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Original Article

What is the effect of peripheral muscle fatigue, pulmonary function, and body composition on functional exercise capacity in acromegalic patients?

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Abstract. [Purpose] The six-minute walk test (6MWT) is increasingly being used as an important tool for analyzing functional capacity in patients with multisystem disorders. The aim of this study was to evaluate the effect of body composition, peripheral muscle function, and pulmonary function on the six-minute walk distance (6MWD) in acromegalic patients. [Subjects and Methods] Thirty-two patients with active acromegaly, with a mean age of 48.6 ± 12.1 years, underwent an evaluation of body composition using electrical bioimpedance, isometric dynamometry with surface electromyography, tests of pulmonary function, and the 6MWT. [Results] The mean ± SD values for the 6MWD, fat-free mass (FFM), and maximal expiratory pressure (MEP) were 65.5 ± 11.7% predicted, 55.1 ± 10.6 kg, and 55.2 ± 16.8% predicted, respectively. There was a significant correlation between the 6MWD and the following parameters: the angle of the linear regression line obtained using the values of the median frequency electromyography signal over time during the fatigability test for the vastus medialis muscle (MDF, r=0.65), FFM (r=0.62), MEP (r=0.60), height$^{(2)}$/resistance index (r=0.52), resistance (r=−0.50), and forced expiratory volume in 1 second (r=0.50). Multivariate analysis showed that MDF, FFM, and MEP were independent predictors of the 6MWD (R^2=0.52). [Conclusion] The fatigability of the peripheral muscles, FFM, and MEP are the primary determinants of the 6MWD in acromegalics.

Key words: Acromegaly, Muscle strength, Exercise

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INTRODUCTION

In addition to progressive somatic disfigurement, acromegaly can cause a wide variety of multisystemic manifestations[1, 2)]. Hypersecretion of growth hormone (GH) affects virtually every organ, causing disorders in morphology, endocrine function, metabolism, body composition, and muscle and aerobic performance[3)]. Thus, expectedly, many conditions might affect the functional exercise capacity in acromegalic patients.

Exercise is the most potent physiological challenge to systemic homeostasis and, consequently, to the entire anatomical and functional organization, linking the environment to cellular metabolism, thereby providing indicators of the integrity of intrapulmonary gas exchange, cardiovascular stress, and sensory stress[4)]. In individuals with an excess of GH, specific studies have shown a reduced maximal aerobic capacity[5, 6)]. More recently, the six-minute walk test (6MWT) has been promoted as a method to analyze various multisystemic diseases, and because it is a submaximal test, it can assess the functional capacity of an individual when performing their normal daily living activities[7)]. Nevertheless, there are still few studies that have used the 6MWT on acromegalic patients[8)].

Several studies have documented the muscle changes in acromegaly[9–12)], but a limited number of studies have been published regarding how the damage to peripheral muscles compromises functional exercise capacity[8)]. GH induces important anabolic actions on skeletal muscle, including the induction of a positive nitrogen balance and the stimulation of protein synthesis[11, 12)]. When examined via muscle biopsy, acromegalic patients generally demonstrate hypertrophy of type 1 muscle fibers and atrophy of type 2 muscle fibers[13)].

In acromegalic patients, respiratory disorders are an important cause of impaired physical performance, contributing to 25% of all patient deaths[1)]. In this condition, both the upper and lower airways are involved as a result of the changes that affect the craniofacial structure, the geometry of the rib cage, and lung volumes[1, 14)]. Respiratory muscle dysfunction has also been described[15, 16)]. Thus, substantial

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effects on pulmonary function should be expected for acromegalic patients, as has been reported by several previous studies[15, 17].

Body composition is another component of health-related physical fitness that undergoes profound changes in acromegalic patients. The reduced fat and increased lean body mass in these individuals are well known[3, 12, 18]. GH induces lipolysis in adipose tissue, potentially via regulatory molecules in both pre-adipocytes and adipocytes[12, 19]. GH also induces activation of the renin-angiotensin system, resulting in extracellular volume expansion, sodium retention, and increased body water[20].

Despite the substantial pathophysiological knowledge about acromegaly that has been acquired in recent decades, the effect of excess GH on functional exercise capacity in these patients still remains largely unknown. A reduced six-minute walk distance (6MWD) has been shown to predict an increased risk of morbidity and mortality in several patient populations[7]. Thus, the identification of factors that affect 6MWT performance in acromegalic patients is important. We hypothesize that multiple mechanisms are responsible for the reduced exercise performance observed in such individuals. Thus, the aim of this study was to evaluate the effect of peripheral muscle function, pulmonary function, and body composition on the functional exercise capacity in acromegalic patients.

SUBJECTS AND METHODS

Subjects

Between August 2012 and May 2014, a cross-sectional study was performed evaluating 62 acromegalic patients who were recruited at the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro. Diagnoses were based on clinical features and were confirmed either by high levels of GH that did not fall below 0.4 ng/ml after an oral glucose tolerance test or by insulin-like growth factor I (IGF-I) levels above the upper bound limit of the age-specific normal range[21, 22].

Patients 18 years of age or older with active acromegaly were included. Patients were considered to have active acromegaly when their IGF-I levels exceeded the reference range adjusted for age and when their baseline GH was >1.0 ng/mL[22]. The exclusion criteria were as follows: 1) history of tobacco use >10 pack-years; 2) the presence of any comorbidities not related to acromegaly; 3) neurological diseases, such as Parkinson's or Alzheimer's disease; 4) disabilities that would make individuals unable to perform the 6MWT; 5) untreated hypothyroidism and hypocortisolism; and 6) the presence of any implantable electronic or metallic device, such as a pacemaker.

According to the World Medical Association Declaration of Helsinki, the protocol was approved by the research and ethics committee of our institution, and written informed consent was obtained from all participants.

Methods

Body mass index (BMI) classification was performed according to the criteria of the World Health Organization[23]. Body composition analysis was performed using a bioelectrical impedance apparatus (BIA 310e, Biodynamics, Seattle, WA, USA). Patients were asked to rest for five minutes before the examination and remained barefoot, without any metallic objects near them and with their feet placed 15 to 30 cm apart[24]. Two electrodes were placed on the dorsal surface of the right hand, and two electrodes were placed on the dorsal surface of the right foot. The resistance and reactance were calculated and used to estimate the fat-free mass (FFM). The selected equation was previously validated for Brazilian individuals: FFM = −4.104 + (0.518 × height $^{(2)}$/resistance) + (0.231 × weight) + (0.130 × reactance) + (4.229 × gender: male = 1, female = 0)[24, 25].

Peripheral muscle function was assessed using isometric dynamometry (TRO-DIN model, EMG System, Brazil), and an endurance test was performed using surface electromyography (EMG 810C model, EMG System, Brazil). Participants were instructed to cross their arms over their chest while the seat was adjusted to allow 90 degrees of flexion of the hip joint. Surface EMG electrodes were placed on the quadriceps (vastus medialis muscle), according to SENIAM recommendations[26]. Active differential electrodes (20× gain) were used to collect EMG signals from surface electrodes for the A/D converter. The sampling frequency was 1,000 Hz, and the signals were amplified with a 2,000× gain. Maximum voluntary isometric contractions (MVIC) were performed at 90 degrees of knee flexion for the quadriceps muscles with leg extension; each test was performed three times with a rest period of 2 minutes between trials, and the highest value was selected. The endurance test consisted of a sustained contraction for 60 seconds using 30% of the MVIC value obtained in the strength test. Linear regression lines were fitted to the median frequency and the root mean square slopes (MDF and RMS, respectively) throughout the isometric contraction plateau. The MDF and RMS values corresponding to the EMG signals during the isometric contraction over time were used to analyze the fatigability of the quadriceps. While the RMS is associated with the amplitude and quantification of the electrical signal generated during muscle contraction, the MDF is associated with the firing rate of the action potential[27, 28].

Using an HD CPL (nSpire Health, Inc., Longmont, CO, USA) device, the following pulmonary function tests were performed: spirometry, whole-body plethysmography, diffusing capacity for carbon monoxide (DLco), and respiratory muscle strength. All of these tests followed the standards established by the American Thoracic Society/European Respiratory Society[29]. The Pereira (spirometry) and Neder (lung volumes, diffusion, and respiratory muscle strength) equations were adopted in the interpretation of the functional parameters[30–33].

The 6MWT was performed in a 30-meter corridor. All of the patients were familiarized with the test procedure prior to testing. The heart rate, peripheral oxygen saturation, and degree of dyspnea on a modified Borg scale were measured prior to the start of the test, in the third minute, and at the end of the test. The predicted values were calculated for each patient using equations previously reported by Gibbons et al.[34], according to the recommendations of the American Thoracic Society[7].

The sample size was calculated using MedCalc version

Table 1. General characteristics of 32 acromegalic patients

Variables	Men (n=13)	Women (n=19)	Total (n=32)
Age (years)	49.2 ± 10.8	47.8 ± 11.0	48.6 ± 12.1
Body composition			
Body mass index (kg/m^2)	31.8 ± 3.38	29.2 ± 4.16	29.7 ± 4.42
Reactance (Ω)	48.1 ± 8.90	50.3 ± 8.64	49.7 ± 9.82
Resistance (Ω)	485.3 ± 47.0	480.1 ± 56.0	481.4 ± 56.8
Fat percentage (%)	32.7 ± 6.68	34.2 ± 7.23	33.5 ± 7.57
Height$^{(2)}$/resistance index (cm^2/ Ω)	2.82 ± 0.25	2.74 ± 0.28	2.76 ± 0.31
Fat-free mass (kg)	56.7 ± 9.50	53.2 ± 10.1	55.1 ± 10.6
Peripheral muscle performance			
Quadriceps muscle strength (kg)	26.6 ± 5.68	22.3 ± 7.79	24.3 ± 6.52
RMS (mV)	0.68 ± 0.31	0.81 ± 0.38	0.77 ± 0.46
MDF (Hz)	−0.27 ± 0.08	−0.39 ± 0.10	−0.38 ± 0.11
Pulmonary function			
FVC (% predicted)	107.6 ± 11.7	104.3 ± 13.1	106.9 ± 14.2
FEV_1 (% predicted)	106.5 ± 10.0	105.1 ± 12.3	105.8 ± 13.5
FEV_1/FVC (%)	78.2 ± 7.24	79.4 ± 7.60	78.5 ± 8.07
TLC (% predicted)	108.9 ± 12.6	106.0 ± 12.8	108.6 ± 13.3
RV (% predicted)	115.8 ± 18.2	114.2 ± 18.5	115.3 ± 19.5
R_{aw} (cm H_2O/L/s)	3.98 ± 0.44	3.72 ± 0.50	3.91 ± 0.52
DLco (% predicted)	103.4 ± 19.8	101.9 ± 20.8	102.9 ± 21.3
MIP (% predicted)	70.2 ± 24.2	68.5 ± 25.3	69.7 ± 26.0
MEP (% predicted)	55.8 ± 15.9	54.3 ± 16.4	55.2 ± 16.8
Six-minute walk test			
6MWD (% predicted)	66.1 ± 10.8	64.2 ± 11.2	65.5 ± 11.7

Results presented as the mean ± SD or number (%). RMS: angle of the linear regression line obtained using the values of the root mean square electromyography signal over time during the fatigability test for the vastus medialis muscle; MDF: angle of the linear regression line obtained using the values of the median frequency electromyography signal over time during the fatigability test for the vastus medialis muscle; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; RV: residual volume; R_{aw}: airway resistance; DLco: diffusing capacity for carbon monoxide; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure

8.2 (MedCalc Software, Mariakerke, Belgium). A minimum of 26 cases were required to test the alternative hypothesis that the correlation coefficient was higher than 0.50 (or less than −0.50), assuming a type I error of 5% and a type II error of 20%[35]. The data distribution was tested using the Shapiro-Wilk test. Pearson's correlation coefficient was used to analyze the association between the 6MWD and various body composition factors (body mass index, reactance, resistance, fat percentage, height index$^{(2)}$/resistance, and fat-free mass), muscle function (quadriceps muscle strength, MDF, and RMS), and pulmonary function. The pulmonary function parameters used in the correlation with the 6MWD included the following: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), total lung capacity (TLC), residual volume (RV), airway resistance (R_{aw}), DLco, maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP). A collinearity analysis was performed prior to construction of the regression model. On the basis of these results, a multivariate regression analysis was performed using only the independent variables that were significantly correlated with the outcome variables in the univariate analysis. The results were expressed as the mean and standard deviation or frequency (percentage). Analyses were performed using the SigmaStat software 3.5 (Systat Software, San Jose, CA, USA). Values were considered statistically significant at $p<0.05$.

RESULTS

Of the 62 acromegalic patients who were initially recruited, 30 patients were excluded for the following reasons: disease controlled from a hormonal perspective (n=24), refusal to participate (n=2), history of smoking >10 pack-years (n=2), failure to generate acceptable criteria for the lung function tests (n=1), and inability to perform the 6MWT (n=1). The study participants ultimately included 19 females and 13 males with a mean age of 48.6 ± 12.1 years. Of these patients, 22 patients had complaints of arthralgia, 12 patients had diabetes mellitus, 18 patients had hypertension, and 3 patients had a history of heart disease.

According to their BMIs, 10 participants had normal weights, 17 were overweight, and 5 had grade I obesity. In terms of pulmonary function, the FEV_1/FVC ratio was <70% in 10 patients. The TLC and RV were >120% of the predicted values in 4 and 8 patients, respectively. The MIP and MEP were reduced in 18 and 25 patients, respectively. The 6MWD was below the lower normal limit in 22 patients. The general characteristics of the acromegalic patients are listed in Table 1.

There was a significant correlation between the 6MWD and the following body composition parameters: fat-free mass (r=0.62; p=0.004), height$^{(2)}$/resistance index (r=0.52; p=0.017), and resistance (r=−0.50; p=0.025). With respect to peripheral muscle performance, there was only a correlation between the 6MWD and MDF (r=0.65; p=0.002). With respect to pulmonary function, there was a significant correlation between the 6MWD and the following variables: MEP (r=0.60; p=0.006) and FEV_1 (r=0.50; p=0.026). Correlations between the 6MWD and the parameters for body composition, peripheral muscle performance, and pulmonary function are shown in Table 2.

A prediction model adjusted using the variables MDF, fat-free mass, and MEP explained 52% of the variance in the 6MWD (R^2=0.52; p=0.001) using the following equation: 6MWD (% predicted) = 10.6 + (27.3 × MDF) + (0.31 × fat-free mass) + (0.25 × MEP).

Table 2. Correlations of the six-minute walk distance with body composition, peripheral muscle performance, and pulmonary function in acromegalic patients

Variables	Six-minute walk distance (% predicted)
Body composition	
Body mass index (kg/m^2)	−0.41
Reactance (Ω)	−0.26
Resistance (Ω)	−0.50*
Fat percentage (%)	−0.11
Height$^{(2)}$/resistance index (cm^2/ Ω)	0.52*
Fat-free mass (kg)	0.62***
Peripheral muscle performance	
Quadriceps muscle strength (kg)	0.41
RMS (mV)	−0.09
MDF (Hz)	0.65***
Pulmonary function	
FVC (% predicted)	0.45
FEV_1 (% predicted)	0.50*
FEV_1/FVC (%)	0.30
TLC (% predicted)	0.40
RV (% predicted)	−0.28
R_{aw} (cm H_2O/L/s)	−0.08
DLco (% predicted)	0.35
MIP (% predicted)	0.43
MEP (% predicted)	0.60**

RMS: angle of the linear regression line obtained using the values of the root mean square electromyography signal over time during the fatigability test for the vastus medialis muscle; MDF: angle of the linear regression line obtained using the values of the median frequency electromyography signal over time during the fatigability test for the vastus medialis muscle; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; RV: residual volume; R_{aw}: airway resistance; DLco: diffusing capacity for carbon monoxide; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. *p<0.05, **p<0.01, ***p<0.005

DISCUSSION

The main findings of this study were that peripheral muscle function, as well as lung function and body composition, affected the functional exercise capacity of acromegalic patients. The main determinants of the performance of these subjects regarding the distance they walked included the fatigability of the peripheral muscles, fat-free mass, and respiratory muscle strength. Currently, there are no studies that have focused on the effect of several variables on the 6MWD in acromegalic patients to create a prediction model.

The limitations on exercise reflect the abnormalities of the respiratory, cardiovascular, neuromuscular, and neurosensory systems in highly variable combinations with multifactorial interactions[4]. In previous studies investigating the exercise capacity of acromegalic patients, a reduced exercise performance was reported[5, 6]. In this study, exercise capacity was examined using the 6MWD and was lower than the predicted values. Several factors may be involved in the reduced exercise performance in patients with acromegaly, including cardiopulmonary dysfunction, musculoarticular involvement, and metabolic changes[6, 8]. In addition, the systemic impairments caused by acromegaly can result in a more sedentary lifestyle, thereby resulting in an overall loss of muscle strength and a consequent reduction in functional capacity.

Fatigue is one of the most distressing symptoms in patients with acromegaly; it significantly affects both functional performance and quality of life[3]. In the present study, we evaluated muscle fatigue using surface electromyography. Electromyographic recording provides two parameters: the RMS, which quantifies the electrical activity during contraction, and the MDF, which demonstrates the shots of the action potential of fiber contraction[28]. Muscle fatigue is directly proportional to the RMS slope and inversely proportional to the MDF slope. Thus, larger RMS values represent more muscle fatigue, while larger MDF values represent less muscle fatigue[36].

Although no previous studies have evaluated the relationship between muscle fatigue and the 6MWT in patients with acromegaly, several studies have shown that skeletal muscle fatigue limits exercise tolerance under various clinical conditions[37, 38]. In our prediction model, the fatigability of the quadriceps was one of the main determinants of a worse performance in the 6MWT. This result is not unexpected, as type 2 muscle fibers undergo significant metabolic changes in acromegalic patients, including a reduction in the number of mitochondria and oxidative enzymes and glycogen accumulation[3]. These muscle fibers are characteristically able to contract faster and more strongly and are thus easily fatigable[3, 9].

In our study, patients with a low fat-free mass showed a lower functional exercise capacity on a submaximal exercise test. To the best of our knowledge, no study has previously investigated the effect of nutritional status on exercise capacity in patients with acromegaly. We evaluated body composition using electrical bioimpedance, which evaluates the fat-free mass rather than the lean mass. Importantly, the fat-free mass consists of all fat-free tissues, including water, muscles, bones, connective tissues, and organs, whereas the lean body mass (measured by dual-energy X-ray absorptiometry) consists of both the fat-free mass and essential fat[39]. The relationship between the fat-free mass and the 6MWD may be explained, at least in part, by the fact that the major contributor to the fat-free mass is the skeletal muscle mass[40]. Interestingly, Sabino et al.[40] demonstrated that fat-free mass was the unique independent predictor of functional exercise capacity in COPD patients (partial r=0.52; p<0.01).

Similar to studies reported by Iandelli et al.[16] and Camilo et al.[17], we observed a reduced MEP in most participants (78.1% of cases). The expiratory muscle strength was significantly and positively associated with the 6MWT performance in our study, indicating that a better respiratory muscle performance is associated with a greater walking distance. In addition, the MEP was one of the explanatory variables in our prediction model proposed for the 6MWT. Muscle biopsy studies have shown segmental degeneration of muscle fibers, foci of cellular infiltration, and variable derangement of both type I and type II fibers[41]. According to Iandelli et al.[16], muscular factors appear to modulate the normal central motor output and can affect ventilation control to produce a more rapid breathing pattern. Interestingly, respiratory complications have been identified as a major cause of morbidity and mortality in acromegalic patients[1].

One of the strengths of this study is that it is the first study to evaluate the effect of various factors on the 6MWD in patients with active acromegaly. Thus, this study indirectly assesses the effect of GH on the functional exercise capacity in these individuals because patients with suppressed GH levels were not evaluated. However, this study has specific limitations that should be considered. First, gender was not considered in the correlation analysis due to the small sample size. However, most of the variables were analyzed with respect to the predicted percentage; this allowed the standardization of absolute values for sex, age, weight, and height. Second, we did not investigate potential exercise performance-limiting factors, such as hemodynamic factors and cardiac autonomic nervous system factors. Furthermore, because cardiopulmonary exercise testing is regarded as the gold standard assessment for evaluating exercise capacity, the tests used in this study may not reflect the true functional exercise capacity. We believe that our results justify additional investigation of the performance of these patients during exercise, particularly to confirm the effects of long-term hormone suppression therapy (controlled disease) and physical reconditioning.

In conclusion, this study demonstrated that the fatigability of peripheral muscles, fat-free mass, and expiratory muscle strength are the main determinants affecting the distance measured using the 6MWT for acromegalic patients. Taken together, these findings suggest that optimization of nutritional status and muscle function should be considered in prevention and rehabilitation programs for acromegalic patients, including the training of respiratory and peripheral muscles.

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