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On the Functional Capacity and Quality of Life of Patients with Acromegaly: Are They Candidates for Rehabilitation Programs?

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Abstract. [Purpose] This study compared patients having active acromegaly with those having controlled acromegaly in terms of peripheral muscle strength, body composition, and functional capacity. We also examined the associations between these measures. [Methods] A total of 14 patients with active acromegaly, 12 patients with controlled acromegaly, and 12 healthy controls were subjected to isometric dynamometry, surface electromyography, electrical bioimpedance, and a six-minute walk test. [Results] The active acromegaly group exhibited significantly more fat-free mass than the control group. With respect to the peripheral muscle performance, the controlled acromegaly group presented a significantly lower electromyographic median frequency than the control group. The quadriceps maximum strength was significantly lower in the controlled acromegaly group than in the control group. The fat-free mass was significantly correlated with the quadriceps maximum strength. The global scores of the Acromegaly Quality of Life Questionnaire were significantly correlated with the six-minute walk distance. [Conclusion] Patients with acromegaly have more fat-free mass, less peripheral muscle strength, and greater fatigability than healthy control subjects. These findings depend on the degree of hormonal control. In acromegalic patients, peripheral muscle strength is related to body composition, and functional capacity is correlated with quality of life.
Key words: Acromegaly, Muscle strength, Exercise tolerance

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INTRODUCTION

Acromegaly is a chronic systemic condition that results from excessive production of growth hormone (GH) and insulin-like growth factor I (IGF-I). In 98% of cases, the condition is caused by GH-secreting pituitary adenoma (somatotropinoma). In approximately 2% of cases, acromegaly is caused by eutopic or ectopic hypersecretion of growth hormone-releasing hormone (GHRH)[1, 2)]. In Europe there is a prevalence of 40 to 70 cases per million inhabitants and an estimated annual incidence of 3 to 4 cases per million persons[3)]. In Brazil, nearly 650 new cases of acromegaly are diagnosed every year[4)]. Acromegaly is most common among persons aged 30 to 50 years, and there is no gender bias. If not properly controlled, acromegaly can lead to serious cardiovascular, respiratory, and metabolic complications[2)].

Muscular hypertrophy associated with weakness is common among acromegalic patients[5)]. Interestingly, studies have shown that hypertrophied muscles offer no functional advantages and that their strength is actually lower than that of normal muscle[6, 7)]. Using muscle biopsies in 18 adults with acromegaly, Nagulesparen et al.[8)] found hypertrophy of type I fibers in 50% of the individuals, while atrophy was more common in type II fibers. According to the authors, excessive GH produces larger but weaker muscles.

Few studies have assessed functional capacity in acromegalic patients[9, 10)]. Arthropathy is certainly the most important cause of morbidity and functional impairment in acromegaly. It is caused by the direct action of GH/IGF-I and by secondary degenerative changes[11, 12)]. Cardiovascular functional impairment also reduces the functional capacity of acromegalic patients, which reduces performance during exercise[8)]. Studies suggest that fatigue and the lactate threshold are closely linked and that there is a physiopathological basis for the physical function deficits and excessive fatigue of adults with increased GH[13)].

In terms of body composition, GH hypersecretion is associated with the total water volume in the body[14)]. Hypersecretion of GH also modulates fat deposition and ac-

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cumulation[15]. Studies have shown that the expansion of the extracellular volume reflects the properties of salt retention that are mediated by the GH stimulation of the renin-angiotensin system, suppression of atrial natriuretic peptide, release of prostaglandins, and production of nitric oxide in acromegalic subjects[16, 17]. GH is an anabolic hormone with the capacity to induce nitrogen retention and insulin resistance, stimulate protein synthesis, and increase lipolysis in adipose tissue. Given the excessive secretion of GH in acromegaly, one would expect reduced fat mass and increased fat-free mass (FFM) in these patients[14, 15, 18].

Although acromegaly has been well studied in terms of physiopathology, there is still much controversy regarding changes in peripheral muscle strength, functional capacity, body composition, and quality of life. These topics depend on individual differences as functions of hormonal control. The primary aim of the present study was to compare the quadriceps strength and endurance, the six-minute walk distance test (6MWT), the body composition, and quality of life between control healthy subjects, subjects with active acromegaly, and subjects with controlled acromegaly. The secondary aim was to test for correlations between those variables.

SUBJECTS AND METHODS

Subjects

This was a cross-sectional study conducted between June 2011 and September 2012. The study involved 32 subjects with acromegaly aged 18 to 50 years who were followed up at the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro. Diagnoses were based on clinical features and were confirmed by high levels of GH that did not fall below 0.4 ng/mL after an oral glucose tolerance test or IGF-I levels above the upper bound of the age-specific normal range[19, 20].

Patients were separated into those with active and controlled conditions according to their serum levels of GH and IGF-I. Patients were considered to have controlled acromegaly when their IGF-I levels were within the reference range adjusted for age and when their baseline GH was less than 1.0 ng/mL[20]. Patients unable to perform the 6MWT and patients with comorbidities unrelated to acromegaly that could interfere with the functional tests were not included in the study. Untreated hypothyroidism and hypocortisolism were also considered as exclusion criteria.

A control group of 12 healthy volunteers from both genders was recruited from the Augusto Motta University Center (UNISUAM). These individuals did not exhibit any evidence of cardiovascular or musculoskeletal disorders.

All participants signed an informed consent form, and the protocol was approved by the Research Ethics Committee of the UNISUAM under number 005/2012.

Methods

The participants underwent an initial anthropometric evaluation, and all the tests were performed on the same day in the Laboratory of Human Movement Analysis at UNISUAM.

The *Acromegaly Quality of Life Questionnaire* (AcroQoL) was used to assess quality of life. This questionnaire takes into consideration physical and psychological issues and has 22 questions with five possible answers that are scored between 1 and 5; the maximum score is 110 and reflects the best possible quality of life[21].

Body composition was analyzed using an electrical bioimpedance device (BIA 310e, Biodynamics, Seattle, WA, USA). Participants were instructed to rest for five minutes before the test. During the resting period, participants remained barefoot, avoided metallic objects, and kept their feet apart 15 to 30 cm[22]. Two electrodes were placed on the dorsal side of the right hand, and another two electrodes were placed on the dorsal side of the right foot. Body resistance and reactance were measured and used to estimate the FFM. For this purpose, we used an equation that was previously validated for the Brazilian population: $FFM = -4.104 + (0.518 \times \text{height } (2)/\text{resistance}) + (0.231 \times \text{weight}) + (0.130 \times \text{reactance}) + (4.229 \times \text{sex: male} = 1, \text{female} = 0)$[22, 23].

Peripheral muscle function was assessed by isometric dynamometry (model DIN-TRO, EMG System from Brasil LTDA, Brazil) and an endurance test using surface electromyography (EMG model 810C, EMG System from Brasil LTDA, Brazil). Participants were instructed to cross their arms over their chest while the seat was adjusted to allow 90-degree hip joint flexion. The surface EMG electrodes were placed on the quadriceps (*vastus medialis*) according to the Surface EMG for Non-Invasive Assessment of Muscles (SENIAM) recommendations[24]. The maximum quadriceps voluntary isometric contractions (MVICs) were performed at 90 degrees of knee flexion. Each test was performed three times with a three-minute rest period between repetitions, and the greatest value was selected. The endurance test consisted of a sustained contraction for 60 seconds at 30% of the MVIC that was obtained from the strength test. The median frequency (MDF) and root-mean-square (RMS) slopes from the EMG signal during isometric contraction over time were used to analyze the quadriceps fatigability[25]. The RMS slope measures the electrical activity during contraction, while the MDF slope is related to the firing rates of motor units. Therefore, muscle fatigability is directly proportional to the RMS slope (since it reflects a greater activation of motor units due to a reduction in the capacity to sustain a contraction) and is inversely proportional to the MDF slope (which reflects the action potential reduction of the fibers during muscle contraction)[26, 27].

The 6MWT followed the American Thoracic Society recommendations[28] and was performed in a 30-meter corridor. Heart rate, oxygen peripheral saturation, and the level of dyspnea on the modified Borg scale were measured before starting the test, at the third minute, and at the end of the test. Predicted values for each patient were calculated using the equations of Gibbons et al[29].

Data distribution was tested using the Shapiro-Wilk and Levene tests. When appropriate, one-way ANOVA (followed by the Tukey test for multiple comparisons) or ANOVA on Ranks (Holm-Sidak) was used to compare the groups. The unpaired t-test or Mann-Whitney tests were used to compare the active acromegaly and controlled acromegaly groups. Pearson or Spearman correlation tests were used to assess the associations between variables. The results were expressed as medians with interquartile ranges and frequencies (percentages). Analyses were performed using the SigmaStat 3.5 software (Systat Software, San Jose, CA, USA). The level of significance was set at $p<0.05$.

RESULTS

Six of the initial 32 acromegalic patients were excluded: two patients had untreated hypothyroidism, two patients had untreated hypocortisolism, and two patients were unable to perform the 6MWT. Therefore, the acromegaly group included 16 females and 10 males [50.0 (44.5–55.7) years old]. Within the acromegaly group, 14 patients had active acromegaly and 12 had controlled disease. Twenty-one patients (80.8%) had undergone surgery, and eight patients (30.7%) had undergone radiotherapy. Six patients (23.1%) had hypopituitarism, but since they were under treatment, their free T4 levels were normal during the study period, without signals of adrenal insufficiency. Three of these patients had active acromegaly, and three had controlled disease. The general characteristics of the acromegalic patients are listed in Table 1.

The control group (eight females and four males) had the following anthropometric characteristics: age = 50 (38.7–57.7) years and body mass index (BMI) = 28.9 (27.6–30.4) kg/m^2. There were no statistical differences between healthy volunteers and acromegalic patients for these anthropometric characteristics ($p>0.05$).

All patients completed the assessments without complications. Table 2 presents the data for body composition,

Table 1. General characteristics of 26 acromegalic patients

Variables	Values
Demographic data	
Age (years)	50 (44.5–55.8)
Sex (male), n (%)	10 (38.5)
Body mass index (kg/m^2)	31.9 (27.4–33.8)
Disease data	
Controlled disease, n (%)	12 (46.2)
Patients submitted to surgery, n (%)	21 (80.8)
Patients submitted to radiotherapy, n (%)	8 (30.7)
Comorbidities	
Diabetes, n (%)	9 (34.6)
Arthralgia, n (%)	19 (73.1)
Cardiomegaly, n (%)	1 (3.8)
Hypopituitarism, n (%)	6 (23.1)
Arterial hypertension, n (%)	15 (57.7)

Results are expressed as medians (interquatile range) or numbers (%).

Table 2. Demographic and functional variables

Variable	Control group (n=12)	Controlled disease (n=12)	Active disease (n=14)
Age (years)	50 (38.7–57.7)	52 (48.5–53.5)	48.5 (37.7–57.5)
Sex (male), n	4 (33.3)	2 (16.6)	8 (57.1)
Disease duration (years)	-	11.5 (12–15.5)	7 (6–9)
Body composition			
Body mass index (kg/m^2)	28.9 (27.6–30.4)	32.0 (26.1–32.6)	31.3 (28.6–34.4)
Fat-free mass (kg)	45.9 (38.6–57.9)	48.9 (45–51.6)	56.2* (48.5–56.5)
Fat percentage (%)	33.8 (29.3–41.4)	34.5 (31.6–41.1)	33.5 (26.3–36)
Peripheral muscle performance			
RMS slope	0.32 (0.15–0.48)	0.78 (0.45–1.57)	1.36 (0.17–2.26)
MDF slope	−0.08 (−0.22– −0.04)	−0.52* (−0.69– −0.37)	−0.18# (−0.32– −0.10)
Quadriceps muscle strength (kg)	38.7 (32.7–46.4)	23.8* (18.1–29.1)	28.7 (21.8–40.7)
Six minute walk distance			
6MWD (m)	552 (515–570.8)	483.5 (435–545.8)	460 (399–519.3)
6MWD (%)	73.9 (70.9–78.2)	67.1 (62.3–76.9)	65 (55.5–69.4)
AcroQol			
Global score	-	79.5 (61–90.3)	69 (54–74)
Physical score	-	28.5 (22.5–34.5)	25 (20–27)
Psychological score	-	52.5 (42.5–60.3)	44 (37–49)

Results are expressed as medians (interquatile range) or numbers (%). Abbreviations: 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; 6MWD, six-minute walk distance

*Significantly different from the control group. #Significantly different from the controlled acromegaly group.

peripheral muscle performance, and the 6MWT. The active acromegaly group presented with more FFM than the control group (p=0.04). The controlled acromegaly group had a lower MDF slope than the control group (p=0.001), and the active acromegaly group had a higher MDF slope than the controlled acromegaly group (p=0.001). The maximum quadriceps strength was significantly lower in the controlled acromegaly group than in the control group (p=0.002).

When considering the whole sample of acromegaly patients, the variables related to body composition and maximum quadriceps strength were significantly correlated, including FFM and strength (r=0.64; p<0.001) and body fat percentage and strength (r=−0.40; p=0.04). There were associations between the AcroQoL global score and 6MWT (r=0.51; p=0.009) and between the AcroQoL psychological score and the 6MWT (r=0.54; p=0.005).

DISCUSSION

The primary findings of the present study are as follows: (1) quadriceps fatigability is greater and muscle is weaker in acromegalic patients compared with controls; (2) patients with active acromegaly have a greater FFM than controls; (3) peripheral muscle strength is significantly correlated with FFM and body fat percentage; and (4) six-minute walk distance is significantly correlated with the global and psychological scores on the AcroQoL. To date, no previous studies have focused on these correlations in acromegaly patients.

Compared with the control group that was matched for age, weight, and BMI, only the patients with active acromegaly had a significantly greater median FFM (56.2 versus 45.9 kg; p=0.04). Other studies have reported an increased FFM in patients with acromegaly[14, 18, 30)]. GH is a hormone that can induce a positive nitrogen balance, stimulate protein synthesis, and increase lipolysis in adipose tissue, possibly by upregulating molecules in pre-adipocytes and adipocytes and modifying transcription factors[13, 15)].

Few studies have assessed the impact of GH on the skeletal muscle of acromegalic patients. As GH increases fluid retention without benefiting the muscle mass or strength, some authors have questioned the anabolic effect of this hormone. However, GH has been proven to promote protein synthesis[5, 31)]. Similar to a study by Khaleeli et al.[6)], the present study found a reduction in quadriceps strength in patients with the active and controlled forms of acromegaly; however, there was a significant difference between the controlled acromegalic patients and the control group (p=0.002). Various factors contribute to the muscle weakness that is observed in acromegaly, including the direct effects of GH on the muscle, and the metabolic changes that are associated with the condition, such as hypothyroidism, hypoadrenalism, and diabetes. Mechanical factors, such as joint instability and the lack of activity that is inherent to the condition, can also contribute to quadriceps weakness[6, 32)]. Despite the lack of statistical difference, it is noteworthy that quadriceps strength was higher in patients with active disease than in those with controlled disease (median 28.7 vs. 23.8 kg). It is possible that some factors observed in our patients with active acromegaly, including younger age (median 48.5 vs. 52 years) and shorter disease duration (7 vs. 11.5 years), may explain, at least in part, this result.

In addition to less quadriceps strength, the present study also found greater fatigability in acromegalic patients and a significant difference in MDF slope between the three groups (p=0.001). Despite the type I muscle fiber hypertrophy, previous studies have shown that acromegalic patients had significant atrophy of type II muscle fibers[33)]. Type II fibers are typically capable of faster and stronger contractions; however, these fibers are easily fatigued, as they have fewer mitochondria and oxidative enzymes and, thus, rely on glycolytic metabolism as their primary energy source[13)]. No other study appears to have assessed fatigue using surface electromyography in acromegalic patients.

Although several functional capacity tests have been described in the literature, submaximal tests have been often indicated for assessing patients with various clinical conditions because they are simple, easy to apply, low costing, safe, reliable, and accessible in clinical practice[28, 33)]. The 6MWT provides indicators of functional capacity, gas exchange integrity, and sensory stress[34)]. In the present work, we found different 6MWT distances between the groups (552 m for the healthy group, 483.5 m for the group with controlled acromegaly, and 460 m for the group with active acromegaly), but without statistical significance. In acromegalic patients, arthropathy has been suggested as the primary limiting factor for functional capacity[11, 12)]. It is likely that the high frequency of arthralgia in our sample (73.1%) contributed to the decreased functional capacity observed in acromegalic patients when compared with the control group. Other possible factors that can impair the performance on the 6MWT in such patients are musculoskeletal disorders, acromegalic cardiomyopathy, and respiratory dysfunction[7, 12)].

In the present study, quadriceps strength was significantly correlated with FFM (r=0.64; p<0.001) and body fat percentage (r=−0.40; p=0.04). Even assuming that FFM includes a significant proportion of extracellular water in these patients (because of the direct activation of GH in the renin-angiotensin system)[17)], it is expected that patients with lower body fat percentages would present with greater muscle strength on dynamometry.

Several factors make acromegaly a condition that considerably impacts quality of life, including body image, depression, mood lability, joint pain, and fatigue[13)]. The AcroQoL was designed as a simple and valid instrument to analyze quality of life in acromegalic patients aged 18 to 70 years[21)]. In the present study, the 6MWT was significantly correlated with the global (r=0.51; p=0.009) and psychological (r=0.54; p=0.005) AcroQoL scores. In acromegalic patients, the occurrence of joint pain in the axial or appendicular skeleton considerably affects quality of life. Biermasz et al.[35)] administered the AcroQoL to 118 acromegalic patients and found that joint complaints were the most substantial contributor to reducing quality of life. As previously mentioned, there was a high frequency of arthralgia in the present study (73.1%).

A critical analysis of the results is important. First, the present study is limited by being cross-sectional; however, the study provides data on the impact of hormonal effects on the parameters provided by BIA, dynamometry, electromyography, and the 6MWT in acromegalic patients. Second, BIA was used instead of dual-energy X-ray absorptiometry (DXA), which is considered to be a more accurate tool for assessing body composition. However, DXA has been criticized for measuring body components of maximum density (mineral bone content) and minimum density (fat), while FFM is considered to be the remaining body mass, including skeletal muscle, viscera, conjunctive tissue, and extracellular water[5, 18]. Third, echocardiograms were not performed on these patients, but echocardiograms could help assess the impact of subclinical acromegalic cardiomyopathy on patients' performance in the 6MWT. Despite these limitations, our results suggest that, in addition to reducing GH levels, physiotherapy may play an important role in increasing functionality of acromegalic patients. Rehabilitative strategies should be directed toward increasing the peripheral muscle performance and exercise tolerance, thereby improving the functional capacity and the quality of life of these subjects. Therefore, the present study can serve as a starting point for future clinical trials that assess the impact of rehabilitation programs for acromegalic patients.

In conclusion, the present study shows that, compared with a control group, acromegalic patients have a greater FFM and less peripheral muscle strength and endurance. These findings depend on the disease control status. Additionally, in acromegalic patients, peripheral muscle strength is significantly correlated with body composition, and functional capacity is correlated with quality of life. The results of this study strongly suggest that acromegalic patients can benefit from rehabilitation programs.

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