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Original Research

Progression of acromegalic joint and psychological complications according to sex, treatments, and disease control

Biagio Cangiano [1,2]*, Matteo Corbetta [2], Caterina Premoli[2], Davide Soranna[3], Giovanni Vitale [1,2], Silvia Grottoli[4], Valeria Cambria[4], Pietro Maffei [5], Francesca Dassie [5], Salvatore Cannavò[6,7], Marta Ragonese[6,7], Antonella Zambon[8], Marco Bonomi [1,2], Luca Persani [1,2], Letizia Maria Fatti [1†] and Massimo Scacchi [9,10*†] on behalf of the "PRO-ACRO" study group on Motor Disability in Acromegaly, of the Italian Society of Endocrinology (SIE)[‡]

[1]Department of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Via Mosè Bianchi 90, Milan 20149, Italy
[2]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan 20133, Italy
[3]Istituto Auxologico Italiano, IRCCS, Milan 20149, Italy
[4]Department of Medical Sciences, University of Turin, Turin 10126, Italy
[5]Department of Medicine-DIMED, University of Padua, Padua 35128, Italy
[6]Department of Human Pathology, University of Messina, Messina 98122, Italy
[7]Endocrine Unit, University Hospital of Messina, Messina 98124, Italy
[8]Division of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan 20126, Italy
[9]Istituto Auxologico Italiano, IRCCS, Division of General Medicine, Ospedale S. Giuseppe, Oggebbio-Piancavallo, Strada Cadorna 90, Verbania 28824, Italy
[10]Department of Clinical Sciences and Community Health, Dipartimento di Eccellenza 2023-2027, University of Milan, Milan 20122, Italy
*Corresponding authors: IRCCS Istituto Auxologico Italiano, Division of Endocrine and Metabolic Diseases, Ospedale San Luca, Via Mosè Bianchi 90, Milan 20149, Italy. Email: b.cangiano@auxologico.it (B.C.); IRCCS Istituto Auxologico Italiano—Division of General Medicine, Ospedale S. Giuseppe, Strada Cadorna 90, Località Piancavallo, Oggebbio-Verbania 28824, Italy. Email: massimo.scacchi@unimi.it (M.S.)
†These Authors equally contributed to this paper.
‡"**PRO-ACRO**" study group: Francesco Cavagnini, Diego Ferone, Giovanna Mantovani, Antonella Giampietro, Sabrina Chiloiro, Maria Laura Tanda, Sabrina Corbetta, Luigi Bartalena, Paolo Beck Peccoz, Maura Arosio, Andrea Lania, Annamaria Colao, Rosario Pivonello, Ettore Degli Uberti, Ezio Ghigo, Andrea Giustina, Enio Martino, Alfredo Pontecorvi, Nicola Sicolo, Francesco Trimarchi.

Abstract

Background **Articular and psychological complications of acromegaly are known to impair patients' quality of life (QoL). This multicenter prospective observational study aimed to (1) identify clinical predictors of the progression of these complications, (2) evaluate their progression in relation to disease activity, and (3) assess their impact on QoL.**

Materials and Methods **Ninety-five patients with acromegaly were enrolled, excluding those with inflammatory rheumatic diseases. Clinical history, hormonal, and physical exams were collected at baseline and after 42 months. Specific questionnaires assessing joint and psychological discomfort (WOMAC, AIMS, VAS) and QoL (AcroQoL) were administered.**

Results **A regression model identified clinical predictors of progression. Female sex was significantly associated with worsening joint symptoms (VAS $P = .0302$; AIMS symptoms $P = .0328$), as was prior radiotherapy (AIMS $P = .0071$). Use of dopamine agonists (DAs) was linked to higher AIMS depression scores ($P = .0224$). Interestingly, patients with disease recurrence showed lower joint pain scores compared with baseline. In contrast, mood scores improved with disease remission. Notably, suicide emerged as a relevant cause of death in this cohort, underscoring the need for comprehensive psychological care.**

Conclusions **Female sex and prior radiotherapy emerged as predictors of progressive joint symptom worsening. Changes in depression and joint complaints alongside disease course suggest a complex involvement of IGF1. Dopamine agonists may negatively affect mood, though further studies are needed. Overall, joint disease had a greater and independent negative impact on QoL compared to mood disorder. Articular and psychological complications remain a significant burden, particularly in women with acromegaly.**

Keywords acromegaly, depression, arthropathy, QoL, dopamine agonists, radiotherapy, suicide

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Significance

Articular and psychological complications of acromegaly markedly impair patients' quality of life and may persist even after disease remission. Our study provides an integrated assessment of how these complications relate to each other and how they affect overall well-being, while also examining their evolution over time. We identified both modifiable and non-modifiable factors that influence this trend, underscoring the need for a personalized clinical approach. Our findings suggest that certain treatments for acromegaly may help shape the course of joint and psychological complications, opening new perspectives for optimizing therapeutic decisions and improving long-term outcomes, if confirmed by future studies.

Introduction

Acromegaly is a rare endocrine disorder resulting from the chronic hypersecretion of growth hormone, usually due to a pituitary adenoma.[1,2] The hormone's proliferative effects contribute to a wide range of systemic complications that can significantly affect both survival and quality of life.[3-5] Among these, joint and psychiatric complications are particularly relevant due to their impact on daily functioning and long-term outcomes. Joint involvement has been reported in 75% of patients,[6] while psychiatric complications affect 40%-50% of patients.[7,8] In recent years, the awareness of articular and psychiatric acromegalic complications and their impact on quality of life (QoL) has increased. In fact, improving QoL represents one of the 3 main patient-reported health outcomes in chronic diseases.[9]

In the acromegalic population, QoL became an important outcome since Broersen et al. reported its improvement during treatment in a systematic review.[10] Wolters et al.[11] conducted a prospective study evaluating QoL before and during the first 2.5 years of treatment for acromegaly. Although all patients achieved disease control through surgery and/or medical therapy, QoL remained impaired throughout the study period and continued to be lower than that of the general population. Similarly, in another prospective study, Kyriakakis et al.[12] reported that the reduced QoL was mainly related to limitations in physical functioning and psychosocial well-being.

An interaction between QoL and psychiatric complication was found also in several studies which highlighted that depression,[13-18] anxiety,[13,17,18] and body image[19,20] were associated with lower QoL scores.

Although disease remission can be achieved in acromegaly through surgical or medical interventions, joint and psychiatric complications often persist. These complications currently lack targeted treatment options, and the existing literature addressing them remains limited.

Therefore, the aims of the present study are (1) to study clinical predictors for the progression of articular and psychological complications, (2) to evaluate the progression of these complications in relation to the activity of the acromegalic disease, and (3) to evaluate how these complications interact to impair the QoL.

Methods

Patients

Ninety-five patients with acromegaly were enrolled in this multicentric prospective observational study which involved IRCCS Istituto Auxologico Italiano in Milan, University Hospital of Turin, University Hospital of Padua and University Hospital of Messina. The recruitment of patients began in July 2012 and ended in October 2020, with each patient receiving a 42-month follow-up. The diagnosis of acromegaly was established according to the Endocrine Society Clinical Practice Guideline.[21] Patients were enrolled regardless of gender, acromegaly disease status, current, or previous therapies. The only exclusion criterion was the diagnosis of inflammatory rheumatic diseases.

The 95 patients included in the present prospective analysis were selected as those who attended the 42-month follow-up visit from the original cohort of 171 patients enrolled in our previous cross-sectional evaluation.[14] Medical history, hormonal and physical exams, as well as pharmacological treatments such as anti-depressant drugs (SSRI) and benzodiazepines, were recorded at the beginning of the study and after 42 months. At the same time, specific questionnaires studying articular and psychological discomfort were administered (see subsection "Questionnaires"). Mortality data were available for all the 171 patients of the original cohort. In patients receiving anti-inflammatory or analgesic therapy, the questionnaires were administered after a washout period of these treatments of at least 1 month. The absolute difference between questionnaire scores at 42 months and baseline was used to evaluate the progression of disease complications.

At study inclusion and at 42 months follow-up, patients were stratified into active or biochemically controlled disease groups according to their IGF1 levels relative to the upper limit of the normal reference range.

All patients provided informed consent for the use of the anonymized clinical and biochemical data for research and publication purposes. The study was approved by the Institutional Review Board of Istituto Auxologico Italiano (02C201) and complied with the Declaration of Helsinki.

Questionnaires

To assess QoL, the AcroQoL questionnaire was administered and analyzed as a continuous scale.[22-24] To evaluate articular complications and psychological discomfort 3 different questionnaires were used: the Visual Analogue Scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[25,26] which consists of 3 continuous scales evaluating joint pain, stiffness and functionality, and the Arthritis Impact Measurement Scale (AIMS),[27] which evaluates both joint symptoms and psychological aspects such as depression and anxiety on a continuous scale. Cutoff values for the AIMS depression scale to identify possible (>3/10) and probable depression (>4/10) were applied according to data published by Hawley et al.[28]

Hormonal evaluation

To avoid the bias associated with inter-assay variability across different laboratories, IGF1 levels were analyzed both as absolute values and as estimated standard deviations (eSDs), as already reported in the cross-sectional evaluation.[5] Assuming a normal distribution of IGF1 concentrations, each measurement was standardized using age-specific reference ranges provided by assay manufacturers, derived from the general population. Specifically, we applied one of the normalization methods described by Christy Chuang-Stein in 1992,[29] which utilizes both the lower (2.5th percentile) and upper (97.5th percentile) limits of the reference range to estimate the standardized value.

The standardized values were obtained as follows:

$$IGF1_{eSD} = (IGF1\text{-}mean)/eSD$$

where eSD = (mean-lower reference value)/2, and mean = (higher reference value + lower reference value)/2. GH values were not standardized.

Statistical analysis

Continuous and sociodemographic variables were reported as mean ± SD, while categorical variables are presented as absolute and relative frequencies. ANCOVA models were implemented to investigate the variables associated with changes (calculated as the difference between follow-up and baseline scores) in WOMAC pain score, total WOMAC score, VAS scale, symptoms reported in the AIMS questionnaire, depression (AIMS), and quality of life adjusting for baseline outcome variable and a priori selected clinical covariates. Regression analyses were performed on SSRI and benzodiazepine therapies at baseline and during follow-up. Furthermore, to assess the impact of psychological and articular complications on changes in quality of life, standardized beta coefficients were calculated.

Table 1 Anthropometric and clinical characteristics of the study population.

	Whole cohort (*N* = 95)
Males, *n (%)*	43 (45%)
Age at recruitment (years), *mean ± SD*	57.24 ± 14.27
Age at diagnosis (years), *mean ± SD*	46.21 ± 13.16
Body Mass Index (kg/m^2), *mean ± SD*	28.10 ± 5.21
N. missing	2
Disease duration (years), *mean ± SD*	10.26 ± 10.59
Positive family history of arthropathy, *n (%)*	14 (29%)
N. missing	46
Macroadenomas at diagnosis, *n (%)*	62 (70%)
N. missing	7
Diameter of adenoma at diagnosis (mm), *mean ± SD*	15.32 ± 11.59
N. missing	28
Hypopituitarism, *n (%)*	6 (6%)
Diabetes mellitus, *n (%)*	4 (4%)

Results

Clinical data were collected from 95 patients, 43 men and 52 women, with a mean age at diagnosis of 46.2 years (Table 1). At the time of diagnosis, macroadenomas were present in 70% of patients with a mean maximum diameter of 15.3 mm, while the prevalence of hypopituitarism was 6%.

Details on the distribution of missing data in Table 1 according to sex are reported in Table S1.

Table 2 reports the treatment received by patients with active and controlled disease.

The all-cause mortality in the cohort of 171 patients described in our previous cross-sectional evaluation[14] was 4.67%, with causes of death reported in Table 3. Ninety-five of these patients were evaluated after a mean follow-up period of 42.93 ± 2.88 months and were included in the present analysis.

The regression model, used to identify clinical predictors of articular and psychological complications progression over a 42-month period, revealed a significant association between female gender and worsening joint symptoms, as measured by VAS ($P = .0302$), and AIMS symptoms ($P = .0328$) scales. For WOMAC pain scores a trend toward statistical significance was observed ($P = .0562$). Similarly, a history of radiotherapy (RT) was significantly associated with worsening joint symptoms as assessed by the AIMS questionnaire ($P = .0071$). Among the patients with a history of radiotherapy, 5 had conventional radiotherapy while 15 underwent Gamma Knife radiosurgery.

Moreover, the analysis of acromegaly treatments revealed a significant association between dopamine agonist therapy and higher AIMS depression scores ($P = .0224$), with a mean increase of 1.1 points in AIMS depression scores, compared to a mean decrease of 0.3 points in patients not receiving this class of drugs. Results of the regression model are presented in Table 4.

Clinical and demographic characteristics of patients receiving dopamine agonists and those not receiving such treatment at the 42-month follow-up are presented in Table S2.

No statistically significant associations were observed for other acromegaly-related medical therapies, SSRIs, or benzodiazepines.

Table 2 Treatment received by patients with active and controlled disease.

	Number of patients	SSA	Pegvisomant	DA	Surgery	CRT	GKRS
Biochemical remission	72	66	14	28	50	4	10
Active disease	23	12	2	6	11	1	5

SSA, Somatostatin analog; DA, dopamine agonist; CRT, conventional radiotherapy; GKRS, Gamma Knife radiosurgery.

Table 3 Distribution of causes of death observed during the 3-year follow-up. Mortality data are presented as absolute frequencies in the population and relative percentages of all observed deaths. Categories include cardiovascular, oncological, infectious and psychiatric-related deaths.

	Patients	Percentage	Relative percentage	Relative percentage in literature[30]	Age at death (years, mean)
Cancer	3	1.75%	37.5%	35%-36%	73.6
Cardiovascular	2	1.16%	25%	23%-27.9%	78
Suicide	2	1.16%	25%		48
Urinary sepsis	1	0.58%	12.5%	36%-42%	80
Total	8	4.67%	100%	100%	69.12

Table adapted from Fatti LM and Cangiano B.[5]

According to regression analysis, variations in AIMS depression scores were not found to be related to the use of SSRIs or benzodiazepines at baseline and at follow-up.

Descriptive analysis of questionnaire score progression related to disease activity was carried out on 90 out of 95 patients. The patients were divided into 4 groups based on disease status (controlled or active) and time (baseline or follow-up): (1) patients with ever controlled disease (60 individuals); (2) patients with ever active disease (9 individuals); (3) patients with controlled at baseline and active at follow-up ("Disease recurrence", 8 individuals); and (4) patients with active disease at baseline and controlled disease at follow-up ("Disease remission", 12 individuals). A paradoxical trend of WOMAC pain was observed among patients with "disease recurrence." Indeed, the mean score decreased from 3.88 to 3.50.

Patients with chronic biochemical control exhibited a slight worsening in scores related to joint symptoms (mean score from 5.27 to 5.80), and a comparable trend was observed in those with chronically active disease (from 4.67 to 4.78). Data from all patient subgroups are presented in Figure 1, with sample sizes and 95% CIs reported in Table S3.

Regarding psychiatric complications, patients with "disease remission" showed a reduction in AIMS depression scores, with mean values decreasing from 2.09 to 1.13. In contrast, other patient subgroups showed a worsening of depression-related questionnaire scores. Specifically, patients with stable biochemical control had a slight increase in mean depression scores (from 3.06 to 3.25), while those without biochemical control during follow-up showed a more pronounced worsening (from 2.13 to 3.89). Patients with disease recurrence also demonstrated an increase in AIMS depression scores, from 2.12 to 3.30. All mean values and their changes over time are shown in Figure 2. Sample sizes and standard deviations for AIMS depression scores are reported in Table S4.

Finally, arthropathy was confirmed to be an independent factor impairing QoL in acromegaly (P-value = .0091). The effect of depression had a borderline statistical significance (P-value = .0548). Arthropathy showed a greater impact than mood as measured with AIMS depression scores on the worsening of patients' well-being ($\beta = -0.28$ and $\beta = -0.21$, respectively). Quality of life is also negatively correlated with age ($\beta = -0.21$, $P = .0422$). Results of this analysis are presented in Table 5.

Discussion

This study highlighted a significant role for sex in the progression of articular complications. Female sex is not only a factor associated with worse articular symptoms but also has a role in the progression of this complication over time, as reflected by 2 out of 4 questionnaire scores, with a trend toward statistical significance for WOMAC pain scores. Similar evidence has been reported in previous studies.[5,31,32] In contrast, female sex did not show a statistically significant association with AIMS depression questionnaire scores at the 42-month assessment.

Obesity induces mechanical overload on the joints, particularly in the lower limbs. In our analysis, however, a trend toward statistical significance for BMI was observed, although the literature has consistently reported this correlation.[5,32,33]

In contrast to previous reports,[31,32,34,35] no significant associations were found between age or disease duration and the variation in articular complications.

Previous radiotherapy treatments represent an additional factor potentially associated with articular complications. RT was linked to worse joint symptom scores, which likely reflect the greater severity of disease in patients requiring this intervention, rather than indicating a direct causal relationship. In fact, the longer time elapsed since diagnosis in these patients may partially explain this association, particularly as we adjusted for the duration of active disease rather than the time since diagnosis in this subgroup. Moreover, most patients who received RT underwent Gamma Knife radiosurgery, a highly precise technique that targets only the pathological tissue. The results were adjusted for the presence of hypopituitarism, which could be the mediator of the negative effects associated with conventional radiotherapy.

The potential role of dopamine agonists in increasing and worsening depressive symptoms found in our evaluation may be explained by a direct pharmacologic effect rather than an adverse psychiatric side effect, although a correlation with the underlying severity of disease cannot be excluded. Indeed, dopamine agonists are typically prescribed as an add-on therapy in patients who do not achieve biochemical control with first-line treatments. In the literature, dopamine agonists have been shown to improve symptoms in treatment-resistant depression and major depressive disorders.[36] However, although rare, some case reports and reviews note that dopamine agonists can trigger mood changes, including depression, mania, or impulse control disorders, particularly in patients with underlying vulnerabilities.[37] In this context, further studies are needed to confirm our findings and clarify the underlying mechanisms, which may also not indicate a direct relationship between the 2 variables, but suggest the influence of a third associated factor.

Table 4 Results of the multivariate analysis for different questionnaires scores (WOMAC Pain, WOMAC Total, VAS, AIMS Symptoms, AIMS Depression). Questionnaire outcomes are expressed as the change in scores from baseline to 42 months. Outcome at baseline refers to questionnaire scores measured at baseline, while standardized IGF1 at follow-up (FU) refer to IGF1 levels measured at 42-months evaluation and standardized as described in Methods section.

	WOMAC pain ($N = 84$)		WOMAC total ($N = 83$)		VAS ($N = 69$)		AIMS symptoms ($N = 86$)		AIMS depression ($N = 84$)	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Age	0.032 (−0.061 to 0.066)	.9301	0.161 (−0.356 to 0.275)	.8012	0.247 (−0.318 to 0.651)	.5033	0.03 (−0.065 to 0.051)	.8215	0.02 (−0.038 to 0.04)	.9697
Female vs Male	0.948 (−0.017 to 3.7)	.0562	4.718 (−2.518 to 15.976)	.1583	7.188 (1.908 to 30.085)	.0302	0.86 (0.186 to 3.555)	.0328	0.586 (−1.209 to 1.088)	.9185
BMI	0.086 (−0.128 to 0.209)	.6369	0.418 (−0.562 to 1.078)	.5399	0.66 (−0.178 to 2.407)	.0968	0.081 (−0.148 to 0.169)	.9003	0.052 (−0.099 to 0.106)	.9496
Active disease (years)	0.064 (−0.033 to 0.218)	.1524	0.313 (−0.42 to 0.806)	.5390	0.5 (−1.069 to 0.892)	.8600	0.06 (−0.205 to 0.031)	.1529	0.04 (−0.102 to 0.057)	.5751
Outcome at baseline	0.103 (−0.622 to −0.217)	.0001	0.114 (−0.438 to 0.009)	.0648	0.119 (−0.924 to −0.458)	<.0001	0.149 (−0.747 to −0.164)	.0031	0.124 (−0.634 to −0.146)	.0025
Standardized IGF1 at FU	0.174 (−0.461 to 0.222)	.4946	0.849 (−2.735 to 0.594)	.2116	1.376 (−4.328 to 1.064)	.2406	0.163 (−0.37 to 0.271)	.7622	0.111 (−0.125 to 0.309)	.4086
Diabetes	1.921 (−3.627 to 3.904)	.9426	9.425 (−22.412 to 14.535)	.6773	14.431 (−41.853 to 14.718)	.3513	1.845 (−2.939 to 4.292)	.7150	1.23 (−1.676 to 3.145)	.5522
Hypopituitarism	1.862 (−3.036 to 4.261)	.7430	9.184 (−7.367 to 28.634)	.2509	13.868 (−19.176 to 35.187)	.5661	1.775 (−3.841 to 3.116)	.8389	1.183 (−2.059 to 2.576)	.8277
Surgery	0.816 (−2.076 to 1.124)	.5617	4.016 (−9.853 to 5.89)	.6233	6.673 (−11.641 to 14.518)	.8301	0.772 (−1.856 to 1.171)	.6589	0.527 (−1.168 to 0.897)	.7980
Gamma-knife	1.309 (−5.097 to 0.035)	.0573	6.304 (−17.828 to 6.885)	.3885	9.726 (−16.142 to 21.984)	.7651	1.247 (1.009 to 5.896)	.0071	0.829 (−1.874 to 1.375)	.7646
SSA treatment	1.133 (−2.939 to 1.504)	.5289	5.594 (−11.2 to 10.727)	.9664	9.498 (−16.747 to 20.485)	.8447	1.078 (−3.615 to 0.61)	.1676	0.73 (−1.606 to 1.255)	.8111
Pegvisomant treatment	1.111 (−1.081 to 3.272)	.3272	5.354 (−8.535 to 12.451)	.7156	9.053 (−10.093 to 25.393)	.4017	1.029 (−0.512 to 3.521)	.1480	0.685 (−1.219 to 1.467)	.8570
DA treatment	0.893 (−1.222 to 2.277)	.5566	4.35 (−6.046 to 11.004)	.5706	7.561 (−17.922 to 11.715)	.6830	0.833 (−0.482 to 2.785)	.1714	0.565 (0.212 to 2.429)	.0224

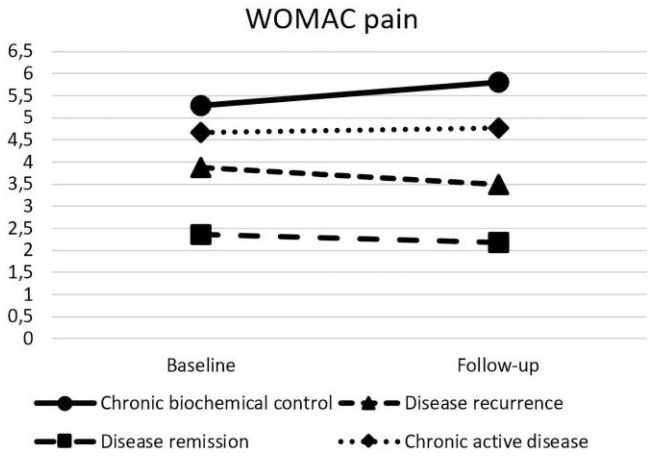

Figure 1 Progression of mean WOMAC pain scores over 42 months in relation to disease activity status. Data are shown for patients with disease remission, recurrence, chronic biochemical control, and chronic active disease.

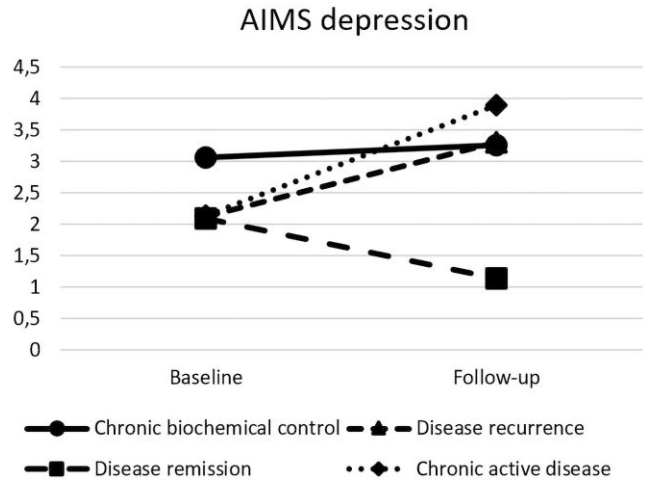

Figure 2 Progression of mean AIMS depression scores over 42 months in relation to disease activity status. Data are shown for patients with disease remission, recurrence, chronic biochemical control, and chronic active disease.

The mortality rates in our population were similar to those reported in the literature,[30] with some a notable exception: if no deaths due to respiratory causes were reported, suicide represented a significant cause of mortality, with rates comparable to those of cardiovascular diseases (Table 3).

Contrary to expectations, our results showed a trend toward improvement (or at least a reduced worsening) of joint symptoms in patients with acromegaly recurrence. A significant inverse correlation between IGF1 levels and arthropathy has also been reported in previous cross-sectional studies.[5,32,38] One hypothesis may involve the role of IGF1 in stimulating cartilage hypertrophy, which leads to an enlargement of the intra-articular space. This structural change may reduce nociceptor activation in the subchondral bone, thereby decreasing pain perception. Furthermore, disease progression also contributes to irreversible joint damage through degenerative changes. Joint alterations consisted of 2 components: a partially irreversible cartilage hypertrophy, which is influenced by biochemical disease control,

Table 5 Standardized beta coefficients (estimated from a multivariate model) and their 95% CI related to the impact of several covariates on changes in quality of life.

	Standardized β	95% CI	*P*-value
AcroQol at baseline	−0.262	−0.487 to 0.041	.0207
Age	−0.214	−0.431 to −0.008	.0422
Female vs Male	−0.158	−0.782 to 0.131	.1593
BMI	−0.163	−0.377 to 0.051	.1339
Active disease (years)	0.102	−0.120 to 0.335	.3493
Difference AIMS depression	−0.208	−0.588 to 0.006	.0548
Difference WOMAC total	−0.281	−0.495 to 0.073	.0091

and joint edema, which is typically responsive to pharmacological treatment.[39] Induced chondrocyte hypertrophy may serve as a protective factor against joint pain. However, somatostatin analogs are also known to exert an independent beneficial effect on pain.[40] In our regression model, acromegaly treatments did not appear to have a statistically significant effect on the progression of this complication, probably due to limited sample size. Further randomized controlled trials are needed to evaluate a potential correlation. IGF1 levels may also contribute to the observed gender disparity. Indeed, due to the effects of estrogens, women exhibit higher GH levels and lower IGF1 levels compared to men, which leads to reduced chondrocyte hypertrophy. These findings need to be confirmed by ad hoc studies.

The achievement of biochemical control of acromegaly was associated with an improvement in AIMS depression questionnaire scores, possibly due to an overall improvement in clinical conditions. In other subgroups, the subjective sense of losing control over the illness may contribute to mood deterioration. Notably, even in cases of biochemical control of the disease, worsening depressive symptoms might persist due to the chronic nature of the disease. Benzodiazepine and SSRIs treatments were not associated with worsening psychiatric complications in our cohort. However, this finding may be influenced by selection bias as these medications were prescribed primarily to patients with more severe mood disturbances.

The assessment of mood disorder and arthropathy impact on quality of life in acromegalic patients revealed a strong correlation between both factors and a decline in well-being. The observed borderline association between mood and QoL supports the findings of previous studies.[13-18] Moreover, other psychosocial factors had an influence on QoL, such as illness perception[41,42] as greater acceptance of the illness was associated with improved QoL,[43] while greater perceived stigma was strongly correlated with lower QoL scores.[44]

The intimate association between psychological complications and arthropathy may be due to a bidirectional cause-and-effect relationship. Chronic pain negatively affects mood, but on the other hand it is well established that depression can reduce pain tolerance and lead to heightened pain perception. Both the articular and psychological aspects independently influence QoL. However,

in our analysis, joint pain played a more significant role than psychiatric symptoms.

Among the limitations of our study, the observational design allowed for the identification of associations between variables but did not establish cause-and-effect relationships. Moreover, the single evaluation of AIMS depression questionnaires does not provide a comprehensive assessment of the patients' psychological status and does not permit a full-fledged diagnosis of depression. Also, our sample size is not sufficient to draw firm conclusions regarding the prevalence of specific causes of death. As such, our findings should be interpreted within the context of the existing literature and viewed as contributing to a broader body of evidence aimed at better understanding mortality patterns in this population. The absence of radiological evaluations may contribute to the underdiagnosis of asymptomatic osteoarthrosis, which is very common in acromegalic population and may affect joint pain and QoL.[45]

Conclusions

Acromegaly is a systemic condition that presents with numerous complications, many of which can be mitigated through effective biochemical control. However, joint and psychiatric complications appear to be largely independent of biochemical disease control and continue to negatively impact quality of life. To reduce the overall burden of the disease, these complications require targeted investigation and personalized management.

We identified female sex as a factor associated with more severe joint involvement at diagnosis and as a predictor of worsening joint symptoms over time. The worsening of articular complications was associated with RT, although this correlation might be explained by a longer time since diagnosis.

Depression scores generally improved with the achievement of disease remission, whereas arthropathy scores also tended to improve in recurrent disease, suggesting a complex interaction between IGF1 and joint symptoms. Additionally, dopamine agonists appeared to be associated with an increase and worsening of depression scores, although this effect warrants confirmation through controlled trials. Arthropathy exerted a greater and independent impact on QoL than mood disorder.

Considering the reported suicide rate in our acromegalic population, especially if confirmed in future dedicated studies, the use of psychological questionnaires may be evaluated as a screening tool in clinical practice. These findings underscore the importance of assessing and monitoring the psychological status of acromegalic patients, which, as shown in previous studies,[46,47] is essential for planning an appropriate rehabilitation program and, if confirmed, may also guide medical therapy.

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Authors' contributions

Biagio Cangiano (Conceptualization, Data curation, Investigation, Methodology, Project administration, Visualization, Writing—original draft [equal]), Matteo Corbetta (Data curation, Methodology, Visualization, Writing—original draft [equal], Investigation [supporting]), Caterina Premoli (Data curation, Investigation, Writing—review & editing [equal]), Davide Soranna (Formal analysis [lead], Investigation, Visualization, Writing—review & editing [equal]), Giovanni Vitale (Investigation, Methodology [equal], Writing—review & editing [supporting]), Silvia Grottoli (Funding acquisition, Investigation, Resources, Supervision, Writing—review & editing [equal]), Valeria Cambria (Data curation, Investigation, Writing—review & editing [equal]), Pietro Maffei (Funding acquisition, Investigation, Resources, Supervision, Writing—review & editing [equal]), Francesca Dassie (Data curation, Investigation, Writing—review & editing [equal]), Salvatore Cannavò (Funding acquisition, Investigation, Resources, Supervision, Writing—review & editing [equal]), Marta Ragonese (Data curation, Investigation, Writing—review & editing [equal]), Antonella Zambon (Formal analysis, Investigation, Writing—review & editing [equal]), Marco Bonomi (Investigation, Resources, Supervision, Writing—review & editing [equal]), Luca Persani (Funding acquisition, Investigation, Resources, Supervision, Writing—review & editing [equal]), Letizia Maria Fatti (Conceptualization, Investigation, Methodology, Project administration, Writing—review & editing [equal]), and Massimo Scacchi (Conceptualization, Investigation, Methodology, Writing—review & editing [equal])

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Data availability

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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