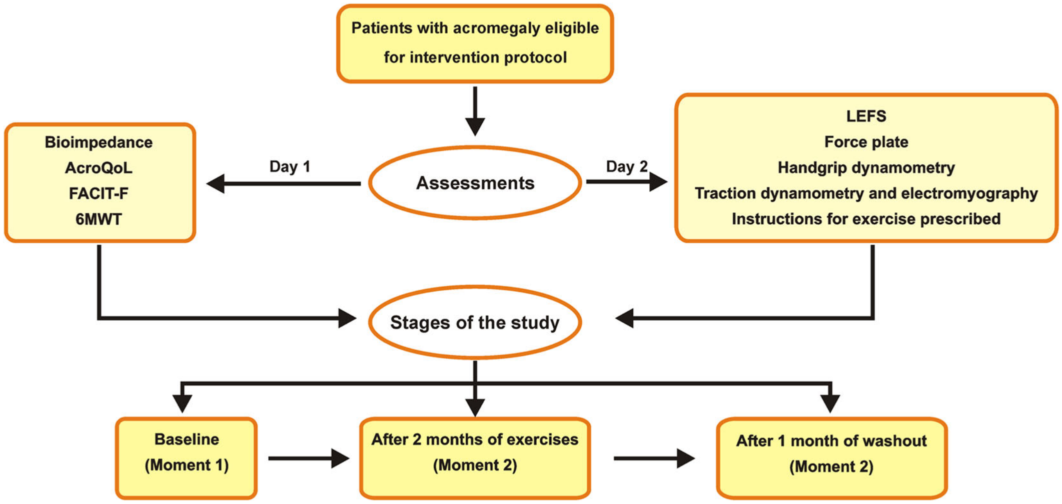

Fig. 1 Flow chart showing the days on which the evaluations were carried out, as well as the sequences of methods used. *AcroQoL* acromegaly quality of life questionnaire, *FACIT-F* functional assessment of chronic illness therapy-fatigue scale, *6MWT* 6-min walk test, *LEFS* lower extremity functional scale

Statistical analysis

Non-parametric methods were applied because the variables did not present a Gaussian distribution according to rejection of the normality hypothesis by the Shapiro-Wilk test along with graphical analysis of the histograms. Inferential analysis was composed of Friedman's ANOVA to verify if there was significant variation in the parameters over 3 timepoints: baseline (moment 1, MO-1), after 2 months of exercise (moment 2, MO-2), and after 1 month of washout (moment 3, MO-3). In addition, the Nemenyi multiple comparisons test was used to identify which moments were significantly different from each other. The association between pre-intervention and post-intervention relative deltas (MO-2 value−MO-1 value/MO-1 value × 100) with disease duration since the onset of symptoms and GH and IGF-1 levels was analysed by the Spearman correlation coefficient (r_s), while the association with disease classification (active vs. controlled) was assessed by the Mann-Whitney test. Data analysis was performed using SAS 6.11 software (SAS Institute, Inc., Cary, NC, USA). The results are expressed as medians and interquartile ranges or by frequencies (percentages), and a value of $P < 0.05$ indicated statistical significance.

Results

We asked 81 patients with acromegaly who were regularly followed in our hospital to participate in the study. Among the 25 patients who accepted to participate in the protocol, 4 were excluded for the following reasons: considered "very active" by IPAQ ($n = 2$); used orthosis for locomotion ($n = 1$); and history of recent orthopaedic surgery ($n = 1$). In addition, 4 patients discontinued the physical exercises during protocol application and therefore were withdrawn from the study. The reasons for the discontinuation of the TOHR programme by these patients were the presence of arthralgia and/or myalgia.

Among the 17 patients who completed the TOHR protocol, the median age was 53 (50.5–57) years-old, and there were 14 women. Disease duration since the onset of symptoms was 12 (8.50–16) years. Five had active disease, while 12 had controlled disease. Sixteen participants had undergone transsphenoidal surgery, while only 3 had undergone radiotherapy. Regarding pharmacological treatment, 9 used somatostatin receptor ligands, while 3 used combination therapy (somatostatin receptor ligand plus GH receptor blocker). Four participants were ex-smokers (all with smoking status < 10 pack-years), 9 participants were hypertensive, and 1 had diabetes. The demographic data, clinical characteristics, and biochemical values at baseline are shown in Table 1.

After performing TOHR, improvements in general fatigue, quadriceps muscle strength (QMS), lower limb functionality, 6MWD and HRQoL parameters evaluated by the AcroQoL were observed. After 1 month of washout, however, this gain was lost for all parameters, except for the LEFS. The results for body composition, functional assessment and HRQoL at baseline, after 2 months of exercise and after 1 month of washout are shown in Table 2.

Regarding body balance, there were improvements in Y SD and V avg after TOHR in the trial performed with feet together and eyes closed. Interestingly, this improvement in

Table 1 Demographic data, clinical characteristics, and biochemical values at baseline

Variable	Value
Demographic data	
Age (years)	53 (50.5–57)
Body mass (kg)	82.5 (74–92.9)
Body height (cm)	165 (158–169)
Clinical characteristics	
Controlled disease, *n* (%)	12 (70.6)
Patients submitted to surgery, *n* (%)	16 (94.1)
Patients submitted to radiotherapy, *n* (%)	3 (17.6)
Laboratory data	
GH (μg/L)	0.60 (0.50–1)
IGF-1 (μg/L)	88 (80.5–101.5)

Note: The results are expressed as the median (interquartile range) or number (%)

GH growth hormone, *IGF-1* insulin-like growth factor 1

balance control was maintained after 1 month of washout. The results of body balance at baseline, after 2 months of exercise and after 1 month of washout are shown in Table 3.

In addition, we evaluated the correlations between the pre-intervention and post-intervention relative deltas (MO-2–MO-1) of the functional parameters HRQoL and body balance with disease duration since the onset of symptoms and hormone levels. In this analysis, IGF-1 levels showed significant and positive correlations with the following stabilometry variables evaluated in the trial with the feet together and eyes closed: Y range ($r_s = 0.70$; $P = 0.001$) and length ($r_s = 0.56$; $P = 0.020$). When the pre-intervention and post-intervention relative deltas (MO-2–MO-1) of the functional parameters HRQoL and body balance were compared according to disease classification, there was no difference between patients with active disease and those with controlled disease.

Discussion

The impact of various currently used acromegaly treatment modalities (including transsphenoidal surgery, hormonal block, and radiotherapy) on physical performance and HRQoL seems to be small or null [24–26]. In addition, there is also a considerable increase in the life expectancy of acromegalic patients in recent decades, which requires the need for new therapeutic approaches that are capable of acting on the physical and emotional consequences and on the long-term burden of disease for the health system. Thus, in addition to normalization of the GH-IGF-1 axis and the treatment of sequelae brought on by the disease, these new forms of treatment must also focus on the HRQoL and functional rehabilitation of this patient population [27]. Within this new perspective, we evaluated the benefits that rehabilitation can bring to patients with acromegaly. The main findings were that after a TOHR programme, there was an increase in the performance of lower limb musculature and in functional capacity, a reduction in general fatigue, and an improvement in HRQoL. However, these benefits were lost and returned to baseline levels after 1 month of washout. In these patients, there was also an improvement in body balance after TOHR, and this benefit was maintained even after rehabilitation interruption. In addition, pre-intervention IGF-1 levels were associated with changes in body balance resulting from TOHR.

Body composition and metabolism in patients with acromegaly show interesting and unique patterns, and BIA can comprehensively assess these abnormalities. Using BIA, Guo et al. [28] have recently shown that body composition (including adipose tissue and body water) and basal metabolism are altered after pituitary adenomectomy in individuals with acromegaly, and that the sex and age influence these changes. In our study, however, we did not observe significant changes in body composition parameters evaluated by BIA after TOHR. This finding suggests that TOHR has no important effect on the GH-IGF-1 axis and that its benefits possibly stem from peripheral gains.

Despite the increase in skeletal muscle mass, muscle weakness has been reported in acromegalic patients, with a decrease in both HGS and lower limb strength [7, 29]. Excess GH results in larger but functionally weaker muscles, with hypertrophy of type 1 muscle fibres and various findings in type 2 fibres [24, 30]. In our study, we observed a significant improvement in QMS assessed by isometric dynamometry and the LEFS after TOHR, although after 1 month of washout, the values returned to close to those observed at baseline. Although we identified an increase in QMS, no change in HGS was noted after TOHR. This finding is in line with Hatipoglu et al. [9], who also did not notice any increase in HGS after 3 months of exercise in individuals with acromegaly. HGS reflects the combined action of the arm and hand muscles and is also associated with total muscle mass in many patient populations. However, carpal tunnel syndrome and swelling of the hand and fingers are common in acromegalic patients, and because these changes can lead to nerve compression, it is possible that this justifies, at least in part, the lack of HGS gain after TOHR [18, 30]. Although the presence of myopathy is not correlated with the magnitude of GH elevation or any secondary endocrine disorder, it is associated with a longer duration of disease [31]. Thus, the findings of our study suggest that strength and endurance training should be started as early as possible in this patient population.

Table 2 Body composition, functional parameters, and quality of life at baseline, after 2 months of exercises and after 1 month of washout with a therapist-oriented home rehabilitation

Variable	MO-1	MO-2	MO-3	*P*-value
Body composition				
Body mass index (kg/m^2)	29.7 (25.4–35.2)	30.9 (27.5–35.3)	31.2 (27.5–35.5)	**0.0001**[a,b]
Reactance (Ω)	66 (62–72.1)	64.9 (60.1–67.5)	64.4 (55.4–70.5)	0.37
Resistance (Ω)	591.6 (512.1–622.6)	583 (535.5–613.5)	545.1 (519.3–606.5)	0.35
Fat percentage (%)	39.2 (31.2–43.4)	39 (34.5–42.5)	38.5 (33.3–43.6)	0.18
Height$^{(2)}$/resistance index (cm^2/Ω)	2.72 (2.50–2.84)	2.72 (2.51–2.84)	2.72 (2.50–2.84)	0.22
FFM (kg)	23.8 (22.6–26.2)	24.6 (21.8–26.3)	23.8 (22.2–26.2)	0.98
General fatigue				
FACIT-F (points)	39 (30–43)	41 (36–48)	40 (35–45.5)	**0.002**[a]
Peripheral muscle performance				
HGS (kgf)	31 (28.5–34)	32 (29–34)	32 (27.5–33)	0.68
QMS (kg)	32.2 (26.5–41.6)	42.1 (32.3–51.3)	35 (27.8–48.2)	**<0.0001**[a,c]
RMS slope	0.63 (0.26–1.44)	0.34 (0.17–1.22)	0.69 (0.27–1.72)	0.26
MDF slope	–0.15 (−0.32–0.07)	−0.18 (−0.32–0.04)	−0.13 (−0.20–0.05)	0.73
LEFS (points)	49 (25–69.5)	56 (33.5–70.5)	55 (33.5–67.5)	**0.006**[a,b]
6-min walk test				
6MWD (m)	484 (415–530)	500 (443–558)	460 (423–555)	**0.0002**[a,c]
6MWD (% predicted)	72.9 (66.2–83.4)	78.3 (70.7–86.2)	73.2 (67.5–87.1)	**0.0002**[a,c]
AcroQol				
Global score (points)	65 (56.5–72.5)	77 (68–89.5)	70 (58.5–80.5)	**<0.0001**[a,c]
Physical function (points)	21 (18–27.5)	26 (25–32)	23 (20–30)	**0.0001**[a,c]
Psychological function (points)	43 (38–50.5)	50 (42.5–58)	49 (38.5–50.5)	**0.0002**[a]
Personal relationships (points)	19 (16.5–25.5)	24 (19.5–28.5)	23 (18.5–28)	**0.011**[a]
Appearance (points)	25 (19–26.5)	27 (21–29)	23 (19.5–27)	**0.036**[a,c]

Note: The results are expressed as the median (interquartile range). The values in bold type show significant differences.

MO-1 baseline MO-2 after 2 months of exercises, *MO-3* after 1 month of washout, *FFM* fat-free mass, *FACIT-F* functional assessment of chronic illness therapy-fatigue, *HGS* handgrip strength, *QMS* quadriceps muscle strength, *RMS slope* angle of the linear regression obtained from the values of the root mean square electromyography signal over time during the fatigability test of the *vastus medialis* muscle, *MDF slope* angle of the linear regression line obtained from the values of the median frequency electromyography signal over time during the fatigability test of the *vastus medialis* muscle, *LEFS* lower extremity functional scale, *6MWD* 6-min walking distance, *AcroQoL* acromegaly quality of life questionnaire

[a]MO-1 # MO-2, [b]MO-1 # MO-3, [c]MO-2 # MO-3

The maintenance of postural balance includes the sensory detection of body movements, the integration of sensory-motor information in the central nervous system (CNS) and the execution of appropriate musculoskeletal responses [6, 7]. In acromegaly, there are several abnormalities that can alter postural control, including musculoskeletal involvement and visual disturbances [6, 7, 9, 32]. However, Lopes et al. [6] observed abnormalities in static equilibrium with displacements of the centre of pressure (CoP) in both the anterior-posterior and medial-lateral directions in a population of individuals with acromegaly. In our study, we observed an improvement in the average velocity of CoP displacement in the anterior-posterior direction, which was maintained even after 1 month of washout. Because anterior-posterior balance is primarily maintained by ankle torque [33], we hypothesized that the TOHR programme improved ankle stability, leading to compensatory adjustment when the CoP projection moves out of the support base.

Regarding balance control, we found that pre-intervention IGF-1 levels showed significant and positive correlations with length and Y range. Changes in these stabilometric variables also point to a CoP oscillation in the anterior-posterior direction. Although physiological levels of IGF-1 maintain cognitive function in the brain through its beneficial effects on synaptic structure and plasticity, excess IGF-1 can cause insulin resistance in the brain with hyperphosphorylation and accumulation of amyloid that, in turn, can result in synaptic loss [34]. Thus, these neurotoxic processes may ultimately contribute to the loss of balance control in patients with acromegaly.

Table 3 Body balance parameters at baseline, after 2 months of exercises and after 1 month of washout with a therapist-oriented home rehabilitation

Variable	Feet apart, eyes open			
	MO-1	MO-2	MO-3	*P*-value
X SD (cm)	0.09 (0.05–0.19)	0.07 (0.05–0.10)	0.08 (0.05–0.14)	0.82
Y SD (cm)	0.44 (0.30–0.55)	0.32 (0.24–0.41)	0.30 (0.23–0.42)	0.66
X range (cm)	0.42 (0.24–0.78)	0.39 (0.30–0.53)	0.41 (0.26–0.83)	0.66
Y range (cm)	1.82 (1.13–2.68)	1.46 (1.10–2.08)	1.48 (1.00–2.54)	0.94
Length (cm)	18.5 (10.6–23.2)	15.6 (12.4–24.2)	13.8 (12.7–23.6)	0.49
V avg (cm/s)	0.63 (0.41–0.86)	0.52 (0.41–0.81)	0.46 (0.43–0.79)	0.90
Variable	**Feet together, eyes closed**			
	MO-1	MO-2	MO-3	*P*-value
X SD (cm)	0.32 (0.25–0.38)	0.27 (0.22–0.38)	0.24 (0.20–0.31)	0.56
Y SD (cm)	0.47 (0.38–0.68)	0.38 (0.29–0.53)	0.36 (0.31–0.54)	**0.042**[b]
X range (cm)	1.37 (1.12–2.03)	1.30 (1.09–1.88)	1.29 (1.12–1.80)	0.90
Y range (cm)	2.97 (2.22–4.25)	2.76 (2.34–3.51)	2.84 (2.05–3.45)	0.53
Length (cm)	38.4 (28.1–45.6)	32.3 (28.1–46.9)	36.4 (27.2–45.7)	0.58
V avg (cm/s)	0.95 (0.56–1.24)	0.75 (0.55–0.95)	0.68 (0.53–0.92)	**0.015**[a,b]

Note: The results are expressed as the median (interquartile range). The values in bold type show significant differences.

MO-1 baseline, *MO-2* after 2 months of exercises, *MO-3* after 1 month of washout, *X SD* medial-lateral standard deviation, *Y SD* anterior-posterior standard deviation, *X range* medial-lateral range, *Y range* anterior-posterior range, *V avg* average velocity

[a]MO-1 # MO-2, [b]MO-1 # MO-3, [c]MO-2 # MO-3

The 6MWT may be an important sub-maximal tool in acromegalic patients because these patients have reduced aerobic metabolism, which in turn is dependent on cardiac function, peripheral blood flow, and the ability of muscle tissue to use oxygen [35]. In the present study, we observed a significant increase in the distance travelled after TOHR, although this benefit was lost after 1 month of washout. In line with our findings, Hatipoglu et al. [9] observed an improvement in maximal oxygen uptake when they compared a group of patients with acromegaly who underwent an exercise protocol for 3 months with a control group. Although joint disease has been described as the main limiting factor for the functional capacity of these individuals, several other factors may also be involved in poor performance during exercise, including impairment of the heart, lungs, and muscles [35, 36].

Acromegalic patients commonly complain of general fatigue, which seems to be more associated with aerobic than muscle performance [24]. Moreover, higher levels of general fatigue are observed in those with more functional limitations [37]. In our study, we observed an improvement in general fatigue after the application of TOHR, which was maintained after the washout period. Walchan et al. [29] observed that high levels of general fatigue were not different between acromegalic patients with active or controlled disease, while Woodhouse et al. [24] did not show any effect of somatostatin receptor ligands on the general fatigue of these individuals. This suggests that the improvement in general fatigue observed in our patients is due to peripheral gain rather than to any modification in the GH-IGF-1 axis.

In addition to controlling excess GH, treating its associated comorbidities, and reducing mortality, the HRQoL approach has increasingly become a target in acromegaly management as therapeutic options improve [3]. Our study showed that HRQoL improved after the application of TOHR and that many of the dimensions of the AcroQoL did not return to baseline levels after the washout period. This finding is consistent with the currently accepted view that the long-term biochemical remission of acromegaly does not seem to have a direct impact on the HRQoL of this population because most of our patients had controlled disease [3, 26, 38]. In fact, a cross-sectional study comparing HRQoL between patients with controlled acromegaly and healthy controls and a longitudinal study evaluating changes in HRQoL in patients with biochemically stable disease during a 6-year follow-up period showed that impaired HRQoL persisted despite disease control over the long term [26]. Many of the dysfunctions of acromegaly are most likely the result of irreversible changes in the CNS that result from excessive GH levels [38], and therefore, the search for alternative treatment (such as the TOHR) becomes essential.

Study limitations

The strength of this study is that it is the first to show the benefits of TOHR on peripheral muscle performance, 6MWD, general fatigue, balance control, and AcroQoL scores in individuals with acromegaly. Despite these strengths, our study also has limitations. First, the study used a small number of participants. However, the chronic physical complications due to acromegaly along with the prolonged duration of functional rehabilitation reduced the patients' motivation to enter into a TOHR protocol. In addition, joint deformities, arthralgia, muscle dysfunction, bone disease, cardiopulmonary involvement, and metabolic complications can make it difficult for the patient to adhere to an exercise programme for long periods. Second, we do not use face-to-face rehabilitation, which can be difficult to perform when patients live far from outpatient clinics or are unable to attend regular appointments. In spite of these limitations, we believe that the results of this study may serve as a basis for new studies aiming at replicating the efficacy of functional rehabilitation programmes in this patient population, especially because TOHR has been shown to improve adherence rates, increase patient satisfaction, reduce costs for the health system and increase long-term efficacy [39, 40].

Conclusions

This study showed that patients with acromegaly may benefit from TOHR because it improves muscle dysfunction, functional capacity, general fatigue, balance control, and HRQoL. Considering the recent advances in functional rehabilitation, multicentre trials may be important to identify its importance in patients with acromegaly and how beneficial it would become in the long term as an adjunctive method to hormonal control therapy. In this context, this study may be a starting point for large randomized controlled trials aiming at the recommendation of functional rehabilitation, especially for those with long-term illness.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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