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Review Article

Body Composition, Sarcopenia, and Serum Myokines in Acromegaly: A Narrative Review

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Patients with active acromegaly have a higher percentage of lean body mass, a lower percentage of fat body mass, and an increase in their extracellular water compartment compared to healthy individuals. However, muscle function appears to be compromised in patients with acromegaly, with some experiencing worsened physical performance and sarcopenia. Myokine alterations, insulin resistance, dysregulation of protein metabolism, muscle oxidative stress, neuromuscular junction impairment, and increased ectopic intramuscular fat deposits may play roles in muscle dysfunction in patients with acromegaly.

Key Words: Acromegaly · Body composition · Myokines · Sarcopenia

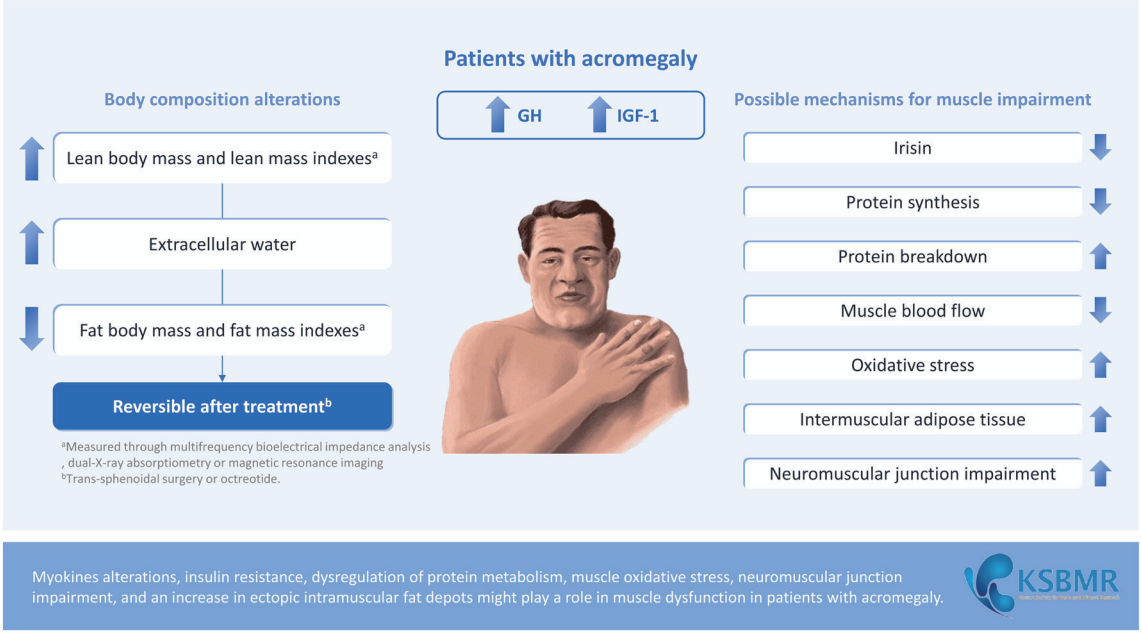
INTRODUCTION

Acromegaly is characterized by high serum levels of growth hormone (GH), which is usually secreted from a pituitary macroadenoma in an unregulated manner.[1,2] Despite being rare, acromegaly can lead to a reduction in life expectancy, which is mainly attributed to an increased risk of cardiovascular, respiratory, and cancer diseases.[2-4]

GH promotes tissue growth in a direct or indirect manner through the production of insulin-like growth factor 1 (IGF-1) from hepatocytes, bone cells, and muscle cells.[5] Typical facial changes are present in most patients, such as protrusion of the frontal bone, prominent cheeks and nose, thickened lips, prognathism, spaced teeth, and macroglossia.[6] When these typical clinical signs are present and serum IGF-1 is >1.3 times the upper limit of normal (ULN) for age, an acromegaly diagnosis can be made.[7] Biochemical control after surgical or pharmacologic treatment is better defined when IGF-1 levels are normalized for age.[7]

GH and IGF-1 are essential for linear growth and muscle mass gain, with skeletal muscle being the primary target of these hormones.[8] It is well established in the literature that GH promotes an increase in muscle mass and lipolysis (with a reduction in adipose tissue mass).[9] IGF-1 in turn, increases muscle strength by stimulating the proliferation, differentiation, and hypertrophy of muscle cells (myocytes).[10]

Graphical Abstract



Despite this, muscle function in patients with acromegaly appears to be compromised, with some patients experiencing worsening physical performance and myopathy, which is characterized by muscle weakness and pain, leading to sarcopenia.[11-15]

We performed a narrative review of the scientific evidence on muscular health in acromegaly, comprising sarcopenia, physical performance, and myokines.

LITERATURE SEARCH

The Cochrane and PubMed Library databases were used to select the articles for this review. The descriptors used were as follows: "acromegaly" AND ("sarcopenia" OR "body composition" OR "physical performance" OR "muscle mass" OR "skeletal muscle" OR "myokines") when advanced searches were performed. Only articles in English were included. A qualitative analysis was performed, selecting those articles with full allusion to the article theme with well-defined inclusion and exclusion criteria, clarity in methodology, and reproducibility. Initially, the articles were selected by two different authors using a double-blind system. In case of disagreement, a third-author analysis was carried out.

Articles that included analysis of a patient's body composition other than dual energy X-ray absorptiometry (DXA), multiscan computed tomography (CT), multifrequency bioelectrical impedance analysis (BIA), and magnetic resonance imaging (MRI) were excluded. Ultrasonography (US) may not be an accurate method to analyze muscle parameters, especially sarcopenia. Thus, articles involving US for compartment muscle analysis were also excluded. Articles on acromegaly, sarcopenia, and myokines pathophysiology were included in this review only for detailed purposes.

The flow diagram summarizes the literature search (Fig. 1).

RESULTS AND DISCUSSION

A total of 181 original studies were initially identified, of which 40 articles were selected after a qualitative analysis; however, 5 were excluded because of an outdated method of body composition analysis (measured through total body potassium or total body water). The remaining 35 articles were included in this review (Table 1). In general, the

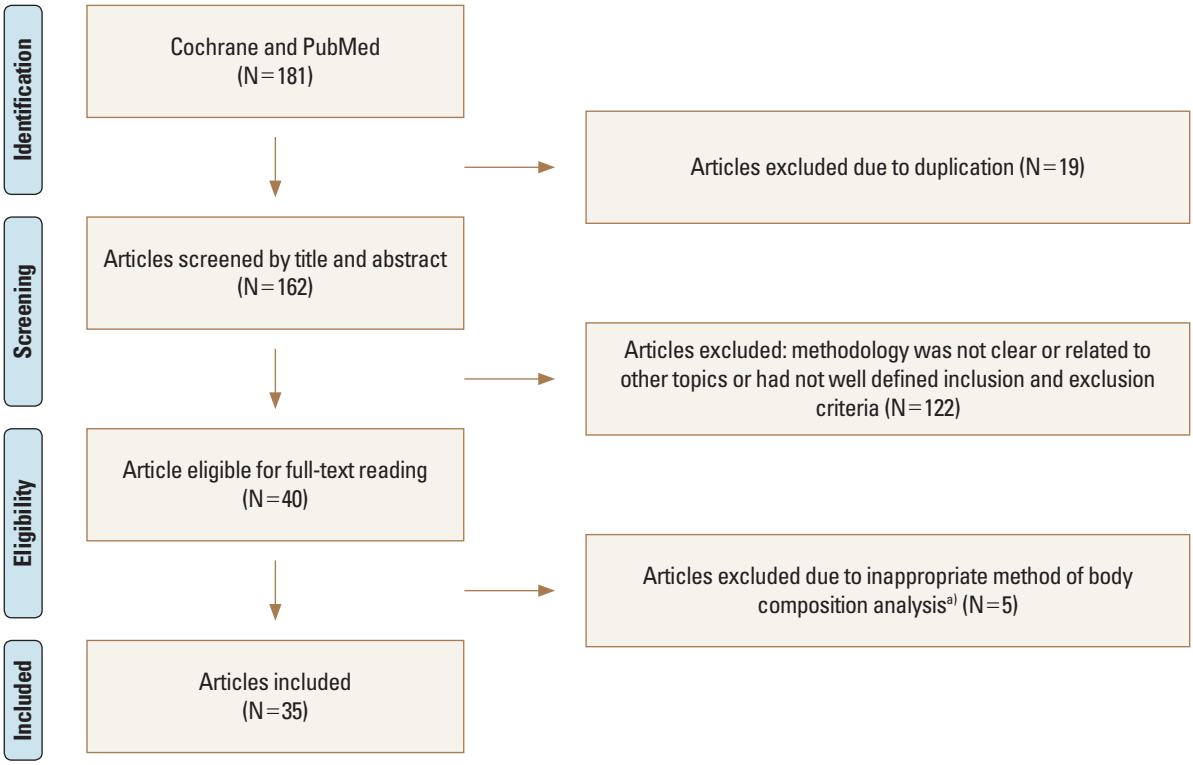


Fig. 1. Flow chart of literature search. [a]Ultrasonography, total body potassium, or total body water.

studies had small sample sizes. Among them, there was great heterogeneity in body composition analysis as follows: 11 studies used DXA,[16-26] 10 used BIA,[27-36] 1 used CT scan,[37] 4 used MRI [38-41] and 3 used two methods combined (MRI and BIA [42,43] or DXA and BIA [44]). Six studies did not undergo patient body composition analysis, but they brought information about sarcopenia, physical performance and myokines in acromegaly.[14,15,45-48]

In one systematic review regarding skeletal muscle health in acromegaly, the authors pointed out the same difficulties in relation to small sample sizes and different methods used in skeletal muscle evaluation in studies so far.[49] However, the authors did not include "physical performance," "sarcopenia," or "myokines" as descriptors in the literature search.[49] Thus, some important studies may have been missed.

1. Body composition in acromegaly

GH and IGF-1 are important hormones for muscle growth,[9] and serum levels of both hormones correlate with muscle mass.[9,50,51]

In a cross-sectional study involving more than 3,000 patients, Bian et al. [51] demonstrated a strong positive association between appendicular muscle mass (arms and legs combined lean mass), measured through BIA, and serum levels of GH and IGF-1 ($P<0.001$). Furthermore, the study showed that those hormones were lower in the group of sarcopenic patients (9.18±2.36 ng/mL for GH and 98.53±28.45 ng/mL for IGF-1, $P<0.001$, respectively) compared to the group without sarcopenia (12.20±3.93 ng/mL for GH and 136.41±48.95 ng/mL for IGF-1, $P<0.001$, respectively).[51] In another cross-sectional study involving 1,800 patients aged >50 years, there was also a positive and independent association between mean serum IGF-1 levels and lean mass.[50]

In one study, Sucunza et al. [16] found that males were more affected than females, using body composition (DXA) from 60 acromegalic patients (19 active, 41 controlled) and 105 controls, matched for age and gender.[16] Males had more total body mass ($P<0.001$) and lean body mass (LBM) ($P<0.001$) than females.[16]

Another study led by Reid et al. [17] showed that not only gender (r=23.45, $P<0.0001$), but age (r=0.124, $P=0.034$), and %ULN IGF-1 (r=0.037, $P<0.0001$) were independent significant predictors of lean mass. The %ULN

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Table 1. Summary of studies on body composition, sarcopenia, and myokines levels in patients with acromegaly

Study	Study design	Body composition	Population	Comments
Haliloglu et al. [14]	Cohort	None	25 patients with acromegaly (20 women and 5 men, and 13 healthy sedentary individuals)	Static and dynamic balance parameters are more affected in patients with acromegaly than healthy controls.
Gagliardi et al. [15]	Cross-sectional	None	42 patients with acromegaly (29 with active disease) and 42 age- and gender-matched control group	A negative correlation between age and the performance of instrumental and routine activities was found in patients with acromegaly.
Sucunza et al. [16]	Cross-sectional	DXA	60 patients with acromegaly (19 with active disease) and 105 age- and gender-matched controls	Male patients with acromegaly had higher LBM than controls. In female patients, no differences were observed in body composition compared to the control group.
Reid et al. [17]	Cross-sectional	DXA	138 adults with newly diagnosed and previously surgically treated acromegaly (77 with active disease)	Patients with active acromegaly have lower insulin sensitivity. This may be reversed with remission.
Hansen et al. [18]	Clinical trial	DXA	12 patients with active acromegaly	Short-term therapy with octreotide promoted a reduction in GH secretion, leading to a decrease in LBM.
O'Sullivan et al. [19]	Cross-sectional and prospective	DXA	20 patients with acromegaly and 20 healthy controls	In acromegaly, FMI is increased. The changes in body composition are reversible after treatment.
Wolf et al. [20]	Retrospective	DXA	201 patients with acromegaly	Reduction in IGF-1 was related to a decreased LBM.
Kaji et al. [21]	Cross-sectional	DXA	26 patients with active acromegaly and 26 healthy patients, similar in age, sex, race, and height	Patients with acromegaly had a higher percentage of LBM than healthy individuals.
Madeira et al. [22]	Cross-sectional	DXA	75 patients with acromegaly (22 males and 53 females), nearly half of the patients were hypogonadal	Patients with active acromegaly had a higher LBM in the trunk and android region than controls.
Eroğlu et al. [23]	Cross-sectional	DXA	33 patients with acromegaly (16 with active disease) and 19 healthy individuals	Patients with active acromegaly have a greater LBM than controlled acromegaly. No differences in skeletal muscle function between the groups.
Gibney et al. [24]	Cross-sectional and cohort	DXA	16 patients with acromegaly and 18 healthy controls. 10 patients with acromegaly were studied in long-term treatment (14 months)	Protein breakdown and synthesis are increased in patients with acromegaly. LBM was significantly correlated with leucine oxidation and incorporation.
Arlien-Søborg et al. [25]	Cohort	DXA	18 patients with acromegaly before and after treatment (8 after surgery and 10 after drug treatment)	In active acromegaly cases, the breakdown and synthesis of proteins are increased.
Mizera et al. [26]	Cross-sectional	DXA	43 patients with acromegaly (12 with active) and 60 age- and sex-matched healthy controls	Serum irisin levels were significantly lower in patients with acromegaly, whereas myostatin levels did not differ between the groups.
Coskun et al. [27]	Cross-sectional	BIA	45 patients with acromegaly and 45 healthy controls with similar age, gender, and body mass index	Patients with acromegaly have increased muscle thickness but decreased forearm muscles stiffness responsible for elbow flexion.
Tominaga et al. [28]	Cohort	BIA	8 patients with acromegaly	The total body water/body weight ratio decreased over the first 3 months after trans-sphenoidal surgery. The extracellular water/total body water ratio did not change within 6 months.
Guo et al. [29]	Cohort	BIA	36 patients with untreated acromegaly and 37 patients with nonfunctioning pituitary adenoma as control group	LBM decreased in the postoperative period in patients with acromegaly, especially after 1 year. Extracellular water increased during this period in the same group.
Hu et al. [30]	Cross-sectional	BIA	9 patients with acromegaly, 11 patients with GH deficiency, and 100 healthy controls	Patients with active acromegaly had a higher extracellular water/total body water ratio than control patients.
Guedes da Silva et al. [31]	Cross-sectional	BIA	26 patients with acromegaly (14 with active disease and 12 with controlled disease) and 12 healthy volunteers as control group	Compared with the control group, patients with acromegaly had greater FFM, lower peripheral muscle strength, and lower endurance, which were dependent on disease control status.

(*Continued to the next page*)

Table 1. Continued

Study	Study design	Body composition	Population	Comments
Lopes et al. [32]	Cross-sectional	BIA	22 patients with active acromegaly	Peripheral muscle fatigability, FFM, and expiratory muscle strength are the main factors determining the distance measured using the 6MWD test in patients with acromegaly.
Hatipoglu et al. [33]	Cross-sectional	BIA	30 patients with acromegaly (14 with controlled disease and 16 with active disease) and 30 age- and BMI-matched controls, mean age was 67.5±6.3 years	Acromegaly can impair cognitive functions, functional mobility, and instrumental activities of daily living in geriatric patients.
Zhang et al. [34]	Retrospective	BIA	20 patients with untreated acromegaly and 17 patients with nonfunctioning pituitary adenoma, as control group	The clinical duration of neuromuscular blockade and the intensity of the blockade duration were shorter in patients with acromegaly.
Sendur et al. [35]	Cross-sectional	BIA	46 patients with acromegaly (15 with active disease) and 81 age-, gender-, body mass index-, and body composition matched controls	Irisin levels were lower in patients with acromegaly than controls. Among patients with acromegaly, levels were similar among those with active or controlled disease.
Lima et al. [36]	Cohort	BIA	17 patients with acromegaly, with 14 women and 3 men (5 with active disease)	Rehabilitation programs showed initial improvements in fatigue, physical performance, balance, and acromegaly quality of live.
Brummer et al. [37]	Cohort	CT	15 patients with acromegaly, 8 males and 7 females	Reduced LBM in acromegalic patients who underwent transsphenoidal surgery, with changes in body composition being more significant in male than female patients.
Freda et al. [38]	Cross-sectional	MRI	24 patients with acromegaly, 15 males and 9 females, and 315 healthy individuals, aged 18–84 years, as a comparative group	GH and IGF-1 are associated with an increase in IMAT depots in patients with acromegaly.
Reyes-Vidal et al. [39]	Cohort	MRI	23 patients newly diagnosed with acromegaly and untreated	Acromegaly is characterized by a relocation of excess lipid to IMAT. After surgery, the pattern is partially reversed in male but not in female patients.
Bredella et al. [40]	Cohort	MRI	16 patients with active acromegaly (9 males and 7 females), and 20 healthy controls	After acromegaly control, insulin resistance improved, but there was a worsening of the anthropometric phenotype (increase in intrahepatic lipid, increase in abdominal fat and decrease in muscle mass).
Kuker et al. [41]	Cross-sectional and cohort	MRI	71 patients with acromegaly, with 45 males, aged ≥18 years	The reduction in insulin resistance after trans-sphenoidal surgery may be related to the re-expansion of subcutaneous adipose tissue.
Freda et al. [42]	Cross-sectional	MRI and BIA	27 patients with active acromegaly (17 males and 10 females) and predicted models developed in 315 healthy subjects	High agreement between the assessment of skeletal muscle mass by DXA and MRI.
Kuker et al. [43]	Cohort	MRI and BIA	21 patients with active acromegaly who were starting pegvisomant (GH receptor signal transduction blocker) therapy	The SMM did not change with long-term pegvisomant therapy.
Lopes et al. [44]	Cross-sectional	DXA and BIA	28 patients (13 with active disease), no control group	A positive correlation between BIA and DXA for muscle mass parameters.
Atmaca et al. [45]	Cohort	None	48 patients with active acromegaly and 41 age- and gender-matched controls	There is balance disturbance and increased fear of falling in patients with acromegaly compared with age- and gender-matched controls.
Lopes et al. [46]	Cross-sectional	None	28 patients with acromegaly (12 with active disease), 19 females and 9 males, >18 years old, same quantity of healthy volunteers	Patients with acromegaly had more displacement of the center of pressure in the anteroposterior and medial-lateral directions.
Thomas et al. [47]	Cohort	None	12 patients with active acromegaly and persistent fatigue, no control group	Impairment of function and physical capacity was consistent with the perception of increased fatigue among patients with acromegaly.
Miller et al. [48]	Cross-sectional	None	58 patients with acromegaly with a minimum diagnostic interval of 5 years (11 with active disease)	Musculoskeletal pain is a problem frequently found in patients with acromegaly and is associated with reduced quality of life.

DXA, dual energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; LBM, lean body mass; GH, growth hormone; FMI, fat mass index; IGF-1, insulin-like growth factor 1; FFM, fat-free mass; 6MWD, 6-min walk distance; IMAT, intermuscular adipose tissue; SMM, skeletal muscle mass.

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IGF1 and nadir GH after oral glucose tolerance test correlated with LBM in male (r=0.527, $P<0.0001$ for %ULN IGF-1 and r=0.527, $P<0.0001$ for nadir GH) and female (r=0.4038, $P=0.004$ for %ULN IGF-1 and r=0.3315, $P<0.0001$ for nadir GH).[17]

A more recent cross-sectional study compared body composition in 45 acromegalic patients with 45 healthy controls using BIA.[27] The height-adjusted appendicular skeletal muscle index (hSMI) was higher in the acromegalic group than in controls (median of 8.49 kg/m^2 vs. 7.48 kg/m^2 respectively, $P=0.004$).[27]

Thus, it seems reasonable to assume that patients with acromegaly, and high serum levels of both GH and IGF-1, tend to have a higher percentage of LBM than healthy individuals. Proper conclusions about the influence of age and gender on body composition in patients with acromegaly cannot be made, based on current data.

2. DXA, BIA, and MRI for body composition analysis

It appears that DXA, BIA, and MRI are equivalent as accurate methods for body composition analysis in acromegaly. In a study involving 27 patients, Freda et al. [42] showed greater LBM in those patients (65.91±15.2 kg) than in the control group (58.73±13.5 kg) ($P<0.0001$). Furthermore, the study pointed out a good positive correlation between DXA and MRI in determining LBM in acromegalic patients (r=0.97, $P<0.0001$).[42] A more recent cross-sectional study showed a strong positive correlation between BIA and DXA in measuring fat mass and lean mass parameters (fat-free mass [FFM] index, Baumgartner index and Foundation for the National Institutes of Health index) in patients with acromegaly (r=0.929, $P<0.001$),[44] although it did not demonstrate statistically significant differences between patients with and without disease control in terms of body composition.[44] There are no studies with proper comparison between multiscan CT with either DXA, BIA, or MRI in patients with acromegaly.

3. Body composition changes according to treatment and hormone control

Body composition changes may be reversible by acromegaly treatment with trans-sphenoidal surgery [28,29,37] or octreotide therapy.[18,19] Although, the same cannot be said about pegvisomant therapy.[43]

In a prospective study, 15 patients with acromegaly underwent multiscan CT to determine their body composition before treatment and 1 year after trans-sphenoidal adenectomy.[37] The muscle mass decreased by 7.4% ($P<0.01$) in males and 11.5% ($P<0.02$) in females after trans-sphenoidal surgery [37]; however, the analysis was spoiled because of the small sample size and lack of a control group.

Likewise, in a short crossover study on 12 patients,[18] DXA was employed to calculate the parameters of body composition.[18] In patients with acromegaly, there was a decrease in body weight (2.51±0.41 kg, $P<0.005$) and LBM (2.44±0.48 kg, $P<0.005$) after 4 weeks of octreotide treatment.[18] Of note, the placebo group received a saline infusion.[18]

In another study, 20 acromegalic patients were compared with 20 healthy controls.[19] The FFM was significantly greater (53.3±2.2 kg vs. 49.2±2.3 kg, $P=0.007$) in patients with acromegaly,[19] and after 12 weeks of treatment with octreotide, the mean FFM decreased by 3.3% ($P=0.004$).[19] Extracellular water in liters was measured before and during treatment in seven subjects and decreased by 7.6% after 12 weeks of treatment ($P=0.002$).[19]

These results showed that FFM is increased in acromegaly, which was reversed with treatment. Also, in both the cross-sectional and longitudinal studies, the increase in FFM in acromegaly was largely attributable to a corresponding increase in extracellular water, suggesting that GH excess also promotes extracellular fluid expansion.

Those findings were confirmed by Hu et al. [30]. He showed that patients with acromegaly had a lower percent body fat and higher percent total body water than normal subjects as a total (body fat/body weight, 11.0±1.3% vs. 17.1±0.4%, $P<0.005$; total body water/body weight, 65.2±1.0% vs. 60.7±0.3%, $P<0.005$). Patients with acromegaly were also associated with a higher percent of extracellular water.[30]

In another small study, the patients were analyzed before and at 2 weeks, 1 month, 3 months, and 6 months after trans-sphenoidal surgery.[28] Total body water decreased significantly 2 weeks after surgery ($P<0.02$) but with no change thereafter ($P<0.03$).[28] But the postoperative change in body composition in acromegaly ceased 3 months after surgery.[28]

On the other hand, another prospective study involving 36 patients with untreated acromegaly and 37 patients with nonfunctional pituitary adenomas was conducted to observe body composition changes through BIA at 3 months and 1 year after surgery.[29] Basal skeletal muscle mass (SMM) (36.23±7.40 kg vs. 30.79±5.33 kg, $P=0.001$) was significantly increased in patients with active acromegaly, as was extracellular water (13.24±2.68 kg vs. 11.19±1.86 kg, $P<0.001$).[29] But after trans-sphenoidal surgery, SMM decreased significantly at 1 year in both male ($P<0.001$) and female groups ($P<0.05$), and extracellular water showed trends of slight growth.[29]

Thus, it appears that an excess of GH and IGF-1 also promotes an increase in extracellular water, maybe transient. The body composition changes seem reversible after acromegaly treatment. But the same conclusions cannot be made after pegvisomant therapy, since there is only one study that evaluated body composition changes with this type of treatment. In this, SMM did not change with pegvisomant therapy, and at the last follow-up, SMM change was -1.6% of baseline in males and 0.03% in females.[43]

4. Active-vs-controlled disease

In a larger study on 200 patients, changes in body composition were compared according to active or controlled disease (A-C) and in another group of patients evaluated twice while the disease was controlled (C-C).[20] IGF-1 was again positively correlated with LBM (r = 0.383, $P<0.001$).[20] Reductions in serum IGF-1 levels were associated with decreases in lean mass in the A-C group, which was four and eight times more pronounced compared to the C-C group (-8±8% vs. -0.2±6%, $P<0.001$).[20]

In a Japanese cross-sectional study involving 26 active acromegaly patients and 26 controls, the active cases had a higher percentage of LBM (76±1.9%) than controls (70.8±7.6%, $P<0.05$).[21] Also, Madeira et al. [22] found that patients with active disease had higher LBM in the trunk (23,639±5,694 kg vs. 20,726±6,205 g, $P=0.033$) and android region (3,238±731 g vs. 3,664±827 g, $P=0.041$) than controls.

In a larger study of 138 patients, absolute LBM was higher in the active disease group overall (30.45±7.5 kg vs. 26.3±5.9 kg, $P=0.0029$), in male (72±9.1 kg vs. 65±7.9 kg, $P<0.001$) and female (48±7.1 kg vs. 43±6.8 kg, $P<0.05$), than in patients in disease remission.[17]

Finally, two more recent studies showed that patients with active acromegaly had higher hSMI, when compared with patients with controlled disease (median of 9.19 kg/m^2 vs. 7.97 kg/m^2 respectively, $P=0.017$) [24] as well as more absolute lean tissue (median of 65.7% vs. 59.3% respectively, $P=0.035$).[23]

Current data confirm what is logically expected: patients with active acromegaly have higher LBM and lean mass indexes (such as hSMI and FFMI) than patients with controlled disease.

5. Muscle thickness and stiffness

Coskun et al. [27] showed that patients with acromegaly had significantly higher thickness of both the biceps brachii ($P=0.034$) and brachioradialis muscle ($P=0.046$) than the control group, with lower stiffness of the biceps brachii ($P=0.001$) and brachioradialis muscle ($P=0.001$). However, the disease activity did not cause a significant difference in muscle thickness and stiffness in the acromegaly group.[19] Brachioradialis ($P<0.001$) and biceps brachii thickness ($P=0.049$) were positively correlated with hSMI, as measured by BIA.[27] Handgrip strength was also positively correlated with hSMI ($P<0.001$), brachioradialis thickness ($P<0.001$), and biceps brachii thickness ($P=0.005$).[27]

6. Physical performance in acromegaly

Muscle function and physical performance appear compromised in acromegaly,[11-15,31,32,45,46] but the available data remain controversial.[23,27,33]

One study compared 26 patients with acromegaly (14 with active disease and 12 with controlled disease) and 12 healthy controls in terms of peripheral muscle strength and body composition, using BIA.[31] Endurance test using electromyography was also performed.[31] Active disease patients had more FFM than control patients (median of 56.2 kg vs. 45.9 kg, respectively, $P=0.04$).[31] In the study, quadriceps strength was positively correlated with FFM (r=0.64, $P<0.001$) and negatively correlated with body fat (r=-0.40, $P=0.04$).[31]

In another study with the aim of evaluating the effect of body composition (through BIA), peripheral muscle function, and pulmonary function on the 6-min walk distance (6MWD) test in acromegaly, 22 patients had active disease.[32] There were significant correlations between the 6MWD test and the following body composition parame-

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ters: FFM (r=0.62, P=0.004), height^2/resistance index (r=0.52, P=0.017), and resistance (r=-0.50, P=0.025).[32] With respect to skeletal muscle performance, the fatigability of peripheral muscles, FFM, and expiratory muscle strength were the main determinants affecting the distance measured using the 6MWD test for patients with acromegaly (P<0.01 for all).[32] However, other potential performance-limiting factors, such as cardiac factors, were not analyzed.

Regarding elderly patients with acromegaly, Gagliardi et al. [15] tested physical performance and mobility skills using the Timed Up and Go test (TUG), Short Physical Performance Battery (SPPB), and handgrip test in a group of patients with a mean age of 73±6 years. Patients with active acromegaly obtained poorer results on the TUG (mean of 16±1.1 sec) and SPPB tests (mean score of 7±0.5) than controls (mean of 11±0.8 sec and mean score of 10±0.3, respectively, P<0,05).[15] Aging was negatively correlated with performance in instrumental and basic daily activities in acromegaly,[15] possibly because of the worse musculoskeletal system condition and the presence of other comorbidities. One limitation of this study was that comorbidities were more frequent in the acromegaly group than in the control group.

Alternatively, Hatipoglu et al. [33] compared 30 acromegalic patients (14 with controlled disease and 16 with uncontrolled disease) with 30 gender- and BMI-matched controls in terms of cognitive and functional assessment. Functional mobility was determined using TUG and muscle strength with the handgrip test.[33] The study found no differences in BIA results (P=0.5), handgrip strength (for right hand P=0.2 and for left hand P=0.3), TUG results (P=0.6), or the presence of sarcopenia (P=0.1) between the two groups.[33] In the study conducted by Coskun et al. [27] the hand grip strength was similar between the acromegaly and control group (P=0.594) and similar between active and controlled acromegaly (P=0.313). Similar results were found in the cross-sectional study led by Eroğlu et al. [23] which showed no statistically significant difference in handgrip strength, gait speed, or quadriceps muscle strength between the acromegaly and control groups.

Additionally, balance control can be affected by deformities and disabilities, such as enlarged feet, visual field defects, and arthropathy, apart from muscle dysfunction.[45] In a study, balance, functional capacity, and fear of falling were evaluated in 48 acromegalic patients with a median age of 48 (ages 25–75) and 41 age- and gender-matched controls with a median age of 50 (ages 25–67).[45] The Berg balance scale (for dynamic balance) and one-leg stance test (for static balance) were used along with the 50-m walking test to evaluate functional capacity, and the Falls Efficacy Scale-International (FES-I) was used to compare fear of falling between groups.[45] The 50-m walking time was significantly longer (median 40.5 sec in the acromegalic group vs. median 30 sec in the control group, P<0.001) and FES-I score was significantly higher (median of 22.5 in the acromegalic group vs. median of 16 in the control group, P<0.001) in patients with acromegaly.[45] In logistic regression analysis, none of the comorbidities (diabetes mellitus, hypertension, malignancy, anemia, hypopituitarism, and arthropathy) were found to affect balance, but there was no statistical difference between patients and controls in terms of dynamic balance (median of 54.5 vs. median of 56, P=0.008) or static balance (median of 30 vs. median of 30, P=0.204).[45] Both dynamic and static balance tests were negatively correlated with age, whereas the FES-I was positively correlated with age.[45]

Similarly, another study with 28 acromegalic patients (12 with active disease and 16 with controlled disease) and 28 healthy individuals showed that patients with acromegaly presented displacement of the center of pressure in the anterior–posterior direction and medial–lateral direction, which might explain some postural deviations found in the same study (P<0.01).[46] Haliloglu et al. [14] also found that patients with acromegaly had impairments in various static and dynamic balance parameters, especially in the posterior direction (P=0.02).

7. Impact of musculoskeletal function and quality of life in acromegaly

Musculoskeletal dysfunction can lead to decreased quality of life in acromegalic patients, especially when pain is present.[52] A cross-sectional study conducted by Miller et al. [48] applied questionnaires to 58 patients with acromegaly (47 with controlled disease and 11 with active disease) to determine how the quality of life is affected by the disease. The Acromegaly Quality of Life Questionnaire (AcroQoL) global score was lower in patients with pain (mean 59.1±16) than without (mean 75.8±13.2) (P=0.018).[52] However, almost all cases of disability were due to arthrop-

athy.[52] Notably, the quality of life of acromegalic patients can be improved with rehabilitation programs, as shown in the study by Lima et al. [36]. After therapist-oriented home rehabilitation, improvements in general fatigue, quadriceps muscle strength, lower extremity functional scale, 6MWD test, balance control, and all AcroQoL dimensions were observed (all $P<0.05$).[53] However, after 1 month of washout, these gains were lost for all parameters, except the lower extremity functional scale and balance control.[53]

8. Possible mechanisms for impaired muscle function in acromegalic patients

Figure 2 illustrates muscle health in acromegaly, the main factors and how they might influence muscle function in patients with acromegaly.

1) Myokines alterations in acromegaly

Myokines are peptides that regulate multiple physiological processes, especially muscle growth and energy metabolism.[52] They are produced by the skeletal muscle and contribute to the maintenance of muscle homeostasis.[52]

Irisin was the first described myokine [53] and was found to increase muscle insulin sensitivity and promote β-cell proliferation, contributing to better muscle performance.[54,55] On the other hand, myostatin is a potent negative regulator of muscle growth through inhibition of myocytes' hyperplasia and hypertrophy.[56] Myostatin also antagonizes insulin action [57] and inhibits irisin secretion.[58] Most acromegalic patients are insulin resistant; therefore, the study of myokine profiles in those patients appears to be important. Mizera et al. [26] showed that irisin concentration was significantly lower in patients with acromegaly (N=43) compared to controls (N=60) (3.91 vs. 5.09 mg/mL, $P=0.006$), with no correlations between irisin and GH/IGF-1 levels.[26] Irisin and myostatin concentrations were also lower in patients with insulin resistance (2.80 vs. 4.18 mg/mL, $P=0.047$; 81.46 vs. 429.58 ng/L, $P=0.018$).[26] There were no differences between the study group and controls in myostatin concentration.[26]

In another study, irisin levels were lower in patients with acromegaly than in controls (median interquartile range [IQR], 44.8 [41.7–46.7] ng/mL vs. 51.7 [45.5–60.1] ng/mL, $P\leq0.001$, respectively).[35] Active and controlled patients had similar irisin levels.[35] In addition, serum irisin levels were not correlated with GH or IGF-1.[35] In fact, when a multiple linear regression model was applied, somatostatin receptor ligand use (β=-20.30; 95% CI, [-34]–[-6], $P=0.006$) was the only independent factor that affected

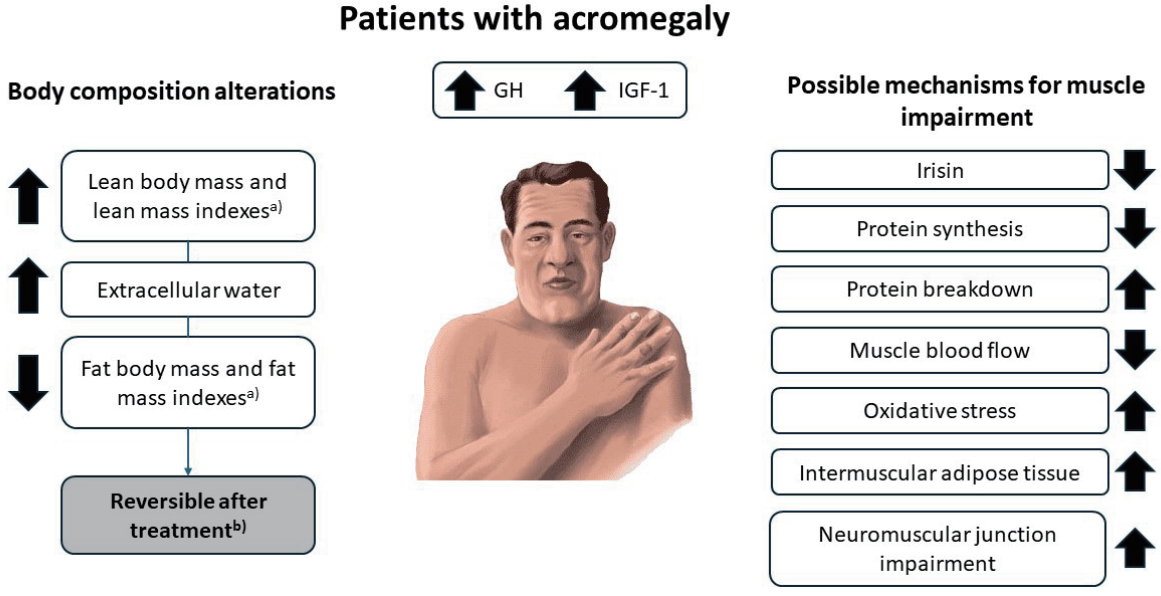

Fig. 2. Body composition alterations and possible mechanisms for muscle impairment in patients with acromegaly. [a]Measured through multifrequency bioelectrical impedance analysis, dual energy X-ray absorptiometry or magnetic resonance imaging. [b]Trans-sphenoidal surgery or octreotide. GH, growth hormone; IGF-1, insulin-like growth factor 1.

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serum irisin.[35]

Taken together, these data suggest that irisin production and action may be impaired in acromegalic patients, thus contributing to decreased muscle performance.

2) Protein metabolism dysregulation

To determine whether there were alterations in protein metabolism in acromegalic patients (rather than only extracellular water expansion [19,30]), Gibney et al. [24] reported protein turnover (leucine incorporation and oxidation) in 16 patients with acromegaly and 18 controls. They showed that LBM was significantly correlated with leucine incorporation (R^2=0.62, P<0.001) and leucine oxidation (R^2=0.37, P<0.001) in healthy and patients with acromegaly.[24] Despite greater leucine incorporation in patients with acromegaly than in controls, differences after adjusting for LBM did not reach statistical significance.[24] Leucine oxidation was not different between the two groups, either unadjusted or adjusted, for LBM or body cell mass.[24] DXA scanning revealed a significant reduction in LBM in patients with acromegaly (61.3 [40.9–76.3] vs. 58.7 kg [39.8–71.5], P<0.05) after long-term treatment.[24]

In another study, protein alterations were evaluated using isotopic tracers.[40] Data from patients were analyzed before and 47±10 weeks after disease control by transsphenoidal surgery (N=8) and/or medical treatment (N=10).[25] Whole-body phenylalanine breakdown decreased after disease control (P=0.005), accompanied by a decrease in the degradation of phenylalanine to tyrosine (P=0.005) and whole-body phenylalanine synthesis (P=0.030).[25] Skeletal muscle protein synthesis tended to decrease after disease control (P=0.122), whereas muscle protein breakdown (P=0.437) and muscle protein loss were unaltered (P=0.371).[25] Thus, active acromegaly was associated with not only increased LBM but also with increased protein breakdown and synthesis, which might indicate a steady-state condition.[25]

The imbalance between protein synthesis and degradation could explain some physical impairment in acromegaly, despite the increase in total LBM.

3) Impaired oxidative muscle metabolism

Some studies have evaluated whether aerobic performance is modified by uncontrolled or active acromegaly. Thomas et al. [47] conducted a study on 12 patients with active disease and persistent fatigue. In the study, parameters of physical function were compared with healthy adults before, after 3, and 6 months of treatment with octreotide.[47] The measured ventilation threshold (VeT; a measure of work rate when breathlessness develops) (13.1±2.9) was significantly (P<0.05) less than that predicted for healthy sedentary adults of the same age, gender, and height (15.9±3.0).[47] After 3 months of octreotide therapy, changes in serum IGF-I were related to changes in VeT (r=0.66, P<0.05) and subjective report of vigor (r=0.85, P<0.05).[47] Changes in fatigue from baseline to 6 months were moderately related to changes in IGF-I levels (r=0.67, P<0.05).[47] The increase in vigor score was paralleled with a significant decrease in fatigue after 3 and 6 months of treatment (P<0.05).[47]

These results suggest that the ability of muscles to use oxygen may be altered in patients with acromegaly. Despite the normal sympathetic nerve activity observed in those patients,[59] there might be some alterations in blood flow and muscle metabolism that can justify these findings. However, in the study, other impaired acromegaly functions, such as cardiac function, were not assessed.

4) Fat mass ectopic deposition and insulin resistance

Insulin resistance is associated with ectopic lipid deposition in the liver and skeletal muscle [60]; however, data on acromegaly are still controversial.

Freda et al. [38] compared 24 acromegalic patients with predicted models developed in 315 healthy subjects and showed that intermuscular adipose tissue (IMAT) was greater (P<0.0052) by 185.6±84% than predicted, which suggests that increased adipose tissue in muscle could be associated with GH-induced insulin resistance and impaired muscle function.[38] Another study enrolled 23 patients with newly diagnosed untreated acromegaly to access body composition changes and adipose tissue redistribution before and up to 2 years after pituitary surgery.[39] IMAT was above predicted values preoperatively in male (average, 147% above) and female (average, 34% above).[39] However, the changes in IMAT after surgery were not correlated with insulin resistance scores in male or female patients.[39] Alternatively, in the study by Bredella et al. [40], there were no differences in intramyocellular lipids in the soleus muscle before (median of 8.2 [IQR,

3.9–11.2]) and after (median of 8.3 [IQR, 6.4–11.6]) acromegaly treatment ($P=0.9$). A more recent study showed that IMAT did not predict insulin resistance in 71 active acromegalic patients.[41] In a longitudinal analysis involving 28 patients with acromegaly in the same study, IMAT did not change, and SMM was lower in male patients after surgery ($P<0.001$).[41]

Acromegaly insulin resistance might not be linked to IMAT depots in patients with acromegaly but could influence physical performance, directly (disturbing muscle contraction) or indirectly (inflammation). More data are needed on this matter.

5) Neuromuscular junction impairment

One study evaluated the clinical and deep neuromuscular blockade durations in patients with acromegaly using rocuronium as a neuromuscular blockade agent.[34] In this study, neuromuscular blockade was evaluated using the train-of-four technique (four consecutive ulnar nerve stimuli).[34] The train-of-four ratio was defined as the amplitude of the fourth response to stimuli divided by the amplitude of the first response. Each time the first response to (T1) recovered to 25%, rocuronium was administered. Deep blockade duration was defined as the recovery time from the train-of-four ratio of zero to the value at T1 after the first dose of rocuronium, and clinical blockade duration was defined as the time when T1 recovered to 25% of its control value.[34] Both clinical and deep blockade decreased in a linear manner in patients with acromegaly (21.99±5.67 vs. 34.96±11.04 min for clinical blockade and 33.26±8.09 vs. 46.21±10.89 min for deep blockade, $P<0.001$).[34] The onset time of rocuronium was also prolonged (110.25±54.90 sec in patients with acromegaly vs. 75.00±27.56 sec in controls, $P=0.01$), indicating insufficient neuromuscular blockade.[34]

More studies are needed to draw a conclusion on the matter of neuromuscular junction's impairments in patients with acromegaly. The duration delay identified in neuromuscular blockade might justify some muscle impairment in patients with the disease.

CONCLUSIONS

There are only a few studies that point out the relationship between acromegaly and muscular health, and most of them have a cross-sectional design, which limits the conclusions. Also, the rarity of acromegaly, small study sample sizes, the heterogeneity of methods used to assess muscle function and physical performance, and the high prevalence of cofounding factors contributes to bring more questions than answers.

It appears that despite increased muscle mass in patients with acromegaly, there might be some decreased muscle function and poorer physical performance, especially in patients with active disease. However, sarcopenia as a condition was not properly assessed in the majority of the studies, which limits generalization. Data also suggests that age and gender might have some influence on muscle performance in patients with active acromegaly. Finally, the disease deformities could have influenced some results obtained in the studies described, especially when considering balance control.

It is difficult to define the impact of muscle impairment on quality of life in patients with acromegaly because there are a lot of confounding factors, which were not analyzed in those studies. As an example, pain was the main subject described by patients, and the studies did not distinguish between muscle pain or arthropathy.

The mechanisms of muscle impairment may involve insulin resistance, dysregulation of protein metabolism, muscle oxidative stress, neuromuscular junction impairment, ectopic intramuscular fat depots, and irisin depletion.

Our narrative review has some strengths because this is the first review to investigate the relationship between sarcopenia and acromegaly and between myokines and acromegaly. We also included studies that could help elucidate the mechanisms contributing to muscle function impairment in patients with acromegaly. As limitations, we highlight the lack of a systematic review design or meta-analysis which would be very difficult due to the high heterogeneity between studies and the small number of patients in each of them.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. List of abbreviations

Abbreviation	Definition
ULN	upper limit of normal
6MWD	6-min walk distance
AcroQoL	Acromegaly Quality of Life Questionnaire
BIA	bioelectrical impedance analysis
CT	computed tomography
DXA	dual energy X-ray absorptiometry
FES-I	Falls Efficacy Scale-International
FFM	fat-free mass
GH	growth hormone
hSMI	height-adjusted appendicular skeletal muscle index
IGF-1	insulin-like growth factor 1
IMAT	intermuscular adipose tissue
LBM	lean body mass
MRI	magnetic resonance imaging
SMM	skeletal muscle mass
SPPB	Short Physical Performance Battery
TUG	Timed Up and Go test
US	ultrasonography
VeT	ventilation threshold

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