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Explanatory models of muscle performance in acromegaly patients evaluated by knee isokinetic dynamometry: Implications for rehabilitation

Agnaldo José Lopes [a,*], Arthur Sá Ferreira [a], Evelyn Mendes Walchan [a], Mauricio Santos Soares [b], Priscila Santos Bunn [b], Fernando Silva Guimarães [a,c]

[a] Rehabilitation Sciences Post-Graduation Program, Augusto Motta University Center, Av. Paris 72, Bonsucesso, Rio de Janeiro, Brazil
[b] Admiral Adalberto Nunes Physical Education Center (Brazilian Navy), Av. Brasil, 10590, Penha, Rio de Janeiro, Brazil
[c] Physical Therapy Department, Federal University of Rio de Janeiro, R. Prof. Rodolpho Paulo Rocco, 255, Cidade Universitária, Rio de Janeiro, Brazil

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ABSTRACT

Purpose: To evaluate the effects of demographics and hormonal variations on knee muscle performance in patients with acromegaly and develop explanatory models of peripheral muscle function in these individuals.
Methods: This was a cross-sectional study in which 53 acromegalics and 27 healthy subjects underwent knee isokinetic dynamometry to evaluate the peak torque value for leg extension at 75°/s (PTE75) and 240°/s (PTE240). Separate multivariable linear regression models for the prediction of PTE75 and PTE240 were tested using variables commonly used as predictors in the clinical setting and other specific variables related to acromegaly.
Results: The final prediction model for PTE75 ($R^2 = 0.888$; adjusted $R^2 = 0.820$, SE of bias = 16.2 Nm, $p < 0.001$) was $-0.221 \times$ growth hormone $+ 36.791 \times sex_{male = 1} - 27.407 \times status_{active = 1} - 0.690 \times$ age + 148.071. The final prediction model for PTE240 ($R^2 = 0.816$; adjusted $R^2 = 0.805$, SE of bias = 8.8 Nm, $p < 0.001$) was $-0.174 \times$ growth hormone $+ 12.522 \times sex_{male = 1} - 0.520 \times$ age + 98.099.
Conclusions: In acromegalics, high growth hormone levels, female gender, and older age are associated with reduced muscle strength and endurance. Additionally, active disease negatively affects peripheral muscle strength in these patients.

1. Introduction

Acromegaly is a chronic, slowly progressing, and insidious disease that is often diagnosed at a late stage (Colao, Ferone, Marzullo, & Lombardi, 2004). The clinical history of most patients suggests that the disease begins seven to 10 years prior to diagnosis. Its annual incidence is three to four million new cases, and its prevalence ranges from 36 to 60 cases per million (Capatina & Wass, 2015; Holdaway & Rajasoorya, 1999). Over 98% of patients with acromegaly have a growth hormone (GH)-secreting pituitary adenoma, and ectopic tumours are a rare cause of the disease (Vieira Neto et al., 2011).

* Corresponding author at: Rua Araguaia, 1266, bloco 1/405, Freguesia, Jacarepaguá, 22745-271 Rio de Janeiro, RJ, Brazil.
E-mail addresses: phel.lop@uol.com.br (A.J. Lopes), arthurde@unisuamdoc.com.br (A.S. Ferreira), evelynwalchan@yahoo.com.br (E.M. Walchan), mauricio-soares@hotmail.com (M.S. Soares), priscilabunn@yahoo.com.br (P.S. Bunn), fguimaraes_pg@yahoo.com.br (F.S. Guimarães).

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The clinical manifestations of acromegaly are insidious and can gradually lead to cardiovascular, respiratory, metabolic, orthopaedic, and neoplastic complications (Dekkers, Biermasz, Pereira, Romijn, & Vandenbroucke, 2008). In addition, acromegaly is associated with several comorbidities, including hypertension, sleep apnoea, glucose intolerance, and diabetes as the most prevalent conditions (Mestron et al., 2004; Vieira Neto et al., 2011). With regard to body composition, these individuals have reduced fat mass and increased lean mass (Madeira et al., 2010). Musculoskeletal system involvement is also common in these patients, with reports of muscle hypertrophy associated with weakness (Freda et al., 2009; Guedes da Silva et al., 2013).

GH binds to the liver receptors and induces the secretion of insulin-like growth factor I (IGF-I), which is bound to proteins when it circulates in the blood. IGF-I mediates most of the growth-promoting effects of GH. It is well known that GH and IGF-I exert anabolic actions on skeletal muscle, stimulating myogenic differentiation (Woodhouse, Mukherjee, Shalet, & Ezzat, 2006). In acromegaly patients, GH seems to have a direct effect on skeletal muscle, and although it stimulates protein synthesis, it is believed that GH does not provide any benefit in terms of muscle mass or strength (Ehrnborg, Ellegard, Bosaeus, Bengtsson, & Rosén, 2005; Freda et al., 2009).

Isokinetic dynamometry has introduced a new dimension to the analysis of muscle function, as it provides high reliability in measurement (Lustosa et al., 2010). It is currently widely used as an indicator of the function and performance of certain muscle groups for both diagnosis and rehabilitation (Carvalho & Puga, 2010; Lustosa et al., 2010). It is known that isokinetic dynamometry is of great value for identifying muscular performance in various clinical conditions and is considered the gold standard tool for evaluating peripheral muscle function (Harbo, Brincks, & Andersen, 2012; Stark, Walker, Phillips, Fejer, & Beck, 2011). In acromegaly, there is evidence to suggest that hormonal, metabolic, and articular impairments at least partially explain the peripheral muscle dysfunction commonly observed in these patients (Khaleeli et al., 1984; McNab & Khandwala, 2005).

As it is a multisystem disease, acromegaly presents several factors that can significantly influence the muscular performance of patients. We hypothesise that the various changes that occur in acromegaly patients cause different forms of interference in peripheral muscle function. Therefore, our objective in the present study was to evaluate the effects of demographics and various hormonal and metabolic changes on the performance of knee muscles in acromegaly patients and to develop explanatory models of muscle function for these individuals.

2. Materials and methods

2.1. Participants

A cross-sectional study evaluating patients with acromegaly and healthy participants was performed between May 2014 and July 2015. The subjects were regularly evaluated at the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro. The diagnosis of acromegaly was based on clinical characteristics and was 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 limit of the age-specific normal range (Giustina et al., 2000, 2010). Patients of both genders aged $\geqslant$18 years and who were clinically stable were prospectively included using a non-probabilistic (convenience) sampling scheme. Patients were considered to have 'controlled acromegaly' when their IGF-I levels were within the reference range adjusted for age and when the GH baseline level was less than 1.0 ng/ml; otherwise, they were considered to have 'active acromegaly' (Giustina et al., 2010). Acromegaly patients with intense arthralgia, the presence of untreated hypothyroidism or hypocortisolism with comorbidities not related to acromegaly, and prior orthopaedic surgery history, along with those patients considered 'very active' by the International Physical Activity Questionnaire (IPAQ) – Short Form, were excluded from the study (Craig et al., 2003; Matsudo et al., 2001). The subjects in the healthy control group did not exhibit any evidence of cardiovascular or musculoskeletal disorders and were paired with acromegaly patients according to physical activity level as well as anthropometric and demographic variables. In accordance with the World Medical Association Declaration of Helsinki, all participants signed a consent form, and the protocol was approved by the Research Ethics Committee of the Augusto Motta University Centre (UNISUAM) under number 27912514000005235.

2.2. Measurements

Patients' current body mass index (BMI) was calculated as the ratio of the current weight (kg) and the height squared (m^2) in accordance with World Health Organization recommendations (World Health Organization, 2015).

Fat-free mass (FFM) was measured by bioelectrical impedance analysis (BIA 310e, Biodynamics, Seattle, WA, USA). Two electrodes were placed on the dorsal surface of the right hand, and another two electrodes were placed on the dorsal surface of the right foot. To estimate the FFM, body resistance and reactance were measured. For this purpose, we used an equation that was previously validated for the Brazilian population (Kyle et al., 2004; Rodrigues, Silva, Monteiro, & Farinatti, 2001). Further, the FFM was divided by height squared (m^2) to determine the "corrected FFM" (CFFM) of each patient (Akpinar et al., 2014).

The IPAQ-Short Form was used to evaluate physical activity during the previous week, and the results were expressed using the following classifications: 'sedentary,' 'irregularly active,' 'active,' and 'very active' (Craig et al., 2003).

Isokinetic knee dynamometry was performed at the Admiral Adalberto Nunes Physical Education Centre (Brazilian Navy). The quadriceps and hamstring muscles were evaluated using a Biodex System 4 PRO dynamometer (Biodex Medical Systems, Shirley, NY, USA). The test was performed only on the dominant body side because there is no significant difference between the lower limbs for isokinetic parameters (Aquino et al., 2002; Santos et al., 2011). Movement execution was programmed to occur concentrically and isokinetically with knee extension. The participants were placed in a sitting position with the torso upright and the back of the chair inclined at 85° (Santos et al., 2011; Sole, Hamrén, Milosavljevic, Nicholson, & Sullivan, 2007). To familiarise the patients with the procedure, each individual initially underwent adaptation training with three repetitions at submaximal effort (Tsepis, Giakas, Vagenas, & Georgoulis, 2004). Strength analysis was then performed at an angular velocity of 75°/s with two sets of five repetitions. After this stage, the individuals performed an endurance evaluation at an angular velocity of 240°/s with two sets of 15 repetitions. An interval of 120 s elapsed between each set of repetitions (Lautamies, Harilainen, Kettunen, Sandelin, & Kujala, 2008; Martin et al., 2006). The individual's heart rate, oxygen saturation, and blood pressure were measured before and after the evaluation. For the examination to be accepted, the coefficient of variation had to be <10%, and the work fatigue could not be negative (Carvalho & Puga, 2010; Harbo et al., 2012). The work fatigue is the relationship between the first and last third of muscular work; when maximum effort is employed in every knee extension, more work must be produced in the first third of a repetition and less in the last third, resulting in a positive value (Carvalho & Puga, 2010). The variables analysed included the peak torque (PT) for leg extension at 75°/s (PTE75) and 240°/s (PTE240) (Dvir, 2004; Harbo et al., 2012; Lautamies et al., 2008).

2.3. Development of the model for predicting knee isokinetic dynamometry in acromegaly

Multivariable linear regression models for the prediction of PT were tested using variables commonly used as predictors in the clinical setting (age, body mass, body height, BMI, FFM, CFFM and gender ['male' = 1 and 'female' = 0]) and other specific variables related to acromegaly (time since symptom onset, GH level, IGF-I level, diabetes and hypertension as separated comorbidities ['yes' = 1, 'no' = 0], and disease status ['active' = 1 and 'controlled' = 0]). Separate models were tested for calculating PTE75 and PTE240. A forward stepwise method was applied using the adjusted R^2 value as a criterion for entry ($p < 0.05$) and removal ($p > 0.10$) of variables.

2.4. Statistical analysis

The overall performance measures of the regression consisted of the R^2 value adjusted for the number of variables retained in the proposed model as well as the standard error ($SE = \sqrt{S^2}/n$) of the difference (bias = measured − predicted). The specific performance of the new prediction model was assessed by regression diagnosis and calibration analyses as follows (Collins, Reitsma, Altman, & Moons, 2015; Collins et al., 2014).

Regression analysis was performed using Pearson's correlation coefficient between the dependent and independent variables and among the independent variables. Derivation of predicted values for each participant using each model was performed using a linear combination (summation) of retained coefficients rounded to the 3rd digit of precision and inputting clinical data from each participant. Multicollinearity was assessed using the variance inflation factor (VIF) (Marquardt, 1970). Analysis of residuals was also performed using empirical distributions of residuals and the Kolmogorov-Smirnov test with Lilliefors correction (Toutenburg, 2002). Calibration was verified by an assessment of the calibration plot (measured *vs.* predicted, along with regression lines showing slope and intercept) and the limits of agreement (LOA) plot (Bland & Altman, 2010).

Statistical analysis was performed using SPSS 22 (IBM Corp., North Castle, NY, USA), and plots were generated in Excel 2011 for Mac (Apple Inc., Cupertino, CA, USA). Descriptive results are shown as the mean ± SD [interquartile range] or frequency (%). Between-group comparisons were performed using independent sample *t*-tests (equal variances not assumed, two-tailed). Statistical significance was considered at a value of $p < 0.05$ (two-tailed) for all analyses.

3. Results

3.1. Clinical characteristics, laboratory data, and peripheral muscle performance

A total of 70 outpatients were selected for inclusion in the present study. Fifty-three patients met the inclusion criteria, while 17 patients were excluded for the following reasons: severe arthralgia ($n = 6$), untreated hypothyroidism or hypocortisolism ($n = 5$), previous history of orthopaedic surgery ($n = 3$), and those considered 'very active' according to the IPAQ-Short Form ($n = 3$). The resulting studied sample included 28 men and 25 women, and the mean age was 46.2 ± 10.3 years. Twenty-three patients had active acromegaly, and 30 patients had controlled acromegaly. The mean time since symptom onset was 12.3 ± 7.18 years. Forty-two patients had undergone surgery, and 13 patients had received radiotherapy. Another 27 healthy subjects (15 men and 12 women with a mean age of 48.9 ± 11.2 years) were invited to participate in the study.

The general characteristics and isokinetic knee dynamometry data are shown in Table 1. Significant differences were observed between groups on levels of GH and IGF-I ($p < 0.001$ for both) as well as PTE75 ($p = 0.001$) and PTE240 ($p = 0.008$). No significant differences were observed for age ($p = 0.302$), body mass, body height, BMI, FFM, or CFFM ($p \geqslant 0.063$).

Table 1
General characteristics and peripheral muscle function of 53 acromegalics and 27 healthy subjects.

Variables	Acromegaly group	Healthy group	*p*-value
Demographic and body composition			
Body mass (kg)	84.4 ± 14.8	80.7 ± 13.8	0.277
Body height (cm)	167 ± 9.53	169 ± 8.32	0.305
Body mass index (kg/m^2)	30.2 ± 4.20	28.3 ± 4.36	0.063
Fat-free mass (kg)	48.2 ± 8.25	45.8 ± 7.92	0.081
Corrected fat-free mass (kg/m^2)	17.1 ± 1.72	16.2 ± 1.67	0.094
Laboratory data			
GH (μg/l)	55.1 ± 81.6 [7.0; 52.4]	3.3 ± 1.2 [2.3; 4.3]	<0.001
IGF-I (μg/l)	273.3 ± 163.4 [156.0; 367.0]	136.5 ± 29.6 [113.4; 155.4]	<0.001
Comorbidities			
Diabetes, n (%)	15 (28.3)	0 (0)	NT
Hypertension, n (%)	25 (47.2)	0 (0)	NT
Knee isokinetic dynamometry			
PTE75 (Nm)	111.5 ± 48.2	148.9 ± 39.9	0.001
PTE240 (Nm)	71.1 ± 22.7	87.4 ± 25.8	0.008

Results presented as the mean ± SD [IQR] or number (%). NT: not tested.
GH = growth hormone; IGF-I = insulin-like growth factor I; PTE75 = peak torque for leg extension at 75°/s; PTE240 = peak torque for leg extension at 240°/s.

3.2. Regression diagnosis

The PTE75 was significantly correlated with the GH level ($r = -0.750$, $p < 0.001$), sex ($r = 0.721$, $p < 0.001$), disease status ($r = -0.707$, $p < 0.001$), diabetes ($r = -0.603$, $p < 0.001$), age ($r = -0.537$, $p < 0.001$), and IGF-I level ($r = -0.381$, $p = 0.005$). The PTE240 was significantly correlated with the GH level ($r = -0.810$, $p < 0.001$), sex ($r = 0.652$, $p < 0.001$), disease status ($r = -0.541$, $p < 0.001$), diabetes ($r = -0.601$, $p < 0.001$), age ($r = -0.560$, $p < 0.001$), IGF-I level ($r = -0.286$, $p = 0.038$), time since symptoms' onset ($r = -0.287$, $p = 0.037$), and body height ($r = 0.285$, $p = 0.038$).

Significant associations among independent variables included the paired analyses of the following: sex with age ($r = -0.501$, $p < 0.001$), body mass ($r = 0.281$, $p = 0.041$), body height ($r = 0.353$, $p = 0.010$), time since symptom onset ($r = -0.299$, $p = 0.029$), GH level ($r = -0.416$, $p = 0.002$), and disease status ($r = -0.393$, $p = 0.004$); diabetes with GH level (0.721, $p < 0.001$), disease status (0.549, $p < 0.001$), sex (−0.329, $p = 0.016$), and IGF-I level (0.307, $p = 0.025$); age with time since symptom onset ($r = 0.358$, $p = 0.009$), GH level ($r = 0.300$, $p = 0.029$), IGF-I level ($r = 0.308$, $p = 0.025$), and disease status ($r = 0.306$, $p = 0.026$); body mass with body height ($r = 0.621$, $p < 0.001$), BMI ($r = 0.741$, $p < 0.001$), FFM ($r = 0.653$, $p < 0.001$) and CFFM ($r = 0.625$, $p < 0.001$); GH level with IGF-I level ($r = 0.278$, $p = 0.044$) and disease status ($r = 0.616$, $p < 0.001$); and IGF-I level with disease status ($r = 0.412$, $p = 0.002$) (Table 2).

3.3. The predictive model and its overall performance

The adjusted R^2 value of the PTE75 model obtained using the stepwise method was 0.554 when the GH level was included as the first variable. Including the variables sex, disease status, and age significantly increased the adjusted R^2 values to

Table 2
Correlation analysis of the peak torque for leg extension at 75°/s and 240°/s with independent variables ($n = 53$).

Independent variables	Pearson's correlation coefficient with *p*-values	
	PTE75	PTE240
GH (μg/l)	**−0.750, $p < 0.001$**	**−0.810, $p < 0.001$**
Sex ('male' = 1)	**0.721, $p < 0.001$**	**0.652, $p < 0.001$**
Disease status ('active' = 1)	**−0.707, $p < 0.001$**	**−0.541, $p < 0.001$**
Diabetes ('yes' = 1)	**−0.603, $p < 0.001$**	**−0.601, $p < 0.001$**
Age (years)	**−0.537, $p < 0.001$**	**−0.560, $p < 0.001$**
IGF-I (μg/l)	**−0.381, $p = 0.005$**	**−0.286, $p = 0.038$**
Time since symptoms' onset (years)	−0.170, $p = 0.223$	**−0.287, $p = 0.037$**
Fat-free mass (kg)	0.126, $p = 0.340$	0.204, $p = 0.079$
Corrected fat-free mass (kg/m^2)	0.118, $p = 0.405$	0.173, $p = 0.220$
Body mass index (kg/m^2)	−0.115, $p = 0.412$	−0.055, $p = 0.694$
Body height (cm)	0.114, $p = 0.414$	**0.285, $p = 0.038$**
Hypertension ('yes' = 1)	−0.051, $p = 0.717$	−0.149, $p = 0.287$
Body mass (kg)	−0.024, $p = 0.862$	0.144, $p = 0.305$

GH = growth hormone; IGF-I = insulin-like growth factor I; PTE75 = peak torque for leg extension at 75°/s; PTE240 = peak torque for leg extension at 240°/s.

0.756, 0.807, and 0.820, respectively. The inclusion of all other independent variables did not significantly increase the adjusted R^2 value, and these variables were therefore not retained in the model (diabetes: $p = 0.587$; hypertension: $p = 0.137$; IGF-I: $p = 0.716$). Evidence of multicollinearity was not noted for any independent variable ($VIF_{GH} = 1.713$, $VIF_{sex} = 1.517$, $VIF_{disease\ status} = 1.685$, and $VIF_{age} = 1.364$). The final prediction model for PTE75 (Eq. (1); $R^2 = 0.888$, adjusted $R^2 = 0.820$, SE of bias = 16.2 Nm, $p < 0.001$) was (Table 3):

$$PTE75 = -0.221 \times GH + 36.791 \times sex_{male=1} - 27.407 \times status_{active=1} - 0.690 \times age + 148.071 \quad (1)$$

The adjusted R^2 value of the PTE240 model obtained using the stepwise method was 0.649 when the GH level was included as the first variable. Including the variables sex and age significantly increased the adjusted R^2 values to 0.767 and 0.805, respectively. The inclusion of all other independent variables did not significantly increase the adjusted R^2 value, and therefore, these variables were not retained in the model (disease status: $p = 0.625$; diabetes: $p = 0.802$; hypertension: $p = 0.704$; IGF-I: $p = 0.612$). Evidence of multicollinearity was not noted for any independent variable ($VIF_{GH} = 1.226$, $VIF_{sex} = 1.489$, and $VIF_{age} = 1.354$). The final prediction model for PTE240 (Eq. (2); $R^2 = 0.816$, adjusted $R^2 = 0.805$, SE of bias = 8.8 Nm, $p < 0.001$) was (Table 3):

$$PTE240 = -0.174 \times GH + 12.522 \times sex_{male=1} - 0.520 \times age + 98.099 \quad (2)$$

3.4. Model calibration

There was no obvious relationship between the bias and the mean (Fig. 1, top) in the PTE75 model; the SD for the bias was −0.3 ± 16.2 Nm (Fig. 1, middle), indicating that the estimate was accurate with a very small bias towards underestimating the PTE75. The histogram plot of the differences showed no apparent skew (Fig. 1, bottom), and the assumption of normality of the distribution was not violated ($p = 0.200$), which is a formal assumption and necessary condition for applying linear regression models. The 95% CI for the bias was −4.7 to 4.2 Nm, and the LOA and respective 95% CI for the lower and upper LOA were −32.0 Nm [−39.8; −24.3] and 31.5 Nm [23.7; 39.2], respectively. These intervals are somewhat wide and reflect both the sample size and the moderate variation in the differences.

There was no obvious relationship between the bias and the mean (Fig. 2, top) in the PTE240 model, again indicating that the estimate was accurate with a small bias towards underestimating the PTE240; the SD of the bias was −1.2 ± 8.8 Nm (Fig. 2, middle). The histogram plot of the differences showed no apparent skew (Fig. 2, bottom), and the assumption of normality of the distribution was not violated ($p = 0.075$). The 95% CI for the bias was −3.7 to 1.2 Nm, and the LOA and respective 95% CI for the lower and upper LOA were −18.5 Nm [−22.7; −14.3] and 16.1 Nm [11.8; 20.3], respectively. These intervals are narrower than the ranges observed for the PTE75, reflecting the smaller variation in the differences between the measured and estimated values.

4. Discussion

The most basic relationship that controls muscle function is the association between muscle length and the magnitude of the corresponding tension. When loads are moved, muscle strength increases in proportion to both the magnitude of the load and its distance from the joint axis; thus, it is expected that effort under isokinetic conditions results in considerable joint forces (Dvir, 2004). The present study used knee isokinetic dynamometry to develop explanatory models for both muscle strength and endurance in individuals with acromegaly. We evaluated the effects of both anthropometric characteristics and the repercussions that the disease can have on various bodily systems. To increase the reliability of the model, we excluded various conditions that can have a confounding effect on the models, including significant changes in the musculoskeletal system due to severe arthralgia and previous orthopaedic surgery. Similarly, we also excluded subjects who were considered 'very active' according to the IPAQ-Short Form (Craig et al., 2003). Moreover, we evaluated a healthy control group matched by age, gender, body mass, body height, BMI, FFM, and CFFM to increase the significance of our findings.

Table 3
Multivariate regression analysis for prediction of peak torque for leg extension at 75°/s and 240°/s in patients with acromegaly ($n = 53$).

Model	Coefficient [95% CI]	Std. Error	t	Sig.
PTE75				
Intercept	148.071 [113.705; 182.437]	17.092	8.663	<0.001
GH (μg/l)	−0.221 [−0.312; −0.129]	0.045	−4.856	<0.001
Sex ('male' = 1)	36.791 [22.711; 50.870]	7.002	5.254	<0.001
Disease status ('active' = 1)	−27.407 [−42.352; −12.463]	7.433	−3.688	0.001
Age (years)	−0.690 [−1.338; −0.042]	0.322	−2.140	0.037
PTE240				
Intercept	98.099 [81.259; 114.939]	8.380	11.707	<0.001
Growth hormone (μg/l)	−0.174 [−0.212; −0.136]	0.019	−9.225	<0.001
Sex ('male' = 1)	12.522 [5.674; 19.370]	3.408	3.675	0.001
Age (years)	−0.520 [−0.837; −0.203]	0.158	−3.299	0.002

GH = growth hormone; PTE75 = peak torque for leg extension at 75°/s; PTE240 = peak torque for leg extension at 240°/s.

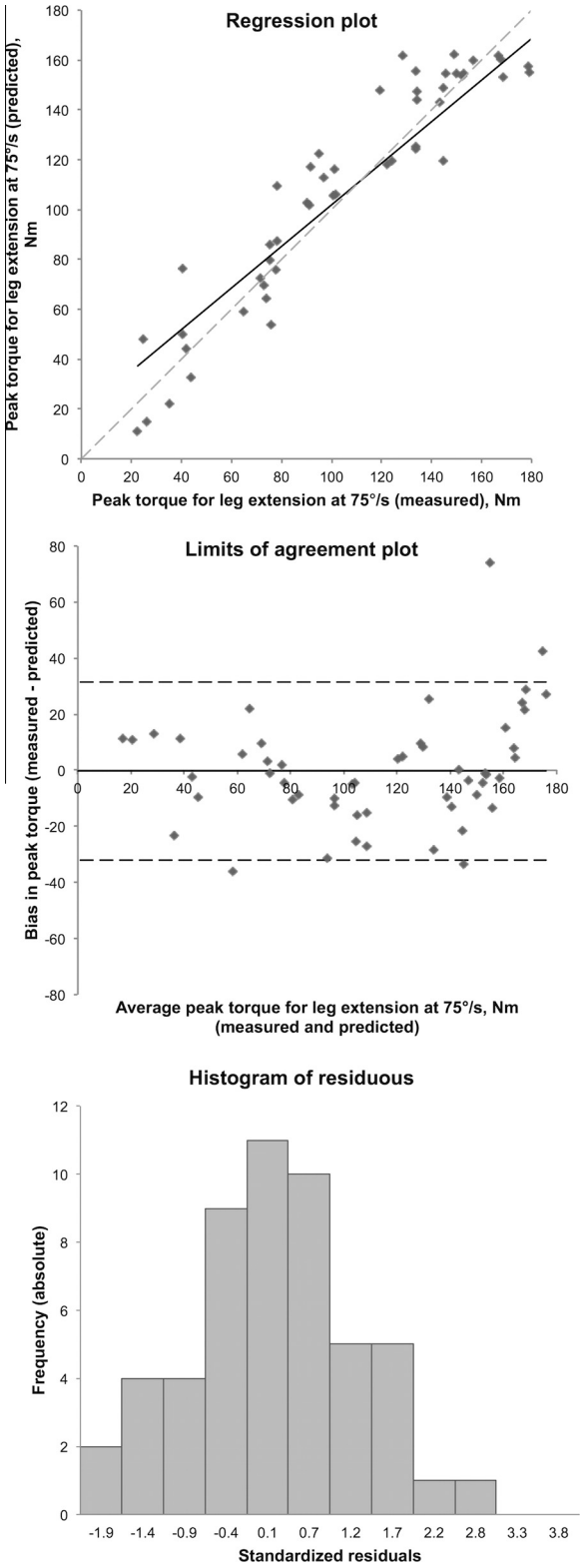

Fig. 1. Analysis of the multivariable linear regression model for peak torque for leg extensions at 75°/s. *Top*: Calibration plot of the measured *vs.* predicted peak torque for leg extensions at 75°/s. *Middle*: Limits of agreement plot of the averaged values and the bias (measured-predicted values). *Bottom*: Histogram of residuals of predicted and measured values.

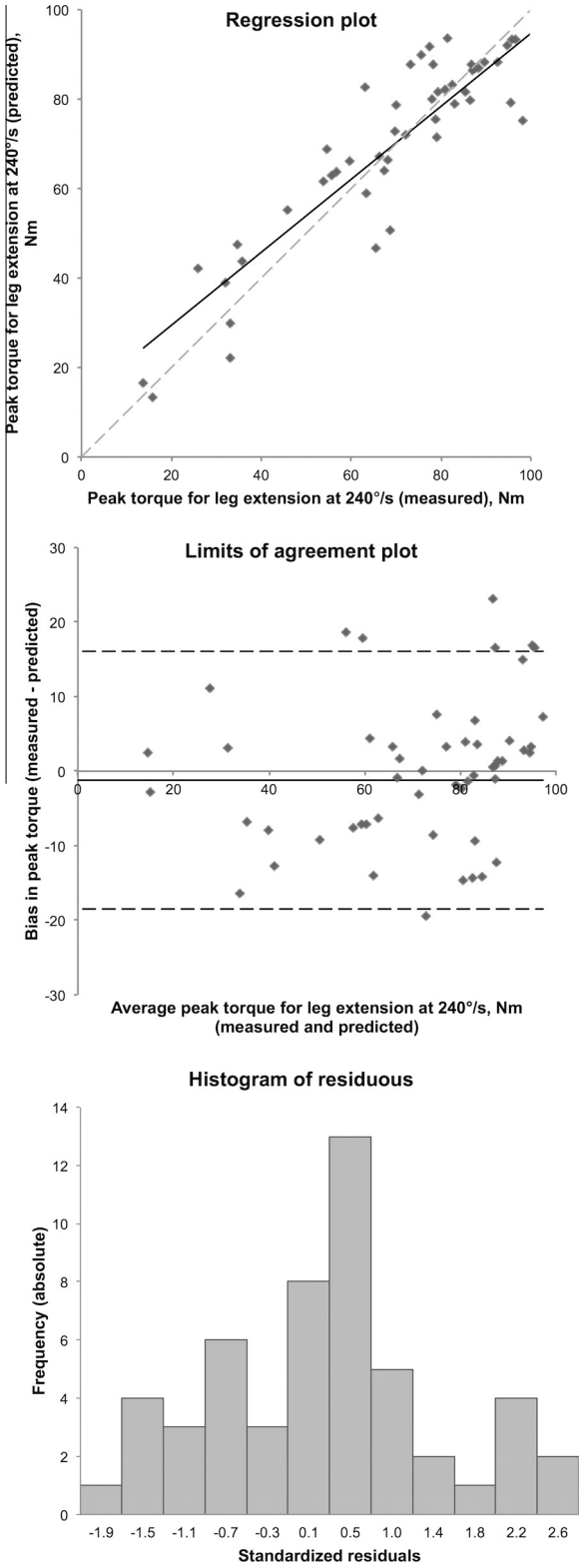

Fig. 2. Analysis of the multivariable linear regression model for peak torque for leg extensions at 240°/s. *Top*: Calibration plot of the measured *vs.* predicted peak torque for leg extensions at 240°/s. *Middle*: Limits of agreement plot of the averaged values and the bias (measured-predicted values). *Bottom*: Histogram of residuals of predicted and measured values.

Compared with control subjects, patients with acromegaly exhibited decreased PTE75 and PTE240, which indicates reduced muscle strength and muscle endurance. Using isometric dynamometry, Guedes da Silva et al. observed decreased maximum strength in the quadriceps in patients with acromegaly (Guedes da Silva et al., 2013). Several factors may be involved in the peripheral muscle dysfunction of these patients, including the direct action of GH on the muscle; associated endocrine diseases such as hypothyroidism, hypoadrenalism, and diabetes; joint instability; and physical deconditioning (Guedes da Silva et al., 2013; Khaleeli et al., 1984; McNab & Khandwala, 2005).

One of the basic isokinetic principles is that the angular contraction velocity is constant due to variable resistance (Dvir, 2004). Because angular velocities <180°/s evaluate strength and angular velocities >180°/s evaluate endurance under isokinetic conditions (Kannus, 1994), the present study showed that high levels of GH, female gender, and older age had negative effects on both strength and muscle resistance in acromegaly patients. Moreover, the coefficients of determination of the two tested models were high and very similar (0.888 and 0.816 for PTE75 and PTE240, respectively), which suggest a strong explanatory power of the models and the importance of the variables that were included.

GH exerts important actions on the musculoskeletal system of acromegaly patients. In fact, the present study showed that the GH level was the major determinant in the explanatory models of PTE75 and PTE240. When evaluating the muscle biopsies of adult acromegaly patients, Nagulesparen et al. observed type I fibre hypertrophy in 50% of patients, while a deficiency or type II fibre atrophy was detected in nearly 70% of cases (Nagulesparen, Trickey, Davies, & Jenkins, 1976). Because isokinetic exercise demands a sudden and intense load displacement with immediate recruitment of type II fibres and increased glycolytic potential, it is expected that a deficiency or atrophy of these fibres in acromegaly patients would result in weaker contractions and early onset of fatigue (Mastaglia, 1973; Thorstensson, Grimby, & Karlsson, 1976; Khaleeli et al., 1984). We also observed that the variable disease state ('active acromegaly' *vs.* 'controlled acromegaly') entered the prediction model for PTE75, but not for PTE240. Future studies could specifically address this issue by longitudinally evaluating individuals with acromegaly before and after achieving disease control.

In the present study, both gender and age were determinants in the two explanatory models developed. Interestingly, in a group of 96 healthy men and women, Neder et al. observed that men had higher strength values than women at all ages when lower limb muscle strength was normalised to the corresponding muscle mass; furthermore, senescence is related to a decrease in strength in both men and women, irrespective of muscle mass reduction (Neder et al., 1999). According to these authors, although a lower muscle mass helps to explain the reduced strength in women and in the elderly, it is possible that qualitative muscle disorders also have a negative impact on these two groups of individuals, including changes in the ability to generate tension, chronic injury induced by repeated contractions, and the reduced ability of the central nervous system to stimulate the peripheral muscles (Neder et al., 1999). In a group of 4,541 healthy individuals, Freedson et al. observed a more rapid loss in PT with age in women (Freedson, Gilliam, Mahoney, Maliszewski, & Kastango, 1993). Thus, despite the importance of GH in reducing PT in acromegaly patients, we propose that gender and age also play a pivotal role in peripheral muscle function in these patients, irrespective of the GH/IGF-I axis.

Because muscle mass increases in proportion to body weight in healthy individuals, heavier individuals generally produce a higher PT. In fact, weight and height are involved in most quadriceps predictive equations in healthy subjects (Decramer, Gosselink, Troosters, Verschueren, & Evers, 1997; Neder et al., 1999; Seymour et al., 2010). In the present study, however, greater weight and height did not have a positive effect on PT. Some of these patients have gigantism, which is a form of acromegaly with intense repercussions for the endocrine and musculoskeletal systems (Woodhouse et al., 2006). Thus, we demonstrate that greater weight and height have a negative impact on peripheral muscle function in acromegaly patients and offset the positive effect that these variables would otherwise have on skeletal muscle under normal conditions. This finding explains, at least in part, the absence of body mass and body height in the PT predictive models developed in the present study. Additionally, we did not observe statistically significant differences in both FFM and CFFM between acromegaly patients and healthy controls in the study sample. Because the FFM consists mainly of skeletal muscle and bone tissues (Minematsu et al., 2012), we believe that the reduced muscle function in patients with acromegaly may not be attributed solely to differences in muscle mass between these two groups of subjects evaluated.

Since acromegaly is associated with comorbidities, it is possible to assume that comorbidities may help explain the differences in muscle strength between patients with acromegaly and healthy subjects. Despite the significant univariate correlation between the presence of diabetes and reduced muscle strength, we observed that diabetes as comorbidity curiously did not enter the forward stepwise regression model for the prediction of PT. Also using multiple regression models, some studies have shown that poor glycemic control (but not controlled diabetes) is an independent factor for the reduction of skeletal muscle strength because of diabetic complications including peripheral arterial insufficiency and neuropathy (Kalyani, Metter, Egan, Golden, & Ferrucci, 2015; Park et al., 2006; Yoon et al., 2016). In line with these findings, Akpinar et al. (2014) and Yoon et al. (2016) demonstrated that muscle mass or strength in patients with diabetes does not differ significantly from healthy subjects, suggesting the presence of diabetes itself does not impact negatively on muscle function.

Some study limitations should be mentioned. First, the study is limited by being cross-sectional, which precludes a cause-effect analysis. Second, we did not perform muscle biopsies on these individuals, which could provide a better understanding of the musculoskeletal function assessed by knee isokinetic dynamometry. Third, BIA was used instead of dual-energy X-ray absorptiometry (DXA), computed tomography, or magnetic resonance spectroscopy, which are considered as being more precise tools for assessing body composition (Ng, Hinton, Fan, Kanaya, & Shepherd, 2016); these tools could allow us to assess leg muscle mass and also muscle quality, which is defined as muscle strength per unit muscle mass (Park et al., 2006; Yoon et al., 2016). Finally, the exclusion of 'very active' acromegaly patients by IPAQ scoring prevents generalisation

of our results; however, we hypothesised that these patients should have a different performance on the isokinetic dynamometer that would influence the explanatory models that have been proposed. Despite these limitations, we believe our findings have interesting clinical implications regarding the functional rehabilitation of acromegaly patients because they highlight factors that affect the peripheral muscle performance of these individuals. In this study, the models predict the strength and endurance of quadriceps muscles with high exactitude in patients with acromegaly.

5. Conclusions

In acromegaly patients, high GH levels, female gender, and older age reduce both muscle strength and endurance. Additionally, the disease negatively affects the peripheral muscle strength of active patients. These findings may be useful in the development of physiotherapeutic intervention programmes for acromegaly patients with peripheral muscle dysfunction.

6. Disclosures

There are no financial conflicts of interest related to the research reported in the manuscript.

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