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

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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 + $36.791 \times \text{sex}_{\text{male}=1} - 27.407 \times \text{status}_{\text{active}=1} - 0.690 \times$ 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 + $12.522 \times \text{sex}_{\text{male}=1} - 0.520 \times$ 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.
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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).

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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 ⩾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).

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