QUALITY OF LIFE IN PATIENTS WITH ACROMEGALY – A ROMANIAN SINGLE CENTER CROSS-SECTIONAL STUDY

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Abstract

Context. Acromegaly, a severe condition characterized by excessive and unmodulated secretion of growth hormone, leads to morphologic disturbances and multisystem complications.

Objective. The purpose of this study was to evaluate the quality of life (QoL) in patients with acromegaly compared to matched obese patients.

Design. This was an observational cross-sectional study.

Subjects and methods. We enrolled 49 patients with acromegaly and 49 obese patients. AcroQoL (acromegaly QoL questionnaire) was applied to all patients and IGF-1 (type 1 insulin-like growth factor 1) was measured.

Results. Patients with acromegaly had a worse QoL compared to patients with obesity (score= 77(53-86) vs. 96(90-102), $p<0.001$). In the group of patients with acromegaly, there was no difference in the QoL regarding the activity of the disease (active, controlled, or cured). Men had a higher AcroQoL score than women (score= 88(55-95) vs. 74(52.75-82), $p=0.02$), but there was no difference between patients with microadenomas and the ones with macroadenomas (score= 82(66-88.5) vs. 73(55-83), $p=0.136$). The most frequent complications were cardiovascular complications (81.63%), articular complications (73.46%), dyslipidemia (65.30%) and digestive complications (63.26%).

Conclusions. Despite complex treatment and hormonal control, the presence of complications reduces the quality of life in patients with acromegaly, even when compared with obese patients.

Keywords: acromegaly, quality of life, AcroQoL score.

INTRODUCTION

Acromegaly, a rare, chronic disease, caused by hypersecretion of GH, in the majority of cases due to a pituitary adenoma, is a severe debilitating disease

due to its slowly progressive nature. It causes acral and facial changes that may or may not be perceived by the patient. As a result, being frequently under-recognized, it is also under-diagnosed. Moreover, the effects of prolonged secretion of GH and IGF-1 lead to severe systemic complications that influence morbidity, QoL and mortality (1-4).

Among the most debilitating complications of acromegaly are: cardiovascular, respiratory, cerebrovascular, metabolic and neoplastic complications, altogether with diabetes mellitus (5). These complications may persist even in successfully controlled patients and are associated with increased morbidity and mortality (6).

Nowadays, the treatment of acromegaly starts, in most cases, with surgery (transsphenoidal or transcranial) and is completed by medical treatment (first generation SSA (somatostatin analogs), dopamine agonists, second-generation SSA or GH receptor antagonists) and $\pm$ or radiotherapy (RT) (7).

Even though the actual treatment is efficient in reducing GH-hypersecretion, it is important to take into consideration that the disease itself, in association with the patient's perception of the disease, altogether with the type of therapeutic approach, duration of the disease until diagnosis and the time needed to achieve hormonal control or cure, may have an important impact on the patients' compliance and health-related QoL (4, 7-9). On the other hand, patients' satisfaction can make a change in their own perception of the quality of life.

The aim of this study was to assess the QoL of patients with acromegaly in comparison with patients with obesity and also to evaluate if the disease status (active, controlled under medical treatment or cured) and the presence of complications influence QoL, by using a specific tool: the Acromegaly Quality of Life Questionnaire (AcroQoL).

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MATERIAL AND METHODS

Study design

This was an observational cross-sectional case-control study that assessed the quality of life (QoL) of patients with acromegaly *versus* subjects with obesity (controls).

Subjects

Each of the acromegaly and the control group included 49 subjects, 36 women (73.4%) and 13 men (26.6%). Patients with acromegaly were admitted to the Department of Endocrinology, at the Clinical Emergency County Hospital in Cluj-Napoca, between 2015 and 2017. Subjects with obesity were clinically healthy volunteers, who were selected from the patients who addressed the Department of Endocrinology, after excluding other endocrinological causes of obesity (Cushing's syndrome, diabetes mellitus etc), by performing anamnesis, objective examination and hormonal and biochemical assays (8 a.m. cortisol, glycaemia, etc). Beside these subjects, we identified other clinically healthy obese volunteers using convenience sampling, by performing anamnesis, objective examination, and medical file history check. The controls were not relatives of acromegaly patients admitted in hospital. We excluded those with history or current diagnosis of major psychiatric disorders (anxiety-depressive syndrome, dementia, and schizophrenia), stroke, uncontrolled systemic arterial hypertension, traumatic brain injury, major stressful life events. The controls were interviewed between 2015 and 2018. They were matched for age, sex, education, place of living (urbane environment *versus* countryside) and studies (elementary school/high school *versus* university) with the acromegaly group.

We included subjects aged between 18 and 70 years old, who signed the informed consent form. Among the acromegaly group, we included patients with active disease, controlled under medication, or patients who were cured after therapy. Patients with pituitary deficits were included only if they were properly treated with replacement therapy. We excluded subjects with empty-sella, with non-secreting adenomas, or with other types of pituitary tumors, excepting the co-secreting adenomas (GH-PRL (prolactin), GH-ACTH (adrenocorticotrophic hormone). Moreover, we included patients newly-diagnosed (untreated) and patients treated with surgery and/or radiotherapy and/or medical treatment.

The clinical and biochemical data of patients

with acromegaly were obtained from the Department of Endocrinology database.

Clinical and demographic evaluation

In all cases, the positive diagnosis of acromegaly was based on signs and symptoms of disease activity (extremities undergoing expansion, characteristic facial changes, arthralgia, asthenia, signs of pituitary tumor expansion: neuro-ophthalmic syndrome, headache, signs of pituitary insufficiency), on the hormonal demonstration of a nonsuppressible GH on an OGTT (oral glucose tolerance test), concerning nadir GH > 1 ng/mL in non-diabetic patients or mean GH/24 hours > 2.5 ng/mL in diabetic patients, and an IGF-1 level above the age/sex-matched normal.

The etiological diagnosis was based on the presence of a pituitary adenoma on the MRI (magnetic resonance imaging). Pituitary adenomas were classified according to size in microadenomas (< 10 mm diameter) and macroadenomas ($\geq$ 10 mm diameter).

Controlled acromegaly, in terms of drug and surgical therapy, was defined as: controlled symptomatology, nadir GH < 1 ng/mL on OGTT or mean GH/ 24 hours < 2.5 ng/mL and normal levels of IGF-1 age/sex-matched (optimally controlled), or nadir GH > 1 ng/mL on OGTT or mean GH/24 hours > 2.5 ng/mL, which reduced more than 50% to the level at diagnosis, and high level of IGF-1, which reduced more than 50% to the level at diagnosis (partially controlled), respectively. In order to eliminate the bias which may have been present due to the high number of subgroups with a small number of subjects, the optimally controlled subgroup and partially controlled subgroup were evaluated as one group, the controlled group. Uncontrolled acromegaly was defined as: specific symptomatology for active acromegaly, nadir GH > 1 ng/mL on OGTT or mean GH/24 hours > 2.5 ng/mL, which did not reduce more than 50% to the level at diagnosis, and high level of IGF-1, which did not reduce more than 50% to the level at diagnosis. Cured acromegaly was defined as nadir GH < 0.4 ng/mL on OGTT and normal age/sex-matched IGF-1 levels. The patients were declared cured at least 6 months before they were introduced in the study.

The following demographic data were recorded: sex, age, age at diagnosis, educational status, place of origin, disease status, previous and current therapy (surgery, medical treatment with SSA – octreotide long-acting release (Sandostatin LAR) or lanreotide prolonged-release (Somatuline PR or Somatuline Autogel), dopamine agonists (Cabergoline)

and growth hormone receptor antagonist – pegvisomant (Somavert)), tumor characteristics and comorbidities.

Assessment instruments

Quality of life was assessed using the Acromegaly Quality of life Questionnaire (AcroQoL), specifically designed for patients with acromegaly, which measured and evaluated the frequency of occurrence or the degree of the subject's agreement with the items, all in the subject's perception. The questionnaire contained 22 questions, of which 8 items for the physical dimension (PHY) and 14 items for psychological dimension (PSY). The latter items were further divided into 2 subcategories (7 items for appearance (PSY/APP) and 7 items for personal relations (PSY/PER)). The questionnaire had five possible responses (from 1 to 5) scored on a Likert-type scale, with a minimum score of 22 points and a maximum score of 110 points. For each, the higher the score, the better the quality of life.

Hormonal assays

Serum IGF-1 (ng/mL) level was measured at 8AM by a chemiluminescent immunometric assay, using an IMMULITE 1000 Analyzer (Siemens, Erlangen, Germany) (intraassay coefficient of variation (CV), 3.1-4.3%; interassay CV, 5.8-8.4%; calibration range, up to 1600 ng/mL; analytical sensitivity, 20 ng/mL). The different age/sex-matched normal ranges were excluded by expressing IGF-1 level as a percentage of the upper limit of the normal range (ULN). Serum GH level was measured by Diametra HGH ELISA kit (Segrate, Italy) (intraassay CV, 3.1-5.5%; interassay CV, 4.5-7%; analytical sensitivity, up to 0.105 μ IU/mL), using a STAT FAX 3200 Analyzer. Basal values of GH were used, in order to overcome GH changing methodology for diabetic or non-diabetic patients.

Ethical considerations

The study protocol was designed in accordance with the ethical guidelines of the 1975 Declaration of Human Rights in Helsinki and was approved by the "Iuliu Hațieganu" University of Medicine and Pharmacy Ethics Committee.

Statistical evaluation

The statistical analysis was performed using R version 3.2.3. Normal distribution of continuous numeric variables was assessed with Shapiro-Wilk test and quantile-quantile plots. Quantitative variables were expressed as mean $\pm$ SD (standard deviation),

if normally distributed, and as median (25th-75th percentile), if not. Categorical variables were expressed as percentages and counts. Chi-square and Fisher exact tests were used in order to analyze the differences between independent groups of categorical variables. Comparisons between groups of quantitative variables were performed using Student t test for independent variables (when comparing two groups of normally distributed variables) and using ANOVA test (when comparing three or more groups of normally distributed variables). Tukey-Kramer test was used for further analysis of normally distributed variables. In the case of non-normally distributed variables, the Mann-Whitney U test was used (in order to compare two variables) and the Kruskal-Wallis test (to compare three or more variables). A value of $p < 0.05$ was considered to have statistical significance, and for all tests, the two-tailed p-value was used.

RESULTS

Subject characteristics

The mean age at diagnosis was 45.10 ± 11.68 years old for patients with acromegaly. Mean age at the time of inclusion in the study was 52.32 ± 10.98 years old for patients with acromegaly *versus* 50.97 ± 10.98 years old for subjects with obesity, $p = 0.54$. Table 1 provides a general view of the subjects' characteristics.

AcroQoL in patients with acromegaly versus controls

Patients with acromegaly had a lower quality of life than patients with obesity (total score: 77 (53-86, Q1-Q3) in acromegaly *versus* 96 (90-102, Q1-Q3) in controls, $p < 0.001$). Moreover, the physical dimension and also the psychological dimension were lower in the acromegaly group than in the control group (physical score: 26 (18-29, Q1-Q3) in acromegaly *versus* 33 (30-36, Q1-Q3) in control group, $p < 0.001$, psychological score: 50 (35-88, Q1-Q3) in acromegaly *versus* 63 (60-67, Q1-Q3) in control group, $p < 0.001$).

AcroQoL in patients with acromegaly

a) Demographic and tumor characteristics

There was no difference among the AcroQoL scores of patients with active, controlled or cured acromegaly (Table 2). Women had lower scores than men concerning the physical dimension and appearance. Patients with elementary school / high school studies had lower scores than patients with university studies. Patients living in cities had higher scores than patients

living in the countryside. There was no difference between patients diagnosed before 40 years old and patients diagnosed after 40 years old (Table 3).

Patients with microadenomas had higher scores than patients with macroadenomas, but patients with GH-only secreting adenomas had similar scores

Table 1. General demographic characteristics in subjects with acromegaly *versus* controls

	Patients	Controls	p
Age at diagnosis (y)	45.10±11.68	-	-
Women (y) (n=36)	47.25±10.64	-	0.03
Men (y) (n=13)	39.15±12.77	-	
Age at inclusion (y)	52.32±10.98	50.97±10.98	0.545
Women (y) (n=36)	53.61±10.19	52±10.52	0.456
Men (y) (n=13)	48.76±12.68	48.73±12.21	1
Educational status			
Elementary school/high school, n (%)	41 (83.7)	27 (55.1)	-
University, n (%)	8 (16.3)	22 (44.9)	-
Place of origin			
Countryside, n (%)	22 (44.9)	24 (48.9)	-
Cities, n (%)	27 (55.1)	25 (51.1)	-

Abbreviations: y = years.

Table 2. AcroQoL scores in patients with active, cured and controlled acromegaly

AcroQoL	Active (n=26)	Controlled (n=15)	Cured (n=8)	p
Physical dimension	26 (19-30.75)	26 (17-29)	25 (17.5-26.5)	0.579
Psychological dimension	52 (34.25-59)	46 (35.5-55)	43.5 (36.75-51.5)	0.454
Appearance	22 (17-28)	21 (16-24)	19.5 (14.75-23)	0.541
Personal relations	29.5 (19.25-33)	26 (16-32)	24.5 (21.75-28.25)	0.518
Total score	80 (53.25-88)	73 (52.5-83.5)	69 (56-78.25)	0.483

Legend: results are expressed as median (interquartile range Q1-Q3).

Table 3. Comparison considering gender, studies and place of living in patients with acromegaly

AcroQoL scores	Women (n=36)	Men (n=13)	p
Physical dimension	23.5 (17.75-28)	30 (21-34)	0.025
Psychological dimension	47 (34-54.25)	58 (38-62)	0.056
Appearance	20 (16-23.25)	27 (22-29)	0.017
Personal relations	26.5 (19.5-30.25)	30 (19-33)	0.358
Total score	74 (52.75-82)	88 (55-95)	0.02
	Elementary school / high school (n=41)	University (n=8)	
Physical dimension	25 (17-29)	29.5 (24.75-32)	0.06
Psychological dimension	45 (34-55)	58.5 (55-61.25)	0.009
Appearance	20 (16-24)	26.5 (23.5-29.25)	0.006
Personal relations	24 (18-30)	32 (29.25-32.25)	0.042
Total score	73 (53-83)	86.5 (81.75-89.5)	0.013
	Countryside (n=22)	City (n=27)	
Physical dimension	19 (15.25-27.5)	27 (21-30.5)	0.025
Psychological dimension	37.5 (33-48.75)	54 (48-60)	0.002
Appearance	16.5 (15-20.75)	23 (20.5-28)	0.001
Personal relations	21.5 (17.25-27)	30 (27-33)	0.01
Total score	56.5 (50.5-80.5)	80 (74-88.5)	0.009
	Age at diagnosis <40 y (n=5)	>40 y (n=44)	
Physical dimension	21 (21-28)	26 (17.75-29.25)	0.869
Psychological dimension	58 (46-61)	49.5 (34-57)	0.192
Appearance	29 (20-29)	21 (16-24.25)	0.095
Personal relations	29 (26-32)	27.5 (18.75-32)	0.667
Total score	82 (67-86)	77 (53-85.25)	0.39

Legend: results are expressed as median (interquartile range Q1-Q3). Abbreviations: y = years.

compared to patients with multiple hormonal secretions (Table 4).

b) Complications

Forty-one (83.7%) patients had complications due to acromegaly itself or due to the treatment (Fig. 1), and presented significant impairment of quality of life. The most debilitating complications that reduced QoL were cardiovascular complications (83.6% of patients), type 2 diabetes mellitus (38.77% of patients), dyslipidemia (65.3% of patients) and articular complications (73.46% of patients). The presence of pituitary deficit (63.26% of patients) was not associated with decreased QoL (Table 5).

c) Treatment

Neither surgery nor radiotherapy, nor the type of surgery (transcranial, transsphenoidal, or both) or radiotherapy (cobalt, conventional radiotherapy or gamma-knife) was significantly related to decreased quality of life in patients with acromegaly. Moreover, there was no difference among the types of medical

treatment (SSA, SSA in combination with dopamine agonists or SSA in combination with dopamine agonists and receptor antagonists) (Table 6).

DISCUSSION

In this study we compared patients with acromegaly and subjects with obesity regarding the quality of life, also focusing on hormonal control, using the AcroQoL questionnaire, developed by Webb *et al.* (10).

We chose subjects with obesity due to the fact that a lot of patients with acromegaly are obese and we considered that the comparison is more appropriate, than to use normal-weight people.

We observed that patients with acromegaly had a decreased quality of life, compared to controls in all dimensions of the questionnaire, in opposition with the study of Solomon *et al.*, who did not find any difference in the personal relationships subscale (11).

Compared to the study of Tseng *et al.* (12), the mean age at diagnosis of our patients was higher, suggesting a longer time lag from the onset of the symptoms till the diagnosis of acromegaly, maybe due to a prolonged diagnostic process and a higher number of doctors visited till reaching the final diagnosis (13).

Our study showed that women had lower quality of life than men, concerning psychological score, appearance, and global score, results which are in accordance with other studies (Anagnostis *et al.* (3), Milian *et al.* (8), Postma *et al.* (14), T'Sjoen *et al.* (1), Vandeva *et al.* (4)). Interestingly, acromegalic women in our study had higher scores than in other studies (total score = 74 in our study, *versus* 46.6% in the study of Celik and Kadioglu (15), and 57% in the study of Rowles *et al.* (16)). Like other studies, the least affected

Figure 1. Percentage of patients with acromegaly suffering from complications.

Table 4. AcroQoL considering type of adenoma and type of secretion in patients with acromegaly

AcroQoL scores	Type of adenoma		p
	Macroadenoma (n=33)	Microadenoma (n=15)	
Physical dimension	26 (17-29)	26 (21-29.5)	0.525
Psychological dimension	46 (34-55)	57 (44.5-59)	0.079
Appearance	20 (16-23)	25 (19-28.5)	0.033
Personal relations	26 (18-32)	30 (24.5-32)	0.242
Total score	73 (53-83)	82 (66-88.5)	0.136
	Type of secretion		p
	GH (n=40)	Multiple secretion (n=9)	
Physical dimension	25.5 (18.75-29.25)	26 (18-29)	0.887
Psychological dimension	49.5 (36.75-58.25)	50 (34-51)	0.47
Appearance	21.5 (16-26.25)	19 (16-22)	0.578
Personal relations	27.5 (20.75-32)	28 (18-30)	0.477
Total score	77.5 (54.75-86.5)	77 (52-80)	0.57

Legend: results are expressed as median (interquartile range Q1-Q3).

Table 5. Complications of patients with acromegaly

	Cardiovascular complications		p
	Yes (n=41)	No (n=8)	
Physical dimension	22 (17-29)	30 (26.5-32.5)	0.024
Psychological dimension	45 (34-55)	58.5 (56-60.25)	0.006
Appearance	20 (16-24)	28 (24.5-29)	0.002
Personal relations	24 (18-31)	31 (29.75-32.25)	0.06
Total score	67 (53-83)	86 (81.75-90.75)	0.006
	Type 2 diabetes mellitus		
	Yes (n=19)	No (n=30)	
Physical dimension	19 (17-29)	26 (21-29)	0.069
Psychological dimension	36 (32-49.5)	53.5 (42-59)	0.004
Appearance	16 (13.5-22.5)	22.5 (19-26.75)	0.011
Personal relations	20 (16-28)	30 (23.25-33)	0.003
Total score	54 (50-78.5)	81 (64.75-88.25)	0.008
	Articular complications		
	Yes (n=36)	No (n=13)	
Physical dimension	21 (17-29)	28 (26-34)	0.002
Psychological dimension	40.5 (33-55.25)	58 (49-60)	0.01
Appearance	19.5 (15-75-24)	24 (21-29)	0.012
Personal relations	22.5 (17.75-30.25)	30 (27-33)	0.036
Total score	61.5 (51.5-82.25)	85 (77-95)	0.005
	Dyslipidemia		
	Yes (n=32)	No (n=17)	
Physical dimension	25 (17-28)	29 (19-32)	0.084
Psychological dimension	47 (34-53.25)	57 (39-60)	0.051
Appearance	20.5 (16-23)	25 (17-29)	0.077
Personal relations	26.5 (17.75-30)	30 (21-33)	0.135
Total score	74 (52.75-80.25)	86 (57-91)	0.033
	Digestive complications		
	Yes (n=31)	No (n=18)	
Physical dimension	26 (17.5-29)	25.5 (18.25-30.75)	0.901
Psychological dimension	50 (33.5-55.5)	51 (36.25-58.75)	0.513
Appearance	21 (16-24)	20 (17-27.25)	0.811
Personal relations	28 (18.5-30.5)	28 (21.25-32.75)	0.467
Total score	77 (53-83.5)	80.5 (54-88)	0.513
	Ophthalmological complications		
	Yes (n=9)	No (n=40)	
Physical dimension	22 (21-29)	26 (18-29.25)	0.887
Psychological dimension	54 (27-55)	48.5 (34.75-88)	0.605
Appearance	20 (15-26)	21 (16-25)	0.836
Personal relations	30 (22-33)	27 (18-32)	0.423
Total score	77 (54-83)	77.5 (53-86)	0.846
	Obstructive sleep apnea syndrome		
	Yes (n=25)	No (n=24)	
Physical dimension	21 (18-29)	26.5 (19-29.25)	0.609
Psychological dimension	41 (34-55)	52 (39.5-58)	0.412
Appearance	19 (16-24)	22.5 (18.5-28)	0.226
Personal relations	22 (19-33)	29 (21.75-32)	0.489
Total score	64 (53-85)	80 (58-86.5)	0.373
	Pituitary insufficiency		
	Yes (n=31)	No (n=18)	
Physical dimension	22 (18-29)	27 (18.75-29.75)	0.285
Psychological dimension	48 (33.5-57)	50.5 (42-59.5)	0.217
Appearance	19 (15.5-24.5)	22 (20-27.75)	0.127
Personal relations	27 (18.5-31.5)	29 (21.75-33)	0.442
Total score	75 (53-85)	78.5 (58.75-88.75)	0.237

Legend: results are expressed as median (interquartile range Q1-Q3).

Table 6. Treatment of patients with acromegaly

	Surgery				p
	Yes (n=32)	No (n=17)			
Physical dimension	26 (18-29.25)	22 (18-29)			0.643
Psychological dimension	48.5 (36.75-56.5)	54 (33-59)			0.966
Appearance	21 (16-24.5)	22 (14-25)			0.76
Personal relations	27 (20.75-30.5)	29 (18-32)			0.636
Total score	76 (54.5-85)	79 (53-88)			0.975
Type of surgery					
	No (n=17)	TC (n=6)	TC+TS (n=2)	TS (n=24)	
Physical dimension	22 (18-29)	25.5 (19-32)	22 (20-24)	26 (18.75-29.25)	0.916
Psychological dimension	54 (33-59)	47 (36.5-59)	42.5 (38.25-46.75)	48.5 (37.75-55)	0.946
Appearance	22 (14-25)	22.5 (16.75-26)	19.5 (17.75-21.25)	20.5 (16.75-24.5)	0.955
Personal relations	29 (18-32)	27.5 (16.75-33)	23 (20.5-25.5)	27 (21-30)	0.911
Total score	79 (53-88)	71.5 (56.5-92.5)	64.5 (58.25-70.75)	76.5 (55.25-85)	0.858
Radiotherapy					
	Yes (n=29)	No (n=20)			
Physical dimension	21 (17-29)	27.5 (20.25-31)			0.299
Psychological dimension	41 (34-54)	55.5 (44.75-58.25)			0.218
Appearance	19 (16-23)	23.5 (19.25-28)			0.129
Personal relations	23 (19-33)	30 (24.75-32)			0.333
Total score	64 (53-83)	81.5 (71-88)			0.211
Type of radiotherapy					
	No (n=20)	Co (n=1)	Conv (n=17)	γ-kn (n=11)	
Physical dimension	27.5 (20.25-31)	29 (29-29)	19 (17-26)	28 (20-31)	0.151
Psychological dimension	55.5 (47.75-58.25)	51 (51-51)	38 (33-46)	54 (43-59.5)	0.123
Appearance	23.5 (19.25-28)	21 (21-21)	16 (15-20)	22 (19.5-25.5)	0.085
Personal relations	30 (24.75-32)	30 (30-30)	22 (17-26)	28 (22.5-35)	0.16
Total score	81.5 71-88)	80 (80-80)	57 (50-67)	79 (64.5-89)	0.146
Medical treatment					
	No (n=16)	SSA (n=18)	SSA+C (n=10)	SSA+C+P (n=5)	
Physical dimension	25.5	23.5	28	17	0.826
Psychological dimension	50.5	48	50	41	0.778
Appearance	21.5	20.5	22.5	19	0.734
Personal relations	28	27	28.5	21	0.674
Total score	77	74	80.5	56	0.791

Legend: results are expressed as median (interquartile range Q1-Q3). Abbreviations: TC = transcranial, TS = transsphenoidal, Co = cobalt, Conv = conventional, γ-kn = gamma-knife, SSA = somatostatin analogs, C = cabergoline, P = pegvisomant.

dimension was found in the personal relations subscale (15, 16).

In the study of T'Sjoen *et al.* [1] as in ours, young age did not correlate with improved QoL, in opposition with the studies of Kauppinen-Makelin *et al.* (17) and Biermasz *et al.* (18).

Moreover, we observed that indirect factors, such as education and environment / place of living, have a different impact on patients' QoL. Education seems to make an impact on the quality of life, patients highly-educated having better QoL. Our results are in accordance with Celik and Kadioglu (15) and Kepicoglu *et al.* (7), and in contradiction with Anagnostis *et al.* (3) and Millian *et al.* (8), who observed that education

made no difference in the patients' perception of the quality of life. Also, we observed that low standards of living have a major impact on the quality of life, patients living in the countryside having a lower quality of life than patients living in cities. Interestingly, this aspect is observed in all 4 domains of the questionnaire, even in the personal relations subscale.

Patients with co-secreting adenomas did not have lower AcroQoL scores than patients with only GH-secretion, similar to other studies (Anagnostis *et al.* (3), Fathalla *et al.* (19), Psaras *et al.* (20), T'Sjoen *et al.* (1)). Also, hypopituitarism, with proper hormonal replacement, does not seem to have an impact on QoL, similar to other studies (Anagnostis *et*

al. (3), Biermasz *et al.* (21), Celik and Kadioglu (15), Hatipoglu *et al.* (22), Kecipoglu *et al.* (7), Raappana *et al.* (23), Rowles *et al.* (6), Kauppinen-Makelin *et al.* (17)).

The goal in treating acromegaly is to reduce the dimensions of the pituitary adenoma responsible for the excessive secretion of GH/ IGF-1, to normalize the hormonal secretion and, when possible, to cure the disease. As a result, the new therapeutic approaches may improve mortality and morbidity in patients with acromegaly. However, less importance is given to acromegaly's associated comorbidities and symptoms. As a result, patients' self-perception on quality of life may be distorted consequently leading to a negative impact on the patients' wellbeing (1).

Of all complications associated or due to acromegaly, articular and bone complications (characterized by vertebral fracture risk, bone microarchitecture alteration, bone turnover increase) (24), type 2 diabetes mellitus, dyslipidemia and cardiovascular complications (ventricle functional impairment, especially left ventricular diastolic dysfunction)(25), seem to lower patients' quality of life, by decreasing their performance of daily life activities, cardiovascular disease representing the leading cause of death in these patients (26), accounting for approximately 60% of deaths (27). Interestingly, neither ophthalmological complications, nor obstructive sleep apnea syndrome decreased QoL. Joint dysfunctions seem to have the most severe impact on QoL, even in patients with long-time remission, as presented in the study of Biermasz *et al.* (18). This may explain the greater decrease of QoL in patients from the countryside, who are supposed to have a greater physical activity compared to urban patients.

In general, sleep problems seem to mostly affect patients' quality of life. In acromegalic patients this might be due to obstructive sleep apnea syndrome (OSAS) and joint pain. It was reported that 60-70% of acromegalic patients suffered from OSAS, and many studies showed a decreased AcroQoL score, therefore an impaired quality of life (15, 28). In our study, the percentage of patients with OSAS was smaller (51%), and the quality of life was not worse compared to those without OSAS.

According to our results, pituitary insufficiency, present in 63.26% of our patients, does not lower QoL, but this may be due to the fact that we enrolled only patients with correct hormonal replacement.

Even though IGF-1 represents a marker of mortality in acromegaly, Kreitschmann-Andermahr

et al. suggest that hormonal control does not impact patients' QoL (12).

Regarding the associations of QoL and the use of SSA, the results are contradictory. Some authors suggested that hormonal control does not impact patients' QoL (1, 15, 13), while others reported either that the use of SSA was associated with a worse QoL (4, 14), or a better one (29). In our study, AcroQoL scores did not relate to the status of the disease, and patients with active, controlled, and cured acromegaly had similar scores, confirming the data by T'Sjoen *et al.* (1) and Celik *et al.* (15). The latter suggested that patients have to cope with a long duration of the therapy, the presence of comorbidities, and adjust behaviorally, emotionally, and cognitively. In the case of an inefficient coping strategy, their quality of life might be altered, even in patients with controlled acromegaly who were supposed to have a better quality of life. As a result, we may sustain other authors' hypothesis that similar scores of AcroQoL, in groups with different degrees of hormonal control, may be a result of persistent facial changes independent of the levels of GH and/ or IGF-1 (1).

Moreover, regardless of the type of treatment, in our study there was no improvement in QoL. In contrast, Trepp *et al.* (2) observed that patients with uncontrolled acromegaly had significantly lower scores. Similar results have also been reported in other cross-sectional studies (1, 6, 30). Sardella *et al.* (31) reported an inverse correlation between IGF-1 levels and total AcroQoL score, and so were the results in our study.

In spite of its side effects in time, radiotherapy – which also leads to a decreased activity and motivation, due to an increase in social isolation (26) – was not significantly related to AcroQoL score, similar to the results of T'Sjoen *et al.* (1) and Tseng *et al.* (13) and in opposition with the results of Biermasz *et al.* (21).

One of the relevant limitations of our study was the cross-sectional nature of the study design, which failed to take into consideration the variability of AcroQoL score over time.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. T'Sjoen G, Bex M, Maiter D, Velkeniers B, Abs R. Health-related quality of life in acromegalic subjects: data from AcroBel, the Belgian Registry on acromegaly. *EJE*. 2007; 157: 411-417.

2. Trepp R, Evertst R, Stettler C, Fischli S, Allemann S, Webb SM, Christ ER. Assessment of quality of life in patients with uncontrolled vs. controlled acromegaly using the acromegaly Quality of Life Questionnaire (AcroQoL). *Clin Endocrinol (Oxf)*. 2005; 63: 103-110.
3. Anagnostis P, Efstathiadou ZA, Charizopoulou M, Selamatzidou D, Karathanasi E, Poulasouchidou M, Kita M. Psychological profile and quality of life in patients with acromegaly in Greece. Is there any difference with other chronic diseases? *Endocrine*. 2014; DOI 10.1007/s12020-014-0166-5.
4. Vandeva S, Yaneva M, Natchev E, Elenkova A, Kalinov K, Zacharieva S. Disease control and treatment modalities have impact on quality of life in acromegaly evaluated by Acromegaly Quality of Life (AcroQoL) Questionnaire. *Endocrine*. 2015; DOI 10.1007/s12020-014-0521-6
5. Kauppinen-Makelin R, Sane T, Sintonen H, Markkanen H, Valimaki MJ, Loyttyniemi E, Niskanen L, Reunanen A, Stenman UH, the Finnish Acromegaly Study Group. Quality of life in treated patients with acromegaly. *J Clin Endocrinol Metab*. 2006; 91(10): 3891-3896.
6. Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ. Quality of life (QoL) in patients with acromegaly is severely impaired: use of a novel measure of QoL: acromegaly quality of life questionnaire. *J Clin Endocrinol Metab*. 2005; 90: 3337-3341.
7. Kepicoglu H, Hatipoglu E, Bulut I, Darici E, Hizli N, Kadioglu P. Impact of treatment satisfaction on quality of life of patients with acromegaly. *Pituitary*. 2013; DOI 10.1007/s11102-013-0544-7.
8. Milian M, Honegger J, Gerlach C, Psaras T. Health-related quality of life and psychiatric symptoms improve effectively within a short time in patients surgically treated for pituitary tumors – a longitudinal study of 106 patients. *Acta Neurochir*. 2013; 155: 1637-1645.
9. Hua SC, Yan YH, Chang TC. Associations of remission status and lanreotide treatment with quality of life in patients with treated acromegaly. *Eur J Endocrinol*. 2006; 155(b): 831-837.
10. Webb SM, Prieto L, Badia X, Albareda M, Catala M, Gaztambide S, Lucas T, Paramo C, Pico A, Lucas A, Halperin I, Obiols G, Astorga R. Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. *Clin Endocrinol (Oxf)*. 2002; 57: 251-258.
11. Solomon E, Branisteanu D, Dumbrava A, Solomon RG, Kiss L, Glod M, Preda C. Executive functioning and quality of life in acromegaly. *Psychol Res Behav Manag*. 2019; 12: 39-44.
12. Tseng FY, Chen ST, Chen JF, Huang TS, Lin JD, Wang PW, Sheu WHH, Chang TC. Correlations of clinical parameters with quality of life in patients with acromegaly: Taiwan Acromegaly Registry. *J Formos Med Assoc*. 2019; 118: 1488-1493.
13. Kreitschmann-Andermahr I, Buchfelder M, Kleist B, Kohlmann J, Menzel C, Buslei R, Koltowska-Haggstrom M, Strasburger C, Siegel S. Predictors of quality of life in 165 patients with acromegaly: results from a single-center study. *Endocr Pract*. 2017; 23: 79-88.
14. Postma MR, Netea-Maier RT, van den Berg G, human J, Sluiter WJ, Wagenmakers MA, van den Bergh ACM, Wolffebuttel BHR, Hermus AdRMM, van Beek AP. Quality of life is impaired in association with the need for prolonged postoperative therapy by somatostatin analogs in patients with acromegaly. *EJE*. 2012; 166: 585-592.
15. Celik O, Kadioglu P. Quality of life in female patients with acromegaly. *J Endocrinol Invest*. 2013; 36: 412-416.
16. Rowles SV, Badia XP, Shalet SM, Webb SM, Trainer PJ. Quality of life (QoL) in patients with acromegaly is severely impaired: use of a novel measure of QoL: Acromegaly Quality of Life Questionnaire. *J Clin Endocrinol Metab*. 2005; 90: 3337-3341.
17. Kauppinen-Makelin R, Sane T, Sintonen H, Markkanen H, Valimaki MJ, Loyttyniemi E, Niskanen L, Reunanen A, Stenman UH. Quality of life in treated patients with acromegaly. *J Clin Endocrinol Metab*. 2006; 91: 3891-3896.
18. Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. *J Clin Endocrinol Metab*. 2005; 90: 2731-2739.
19. Fathalla H, Cusimano MD, Alsharif OM, Jing R. Endoscopic transsphenoidal surgery for acromegaly improves quality of life. *Can J Neurol Sci*. 2014; 41(6): 735-741.
20. Psaras T, Milian M, Hattermann V, Will BE, Tatagiba M, Honegger J. Predictive factors for neurocognitive function and quality of life after surgical treatment for Cushing's disease and acromegaly. *J Endocrinol Invest*. 2011; 34(7): e168-177.
21. Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA, Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *J Clin Endocrinol Metab*. 2004; 89(11): 5369-5376.
22. Hatipoglu E, Yuruyen M, Keskin E, Yavuzer H, Niyazoglu M, Doventas A, Erdinciler DS, Beger T, Kadioglu P, Gundogdu S. Acromegaly and aging: a comparative cross-sectional study. *Growth Horm IGF Res*. 2015; 25(1): 47-52.
23. Raappana A, Pirila T, Ebeling T, Salmela P, Sintonen H, Koivukangas J. Long-term health-related quality of life of surgically treated pituitary adenoma patients: a descriptive study. *ISRN Endocrinol*. 2012; 2012:675310 doi: 10.5402/2012/675310.
24. Gheorghiu ML. News in acromegaly. *Acta Endocrinol (Buchar)*. 2017; 13(1): 129-130.
25. Natchev E, Kundurdjiev A, Zlatareva N, Vandeva S, Kirilov G, Kundurzhiev T, Zacharieva S. Echocardiographic myocardial changes in acromegaly: a cross-sectional analysis in a tertiary center in Bulgaria. *Acta Endocrinol (Buchar)*. 2019; 5(1): 52-61.
26. Szczesniak D, Jawiarczyk-Przyłowska A, Rymaszewska J. The quality of life and psychological, social and cognitive functioning of patients with acromegaly. *Adv Clin Exp Med*. 2015; 24(1): 167-172.
27. Mizera L, Elbaum M, Daroszewski J, Bolanowski M. Cardiovascular Complications of Acromegaly. *Acta Endocrinol (Buchar)*. 2018; 14(3): 365-374.
28. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. *Endocr Rev*. 2004; 25: 102-150.
29. Geraedts VJ, Andela CD, Stalla GK, Pereira AM, van Furth WR, Sievers C, Biermasz NR. Predictors of quality of life in acromegaly: no consensus on biochemical parameters. *Front Endocrinol (Lausanne)*. 2017; 8: 40.
30. Webb SM, Badia X, Surinach NL, Spanish AcroQoL Study Group. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study. *EJE*. 2006; 155: 269-277.
31. Sardella M, Lombardi M, Rossi G, Cosci C, Brogioni S, Scattina I, Webb SM, Gasperi M, Martino E, Bogazzi F. Short and long term changes of quality of life in patients with acromegaly: results from a prospective study. *J Endocrinol Invest*. 2010; 33: 20-25.