

Functional evaluation of the joints in acromegalic patients and associated factors

Leandro Lemgruber Kropf · Miguel Madeira ·
Leonardo Vieira Neto · Mônica Roberto Gadelha ·
Maria Lucia Fleiuss de Farias

Received: 12 October 2012 / Revised: 3 February 2013 / Accepted: 21 February 2013 / Published online: 13 March 2013
© Clinical Rheumatology 2013

Abstract This study aims to evaluate the presence of arthropathy in the large peripheral joints most commonly affected in acromegaly and to classify the severity according to the functional assessment of each joint to identify any factor that could predict the development of arthropathy and its level of severity. Seventy-one acromegalic patients were interviewed and underwent a physical examination of the knees, hips, and shoulders to identify the presence of arthropathy. The disease was functionally classified as more severe or less severe, according to a specific functional scale. We studied 21 males (29.5 %) and 50 females (70.5 %) with a mean age of 49.5 ± 14.5 years. Arthropathy in the studied joints was observed in 40 patients (prevalence of 56 %), and a statistically significant association with the presence of arthropathy was observed for three of the evaluated factors: increased body mass index (BMI), older age at diagnosis of acromegaly, and female gender. There was no association with disease control or other factors related to acromegaly. We classified 19 patients as having more functionally severe arthropathy and identified two factors associated with its development: increased BMI

and lower levels of insulin-like growth factor type I. The relationship of factors such as female sex and BMI, which are also related to osteoarthritis, with arthropathy in acromegalic patients suggested a high prevalence of irreversible joint disease present at diagnosis of acromegaly. We highlight the BMI, which was associated with either the presence of arthropathy or more severe arthropathy, which demonstrates the importance of body weight control in the management of acromegalic patients.

Keywords Acromegaly complications · Body mass index · Joint diseases · Osteoarthritis

Introduction

Acromegaly is a rare chronic disease with an estimated prevalence of 40 to 70 cases per million people, and it was first described more than 120 years ago. It is characterized by an insidious onset and exaggerated somatic growth due to the hypersecretion of growth hormone (GH) and insulin-like growth factor type I (IGF-I). The cause is usually a pituitary tumor [1, 2].

Arthropathy is one of the most frequent complications of acromegaly [3] and is considered the most important cause of morbidity and functional disability [4, 5]. Both weight-bearing and non-weight-bearing joints are affected [6], and large peripheral joints, such as the knees, hips, and shoulders, are most commonly affected, with a prevalence at diagnosis of up to 70 % [4, 7]. In a significant number of patients, joint complaints may present as the earliest symptom [8], and its intensity increases with the duration of uncontrolled disease [9]. Arthropathy can result in a severely disabling pathology [4, 10–12], which causes a considerably impaired quality of

L. L. Kropf (✉) · M. Madeira · L. V. Neto · M. Roberto Gadelha ·
M. L. F. de Farias
Division of Endocrinology, Department of Internal Medicine,
Hospital Universitário Clementino Fraga Filho/Universidade
Federal do Rio de Janeiro, R Marechal Ramon Castilla 265/105,
22290-175 Rio de Janeiro, RJ, Brazil
e-mail: leandrokropf@hotmail.com

L. L. Kropf
Instituto Nacional de Traumatologia e Ortopedia (INTO),
Rio de Janeiro, Brazil

L. V. Neto
Hospital Federal da Lagoa, Rio de Janeiro, Brazil

life despite successful long-term treatment of acromegaly [13, 14].

The pathogenesis of arthropathy in acromegaly is biphasic in nature, involving two mechanisms [3]. Initially, high levels of GH and IGF-I promote the growth of articular cartilage and periarticular ligaments. Consequently, there is a thickening of cartilage leading to joint space congestion and limited range of motion. Simultaneously, there is a laxity of the joint due to ligament overgrowth. These changes occur very early in the disease and can be fully reversed [3, 15].

At a later stage, the altered joint geometry results in repeated intra-articular trauma that will lead to reactions of repair. Consequently, scar, cyst, and osteophyte formation causes a greater distortion of joint geometry. At this point, the manifestations are characteristic of osteoarthritis, a degenerative joint disease. These changes are irreversible, and biochemical control of acromegaly, as evidenced by normal levels of IGF-I, will have limited efficacy in improving the patient's condition [3, 10].

Several personal and disease-specific parameters have been investigated in the search for a correlation with prognosis and development of arthropathy, but it has been difficult to find a significant influence of any characteristic [4, 14, 16, 17].

In this study, we evaluated the presence of arthropathy in the large peripheral joints most commonly affected in acromegaly (knees, hips, and shoulders). We also classified the affected patients according to the functional assessment of each joint and divided them into two groups: more severe arthropathy or less severe arthropathy. These data were then correlated with comorbidities, personal characteristics, and disease-specific parameters that could predict the development of arthropathy and greater or lesser severity.

Patients and methods

Patients

Seventy-one patients with acromegaly, regularly seen at the Clementino Fraga Filho University Hospital, were consecutively enrolled in this study. The diagnosis of acromegaly had been suspected by clinical features and confirmed by high serum GH levels not suppressible below 1.0 ng/mL after oral glucose tolerance test, as well as IGF-I levels above the upper limit of the normal range [18].

There were no inclusion restrictions in terms of gender, age, comorbidities, stage of disease, and current or previous treatments. According to their GH and IGF-I serum levels, patients were separated into the “active” and “controlled” subgroups. In the “controlled” group, IGF-I was within the specific age-adjusted reference range, and GH levels were

below 1.0 ng/mL, which is actually considered the upper limit for the adequate control of acromegaly [19].

The protocol was approved by the Ethical Committee of Clementino Fraga Filho University Hospital, and all patients gave their witnessed informed consent before entering the study. The study was designed according to the Helsinki Declaration II.

Study protocol

The presence of arthropathy was defined as self-reported joint complaints in at least one of the six joints evaluated, confirmed by physical examination. All patients were interviewed and underwent a physical examination of the studied joints, which was always performed by the same musculoskeletal specialist.

If any previous condition not associated with acromegaly could justify the presence of complaints on site, the affected joint (not the patient) was excluded. One patient had previously undergone amputation at the level of the left femur and did not walk, which hindered a proper assessment of these joints, and his knee and both hips were therefore excluded from this study. Another patient's joint was excluded owing to a total knee arthroplasty. Two shoulders were also excluded from the study due to the presence of a painful lipoma (factor unrelated to acromegaly) and another because of neurological pain. In total, we evaluated 140 hips, 139 knees, and 140 shoulders from a total of 71 patients.

All joints studied were classified as having an excellent, good, fair, and poor articular status, according to a specific scale for each joint. The functional scales used were the Merle d'Aubigné and Postel modified by Charnley for the hips [20, 21], Knee Society Score for the knees [22, 23], and the UCLA shoulder rating scale for the shoulders [24, 25].

Patients were considered to have functionally more severe joint disease if at least one of the six joints assessed was rated as “fair” or “poor” according to their specific functional scale. A patient was considered to have functionally less severe joint disease if all of his or her joints were classified as “excellent” or “good” according to their specific scale.

Body mass index (BMI) was estimated by the ratio of weight (in kilograms)/height² (in meters) and expressed as kilograms per square meter.

Body composition was evaluated by dual-energy X-ray absorptiometry using a Prodigy-GE densitometer. Lean body mass (grams) and fat mass (percentage) were assessed at the following regions: arms, legs, trunk, android, gynoid, and total body.

Biochemical parameters

The serum concentrations of GH and IGF-I were routinely measured by commercial two-site chemiluminescence

immunometric assays (Immulite, Diagnostic Product Corporation, Los Angeles, CA) at the time of the physical examination. The growth hormone detection limit of the assay was 0.01 $\mu\text{g/L}$ (0.026 mU/L). The inter- and intra-assay coefficients of variation (CV) were 6.2 and 6.5 %, respectively.

The low detection limit of IGF-I as measured by Immulite was 20 ng/mL, and the intra- and inter-assay CVs were 3.6 and 6.6 %, respectively. This assay uses murine monoclonal anti-IGF-I antibodies. IGF binding protein (IGFBP) interference was prevented by acid ethanol extraction of IGFBPs.

The International Reference Preparation was 98/574 for GH and 87/518 for IGF-I.

The scores of IGF-I used in the statistical analysis (expressed as standard deviation (SD) for each age) were calculated according to Elmlinger et al [26].

Statistical analysis

Data were statistically analyzed using the SPSS software for Windows, version 16.0 (SPSS, Inc., Chicago, IL, USA). The results are expressed as the mean $\pm$ SD or median (minimum–maximum). The nonparametric Mann–Whitney test was used for comparison of numerical variables, and the nonparametric tests of chi-square or Fisher were used to compare categorical variables between groups. A *p* value of less than 0.05 was considered statistically significant.

Results

The study population comprised 50 women (22–80 years) and 21 men (26–69 years), with a mean age of 49.5 ± 14.5 years. The age at diagnosis (mean 44.2 ± 14.8 years) was assessed by chart review, and the duration of disease until diagnosis (mean 7.8 years) was estimated with the patient's reported time of onset of acral enlargement and the patient's photographs over the previous decades.

The general characteristics of the individuals and disease, biochemical data, and endocrine comorbidities are summarized in Table 1. None of the patients had growth hormone deficiency.

Arthropathy

Forty out of the 71 patients (56 %) reported pain in at least one of the six joints assessed and were classified as having arthropathy, and 31 (44 %) had no pain complaints.

The presence or absence of joint disease was compared with epidemiological, biochemical, and disease data, and a statistically significant difference between the two groups was noted in three of the evaluated variables: BMI, age at diagnosis of acromegaly, and gender.

Table 1 General characteristics of the 71 acromegalic patients

Epidemiological data	
Current age (years)	49.5 ± 14.5 47 (22 to 80)
Gender (n/%)	
Male	21 (29.5 %)
Female	50 (70.5 %)
Body mass index (kg/m^2)	29.7 ± 4.2 29.2 (18.5 to 38.5)
Fat mass (%)	35.5 ± 10.3 34.9 (8 to 53)
Lean mass (kg)	49.5 ± 10.6 47.5 (32.9 to 73.8)
Disease data	
Age at diagnosis (years)	44.2 ± 14.8 43 (20 to 74)
Estimated age of acromegaly onset (years)	36.3 ± 14 35 (11 to 71)
Estimated period without treatment (years)	7.8 ± 7.8 5 (0 to 47)
Controlled disease/active disease (n/%)	9 (13 %)/62 (87 %)
Tumor size (micro/macroadenoma)	14/57
Patients submitted to surgery	47
Patients submitted to radiotherapy	16
Biochemical data	
GH (ng/mL)	11.2 ± 28.6 3.3 (0.1 to 209)
IGF-I	2.86 ± 2.81 3.06 (−2.38 to 7.91)
Endocrine comorbidities	
Hypogonadism (n/%)	31 (43 %)
Hypothyroidism on hormone replacement (n/%)	12 (17 %)
Hypocortisolism on hormone replacement (n/%)	18 (25 %)

Data expressed as mean $\pm$ standard deviation (SD) and median (minimum–maximum)

GH growth hormone, IGF-I insulin-like growth factor type I, kg kilogram

Patients with arthropathy had a higher BMI and older age at diagnosis of acromegaly than patients without joint complaints. Female gender was also positively associated with the presence of joint complaints (Table 2).

No associations were observed between the presence of arthropathy and serum levels of GH, current IGF-I, IGF-I at the time of diagnosis, current age, period without treatment, disease control, fat mass, and lean mass (Table 2).

We searched for associations in the groups of patients with GH <1.0 ng/mL, IGF-I levels below the upper limit of the normal range, and diagnoses received up to 30 years of age. We also tested the patients with a short interval between

Table 2 Associations between epidemiological, biochemical, and acromegalic disease data with the presence or absence of arthropathy

	Presence of arthropathy N=40 (56 %)	Absence of arthropathy N=31 (44 %)	p value
Epidemiological data			
Current age (years)	51.6±14.9 49.5 (22 to 78)	46.7±13.6 45 (25 to 80)	0.167
Female gender (n/%)	32 (64 %)	18 (36 %)	0.045
Body mass index (kg/m ²)	30.7±4.7 30.5 (18.5 to 38.5)	28.3±3.1 28.8 (20.5 to 34.7)	0.016
Fat mass (%)	37±10.1 36.7 (8 to 52)	33.6±10.3 33.4 (17 to 53)	0.574
Lean mass (kg)	48.1±9.8 47 (32.9 to 72.9)	51.3±11.5 48.2 (33.5 to 73.8)	0.295
Disease data			
Age at diagnosis (years)	47.2±15 45 (20 to 74)	40.3±13.8 36 (23 to 72)	0.044
Estimated age of acromegaly onset (years)	38.9±15.5 37 (11 to 71)	33.1±11.2 31 (15 to 56)	0.149
Estimated period without treatment (years)	8.3±7.1 6.5 (0 to 28)	7.1±8.8 5 (1 to 47)	0.175
Active disease (n/%)	35 (56 %)	27 (44 %)	0.616
Biochemical data			
GH (ng/mL)	9.4±19.8 2.8 (0.2 to 109)	13.5±37 5 (0.1 to 209)	0.369
Current IGF-I	2.7±2.6 3.1 (−2.3 to 7.4)	3±2.9 3 (−1.4 to 7.9)	0.651
IGF-I at diagnosis	5.8±1.3 5.9 (3 to 8.3)	5.6±0.85 5.8 (3.9 to 6.8)	0.655

Data expressed as mean±standard deviation (SD) and median (minimum–maximum)

GH growth hormone, IGF-I insulin-like growth factor type I, kg kilogram

the onset of symptoms and diagnosis of acromegaly (up to 2, 3, and 5 years). None of these groups presented a statistically significant association with the presence or absence of arthropathy.

The most affected joints were the knee (56 knees in 33 patients), shoulder (42 shoulders in 25 patients), and hip (14 hips in 9 patients). Therefore, the prevalence of joint disease in the acromegalic patients was 46 % in the knees, 35 % in the shoulders, and 13 % in the hips.

Severity of arthropathy

The 40 patients with joint complaints were classified according to the degree of joint involvement. Twenty-one patients (52.5 %) were classified as having functionally less severe arthropathy and 19 (47.5 %) as having functionally more severe arthropathy.

The severity of joint disease was compared with epidemiological, biochemical, and disease data, and a statistically significant difference between the two groups was found in two of the evaluated variables: BMI and current IGF-I.

Patients with functionally more severe arthropathy had a higher BMI than those with less severe arthropathy. Current IGF-I, however, was higher in patients with less severe joint disease than in the other group (Table 3).

No association was observed between the severity of joint disease and serum levels of GH, IGF-I at the time of diagnosis, gender, current age, age at diagnosis, period without treatment, disease control, fat mass, and lean mass (Table 3).

We searched for associations in the groups of patients with GH <1.0 ng/mL, IGF-I levels under the upper limit of the normal range, and those with diagnoses received up to 30 years of age. We also tested the patients with a short interval between the onset of symptoms and diagnosis of acromegaly (up to 2, 3, and 5 years). None of these groups presented a statistically significant association with more severe or less severe arthropathy.

Body mass index

Due to the expected greater influence of body weight excess in weight-bearing joints (hip and knee) than in non-weight-bearing joints (shoulder), we tested the influence of body mass index for each of the three joints analyzed. A statistically significant higher BMI was observed in patients with knee and hip joint disease compared with patients without pain complaints in these joints. This association was not found in patients with shoulder joint disease (Table 4).

Table 3 Associations between epidemiological, biochemical, and acromegalic disease data with the functionally more severe or less severe arthropathy

	More severe arthropathy (N=19)	Less severe arthropathy (N=21)	p value
Epidemiological data			
Current age (years)	53±15 53 (22 to 76)	50.2±15.1 45 (29 to 78)	0.390
Female gender (n/%)	14 (44 %)	18 (56 %)	0.442
Body mass index (kg/m ²)	32.1±4.3 33 (18.5 to 38.5)	29.4±4.8 28.4 (20.9 to 38.5)	0.036
Fat mass (%)	38.9±8.9 40.2 (21 to 52)	35.2±11.1 35.5 (8 to 50)	0.317
Lean mass (kg)	49.1±10.8 48.4 (36.5 to 72.9)	47.2±9 46.1 (32.9 to 64.7)	0.667
Disease data			
Age at diagnosis (years)	49.4±15.5 50 (20 to 74)	45.2±14.5 41 (26 to 74)	0.320
Estimated age of acromegaly onset (years)	41.4±15.1 38 (18 to 71)	36.6±15.9 37 (11 to 70)	0.361
Estimated period without treatment (years)	8±7.2 6 (0 to 27)	8.6±7.2 7 (2 to 28)	0.708
Active disease (n/%)	15 (43 %)	20 (57 %)	0.172
Biochemical data			
GH (ng/mL)	11.7±26.8 1.6 (0.3 to 109)	7.3±9.6 4 (0.2 to 38.2)	0.134
Current IGF-I	1.58±2.44 1.84 (−1.87 to 6.26)	3.75±2.52 4.3 (−2.38 to 7.43)	0.009
IGF-I at diagnosis	5.51±1.14 5.86 (3 to 6.6)	6.09±1.49 6.6 (4.05 to 8.34)	0.300

Data expressed as mean±standard deviation (SD) and median (minimum–maximum)

GH growth hormone, IGF-I insulin-like growth factor type I, kg kilogram

Discussion

Considering the self-reported joint complaints, confirmed by physical examination, to be an accurate diagnosis of arthropathy, we found that 56 % of patients surveyed reported pain in at least one of the six joints tested, which reflects a very high prevalence of arthropathy. In comparison with other studies in the literature, our group evaluated one of the greatest numbers

Table 4 Association between body mass index (BMI) and the presence of arthropathy in each joint

	Presence of arthropathy	Absence of arthropathy	p value
Knee	N=33	N=38	
BMI (kg/m ²)	31.5±4.6 31.2 (18.5–38.5)	28.1±3.1 28 (20.5–34.7)	<0.001
Hip	N=9	N=62	
BMI (kg/m ²)	32.9±4.1 34.2 (24.9–38.5)	29.2±4.1 29 (18.5–38.5)	0.013
Shoulder	N=25	N=46	
BMI (kg/m ²)	30.5±4.9 30.6 (18.5–38.5)	29.2±3.8 29 (20.5–38.5)	0.245

Data expressed as mean±standard deviation (SD) and median (minimum–maximum)

of acromegalic patients, all from the same center, in relation to their arthropathy features.

The only factors associated with the presence of arthropathy in the three assessed joints were older age at diagnosis of acromegaly, female gender, and increased BMI.

Age is considered the main risk factor for the development of osteoarthritis, which affects up to 30 % of people over 60 years of age [27]. In our study, however, arthropathy was not associated with current age and only with older age at diagnosis of acromegaly. Similarly, Biermasz et al reported a positive correlation between older age at diagnosis with osteoarthritis in acromegalic patients [28].

Female gender was also associated with a higher prevalence of arthropathy in the evaluated acromegalic patients, as previously reported by Biermasz et al [14]. However, even in individuals without acromegaly, a greater number of joints affected by osteoarthritis is usually reported in females, especially after 55 years of age when the postmenopausal estrogen deficiency increases the risk for the development of osteoarthritis [29, 30]. This finding may be related to our results.

Higher BMI identifies overweight or obesity in the general population. Although the pathogenesis of osteoarthritis is multifactorial, obesity is strongly associated with osteoarthritis of the knee and hip (weight-bearing joints), especially in women [31]. The role of obesity in the genesis and progression of the

disease is based on the fact that increased body weight generates a weight overload on the articular cartilage and subchondral bone [32]. In the acromegalic patients studied, we also found an association between higher BMI and the presence of arthropathy. However, when we searched for this association in each joint, we observed the influence of BMI only in the cases of hip and knee arthropathy (weight-bearing joints) and not in the shoulder (non-weight-bearing joint) cases. This finding suggests a similar pattern to the one observed in patients with osteoarthritis only.

It must be noted that the evaluation of body composition by densitometry, a measure of lean body mass (muscle and soft tissue), here included the subcutaneous tissue, which was increased in acromegaly, and fat mass, which was increased in obese subjects. In patients with active acromegaly, lean body mass is higher compared with fatty tissue in patients with controlled disease, which is a direct effect of IGF-I in muscle and adipose tissue, as described by Madeira et al. [33]. Therefore, the absence of a relationship in our patients between lean body mass or fat mass, individually, and arthropathy, suggests that both factors contributed equally to the BMI.

We found no association between the presence of arthropathy and particular features of acromegaly, such as serum levels of GH and IGF-I and duration of disease until diagnosis. Biermasz et al reported an association between levels of IGF-I before treatment and the presence of radiographic signs of osteoarthritis [28]. In our study, no association was observed between the presence of arthropathy and pretreatment serum levels of IGF-I, although we did not evaluate radiographic characteristics. We also found no relationship between arthropathy and active or controlled acromegaly. Nevertheless, because we considered the new criteria established for disease control (GH <1.0 ng/mL and IGF-I within the normal range), we obtained only 9 out of 71 patients (13 %) classified as controlled. This comparatively small percentage may have hindered a better analysis of this relationship, although there are no reports relating acromegalic disease control and the prevalence of arthropathy.

This is the first study that ranks the magnitude of joint involvement in acromegalic patients and attempts to identify variables associated with increased severity of arthropathy. Theoretically, more functionally severe arthropathy tends to result in greater functional disability and therefore greater impairment of quality of life. Therefore, the identification of an associated factor, if modifiable, would be beneficial to these patients.

We identified two factors associated with the development of functionally more severe arthropathy compared with less severe arthropathy: increased BMI and lower levels of IGF-I.

Obesity, as already discussed, has a strong association with osteoarthritis. Furthermore, the joints of obese patients, especially weight-bearing joints, undergo greater load.

Therefore, it is expected that among patients with joint pathology, those with higher body weight (subjected to a greater functional demand) have more severe joint complaints, which explains the findings of our study.

Based on the theoretical adverse effects of IGF-I excess in the joints, we expected to observe an association between more severe arthropathy and higher IGF-I levels compared with less functionally severe joint disease. The synthesis and maintenance of articular cartilage matrix is enhanced by several growth factors, and IGF-I is the most important of them [34, 35]. In addition to its anabolic effects on normal articular cartilage, IGF-I has demonstrated to be beneficial to injured cartilage in multiple animal models, improving cartilage repair [34–37]. Wassenaar and colleagues reported that patients with osteoarthritis caused by acromegaly have wider joint space and better function scores than patients with primary generalized osteoarthritis, suggesting that IGF-I may protect against joint space narrowing and prevent acromegaly patients from a decrease in functional capability [38]. These data may explain our findings that IGF-I was higher in patients with less severe joint disease.

The absence of an association of arthropathy with specific factors of acromegaly in our study and in published data, as well as the association with factors also related to osteoarthritis, suggest that acromegalic arthropathy is caused by osteoarthritic changes in the affected joints. Therefore, the treatment of acromegaly, through the control of GH and IGF-I, would have no significant effect on joint complaint prevention because arthralgia persists even after long-term remission of acromegaly, as previously reported [13, 14]. Therefore, despite treatment of acromegalic disease, we assume that most patients already show irreversible joint disease at the time of diagnosis, and treatment should be directed to the osteoarthritis itself at identification.

Obesity is considered the most significant and modifiable factor in the onset and progression of osteoarthritis [39, 40]. In the acromegalic patients assessed, increased BMI was associated with the presence of arthropathy and its more severe progression. Therefore, when treating acromegalic patients with joint complaints, the importance of controlling body weight must be emphasized to avoid the development and progression of arthropathy.

Osteoarthritis has significant importance within public health services because of its harmful effects, impact on quality of life, and causation of early retirement and work absenteeism [39, 40]. Although acromegaly is a rare and underdiagnosed disease, the indiscriminate use of exogenous GH by people without disabilities is suggested to also expose these subjects to the common complications caused by excess GH [2]. These complications may include arthralgia and, eventually, degenerative disease.

The hypothesis that degenerative joint disease is already present at diagnosis highlights the importance of achieving a definitive and early diagnosis for acromegaly. Because no association between the estimated period without treatment and the presence or absence of arthropathy was observed in our study, we assume that the estimated onset of acromegalic symptoms is not useful in defining the real time of onset of acromegaly, an insidious disease without obvious symptoms in early stages, which leads to a delay in seeking medical care. Thus, physicians should be aware of possible symptoms of the disease in the general population and, in cases of suspicion, perform the appropriate laboratory tests to anticipate the diagnosis of acromegaly and avoid its many complications [41–43].

Conclusions

In the present study, we observed an association of female sex and older age at diagnosis of acromegaly with the presence of arthropathy. Increased BMI was associated with the presence of arthropathy and with more functionally severe arthropathy. The lack of association between arthropathy and specific factors of acromegaly, as well as its association with factors that are also related to osteoarthritis, suggest that acromegalic arthropathy is caused by osteoarthritic changes in the affected joints. Despite treatment for acromegaly, we assume that most patients present with irreversible joint disease at diagnosis. Therefore, acromegalic arthropathy treatment should be performed with a particular focus on body weight control.

Disclosures None.

References

1. Marie P (1886) On two cases of acromegaly: marked hypertrophy of the upper and lower limbs and head. *Rev Med* 6:297–333
2. Shlomo AB, Melmed S (2008) Acromegaly. *Endocrinol Metabol Clin N Am* 37:101–122
3. Barkan AL (2001) Acromegalic arthropathy. *Pituitary* 4:263–264
4. Detenbeck LC, Tressler HA, O'Duffy JD, Randall RV (1973) Peripheral joint manifestations of acromegaly. *Clin Orthop* 91:119–127
5. Colao A, Pivonello R, Scarpa R, Vallone G, Ruosi C, Lombardi G (2005) The acromegalic arthropathy. *J Endocrinol Invest* 28(Suppl 8):24–31
6. Colao A, Marzullo P, Vallone G, Marino V, Annecchino M, Ferone D et al (1998) Reversibility of joint thickening in acromegalic patients: an ultrasonography study. *J Clin Endocrinol Metab* 83:2121–2125
7. Podgorski M, Robinson B, Weissberger A, Stiel J, Wang S, Brooks PM (1988) Articular manifestations of acromegaly. *Aust N Z J Med* 18:28–35
8. Dons RF, Rosselet P, Pastakia B, Doppman J, Gorden P (1988) Arthropathy in acromegalic patients before and after treatment: a long-term follow-up study. *Clin Endocrinol* 28:515–524
9. Layton MW, Fudman EJ, Barkan A, Braunstein EM, Fox IH (1988) Acromegalic arthropathy. Characteristics and response to therapy. *Arthritis Rheum* 31:1022–1027
10. Barkan A (1997) Acromegalic arthropathy and sleep apnea. *J Endocrinol* 155(Suppl 9):41–44
11. Lieberman SA, Bjorkengren AG, Hoffman AR (1992) Rheumatologic and skeletal changes in acromegaly. *Endocrinol Metab Clin North Am* 21:615–631
12. Forgacs SS (1998) Acromegaly. In: Klippel JH, Dieppe PA (eds) *Rheumatology*. Mosby, London
13. Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW et al (2004) Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *J Clin Endocrinol Metab* 89:5369–5376
14. Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F (2005) Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. *J Clin Endocrinol Metab* 90:2731–2739
15. Chipman JJ, Attanasio AF, Birkett MA, Bates PC, Webb S, Lamberts SW (1997) The safety profile of GH replacement therapy in adults. *Clin Endocrinol* 46:473–481
16. Bluestone R, Bywaters EG, Hartog M, Holt PJ, Hyde S (1997) Acromegalic arthropathy. *Ann Rheum Dis* 30:243–258
17. Scarpa R, De Brasi D, Pivonello R, Marzullo P, Manguso F, Sodano A et al (2004) Acromegalic axial arthropathy: a clinical case-control study. *J Clin Endocrinol Metab* 89:598–603
18. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K et al (2000) Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab* 85(2):526–529
19. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF et al (2010) A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab* 95(7):3141–3148
20. D'Aubigné RM, Postel M (1954) Functional results of hip arthroplasty with acrylic prosthesis. *J Bone Jt Surg Am* 36-A(Suppl 3):451–475
21. Charnley J (1972) The long-term results of low friction arthroplasty of the hip performed as a primary intervention. *J Bone Jt Surg Am* 54-B:61–76
22. Insall JN, Dorr LD, Scott RD, Scott WN (1989) Rationale of the Knee Society clinical rating system. *Clin Orthop Relat Res* 248:13–14
23. Asif S, Choon DS (2005) Midterm results of cemented press fit condylar sigma total knee arthroplasty system. *J Orthop Surg (Hong Kong)* 13:280–284
24. Amstutz HC, Sew Hoy AL, Clarke IC (1981) UCLA anatomic total shoulder arthroplasty. *Clin Orthop Relat Res* 155:7–20
25. Nutton RW, McBirnie JM, Phillips C (1997) Treatment of chronic rotator-cuff impingement by arthroscopic subacromial decompression. *J Bone Joint Surg Br* 79:73–76
26. Elmlinger MW, Kühnel W, Weber MM, Ranke MB (2004) Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP3). *Clin Chem Lab Med* 42:654–664
27. Fellet A, Fellet AJ, Fellet L (2007) [Osteoarthritis: a review]. *Rev Bras Med* 64:55–61, Portuguese
28. Biermasz NR, Wassenaar MJ, van der Klaauw AA (2009) Pretreatment insulin-like growth factor-I concentrations predict radiographic osteoarthritis in acromegalic patients with long-term cured disease. *J Clin Endocrinol Metab* 94(7):2374–2379
29. Giorgi RDN (2005) [Osteoarthritis in clinical practice]. *Temas Reumatol Clin* 6:17–30, Portuguese
30. Spector TD, Nandra D, Hart DJ, Doyle DV (1997) Is hormone replacement protective for hand and knee osteoarthritis in women? The Chingford study. *Ann Rheum Dis* 56(7):432–434

31. Cimmino MA, Sarzi-Puttini P, Scarpa R, Caporali R, Parazzini F, Zaninelli A et al (2005) Clinical presentation of osteoarthritis in general practice: determinants of pain in Italian patients in the AMICA study. *Semin Arthritis Rheum* 35(Suppl 1):17–23
32. Teichtahl AJ, Wluka AE, Proietto J, Cicuttini FM (2005) Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects. *Med Hypotheses* 65(2):312–315
33. Madeira M, Neto LV, de Lima GA, Moreira RO, de Mendonça LM, Gadelha MR et al (2010) Effects of GH-IGF-I excess and gonadal status on bone mineral density and body composition in patients with acromegaly. *Osteoporos Int* 21(12):2019–2025
34. Goodrich LR, Hidaka C, Robbins PD, Evans CH, Nixon AJ (2007) Genetic modification of chondrocytes with insulin-like growth factor-1 enhances cartilage healing in an equine model. *J Bone Joint Surg Br* 89-B:672–685
35. Fortier LA, Mohammed HO, Lust G, Nixon AJ (2002) Insulin-like growth factor-I enhances cell-based repair of articular cartilage. *J Bone Joint Surg Br* 84-B:276–288
36. Miller RE, Grodzinsky AJ, Cummings K, Plaas AH, Cole AA, Lee RT et al (2010) Intraarticular injection of heparin-binding insulin-like growth factor 1 sustains delivery of insulin-like growth factor 1 to cartilage through binding to chondroitin sulfate. *Arthritis Rheum* 62(12):3686–3694
37. Madry H, Kaul G, Cucchiaroni M, Stein U, Zurakowski D, Remberger K et al (2005) Enhanced repair of articular cartilage defects in vivo by transplanted chondrocytes overexpressing insulin-like growth factor I (IGF-I). *Gene Ther* 12:1171–1179
38. Wassenaar MJ, Biermasz NR, Bijsterbosch J, Pereira AM, Meulenbelt I, Smit JW et al (2011) Arthropathy in long-term cured acromegaly is characterised by osteophytes without joint space narrowing: a comparison with generalised osteoarthritis. *Ann Rheum Dis* 70(2):320–325
39. Rosis RG, Massabki PS, Kairalla M (2010) [Osteoarthritis: clinical and epidemiological assessment of elderly patients in long-term institution]. *Rev Bras Clin Med* 8(2):101–108, Portuguese
40. Woolf AD, Pfleger B (2003) Burden of major musculoskeletal conditions. *Bull World Health Organ* 81(9):646–656
41. East HE, Subauste JS, Gandhi A, Koch CA (2012) About secondary causes of diabetes mellitus. *J Miss State Med Assoc* 53(11):380–383
42. Wiesner TD, Trantakis C, Meixensberger J, Koch CA, Zimmer C, Paschke R (2005) Structure of an interdisciplinary pituitary outpatient care unit at the University Hospital of Leipzig and the results for treatment of prolactin and growth hormone secreting pituitary tumors. *Med Klin* 100(4):173–179
43. Watson JC, Stratatki CA, Bryant-Greenwood PK, Koch CA, Kirschner LS, Nguyen T, Carney JA, Oldfield EH (2000) Neurosurgical implications of Carney complex. *J Neurosurg* 92(3):413–418