



## Original Article

## Quality of Life in Acromegaly Disease Among Iranian Population: One Longitudinal Before-After Study

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## ABSTRACT

**Background:** The current study aimed to determine the quality of life (QoL) scores before and after treatment in patients with acromegaly.

**Methods:** In this longitudinal before-after study, the acromegaly quality of life (AcroQoL) questionnaire was used to assess the QoL. Demographics, clinical manifestations and co-morbidity data, pituitary axis involvement, biochemical and hormonal component tests, and health-related quality of life (HRQoL) before and after treatment (endoscopic transsphenoidal surgery, medication, radiotherapy) were evaluated in patients over 18 years of age. To compare the mean of continuous data, the independent t and Mann-Whitney tests were used. To compare the mean QoL score before and after the study, the paired-t and Wilcoxon tests were performed. The significance level was set at  $P < 0.05$ .

**Results:** Among 80 patients with acromegaly who underwent trans-sphenoid surgery with or without radiotherapy or medication therapy with somatostatin analogs, 52 (65%) entered the remission phase within 6 months. Associations were found between the remission phase and female gender ( $P = 0.004$ ) and lower growth hormone (GH) ( $P = 0.04$ ) but not between remission and lower insulin-like growth factor-I (IGF1) after surgery ( $P = 0.02$ ) or gonadal axis disorder after treatment ( $P < 0.001$ ) statistically. Moreover, a significant association was found between not being in the remission phase and gonadal axis disorder before treatment ( $P = 0.04$ ). The QoL score in all dimensions of the AcroQoL questionnaire increased 6 months after treatment ( $P < 0.001$ ). Total AcroQoL score was higher after treatment in the remission group ( $P = 0.03$ ). The psychological scale had a significantly higher score both on the total scale ( $P < 0.001$ ) and on the two subscales of appearance ( $P < 0.001$ ) and personal relationship ( $P = 0.003$ ).

**Conclusion:** Because of the importance of QoL in acromegaly patients, further studies in this field are recommended.

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## Introduction

Acromegaly is a chronic disease characterized by excessive levels of growth hormone (GH) and insulin like growth factor-I (IGF-I) secretion which increase morbidity and mortality mostly through cardiovascular,

metabolic, and neoplastic complications [1]. Acromegaly usually affects middle-aged adults, though it can exist at any age. The most common symptom of acromegaly is enlargement of the feet, hands, and/or face due to abnormal growth of bones, cartilage, and other body tissues. Because acromegaly tends to occur gradually, early signs may not be obvious for years [2, 3]. Common treatment methods cure most patients with acromegaly including trans-sphenoidal surgery as a first option in

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many cases, radiotherapy when tumor cells remain after surgery, or if the tumor extends beyond the pituitary gland, medical treatment with dopamine agonists (DA), somatostatin analogs (SSA), or GH receptor antagonist (GHRA) drug (pegvisomant) in many patients use to control GH and IGF-1 levels throughout their lives [4]. The initial focus on reducing mortality and improving morbidity as well as normalizing biochemical target values include IGF-I and GH, in patients with acromegaly has shown successful results [5, 6]. Nevertheless, disease activity by biochemical control of hormones is not yet clear [7]. It is expected that by correcting hormone levels with appropriate treatment, the condition and quality of life score in acromegaly patients will be improved; however, various studies on other treatment modalities have been too limited to design conclusions on the effects on QoL [7]. It seems other factors, such as treatment approach, concomitant co-morbidities, disease duration, or lifestyle, body image, pain, depression, energy and strength level, could also affect QoL [8]. The aim of this study was to demonstrate the quality of life (HRQoL) in patients with acromegaly before and after surgery and other treatments in remission and non-remission groups in one tertiary hospital in Tehran, Iran.

## Material and Methods

This longitudinal before-after study was conducted on patients with acromegaly disease between 2016 to 2020 in the subspecialized hospital Loghman Hakim Center, Tehran, Iran. Patients over 18 years of age who were selected for the study through convenience sampling underwent endoscopic trans-sphenoidal surgery (ETSS) with or without radiotherapy and medication with somatostatin analogs with or without cabergoline. Surgical procedures were performed by four skilled neurosurgeons. The data collected comprised demographic characteristics (age, sex), background diseases (diabetes, hypertension, or sleep apnea syndrome confirmed by polysomnography test), MRI results (postoperative and 3 and 6 months after surgery to ensure total excision and removal of the adenoma), and lab tests (biochemical tests included GH and IGF-1 levels, other pituitary axes of prolactin, free T4, thyrotropin, thyroid-stimulating hormone [TSH], cortisol, adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], testosterone) before and after surgery, treatment type and monitoring of improvement in hormonal levels of pituitary axes were recorded.

Biochemical remission was defined as normal IGF-1 level and either a suppressed GH serum level less than 0.4 ng/mL during an oral glucose tolerance test or a random GH level less than 1.0 ng/mL at least 3 months after surgery using the 2010 consensus criteria for biochemical remission. Control or remission during treatment with somatostatin analogs or cabergoline was defined by a normal serum IGF-I level for age [9]. Hypothyroidism was considered when the following biochemical features were observed: low T4 in association with disproportionate or decreased TSH, central adrenal insufficiency in the form of cortisol levels

less than 5 µg/dl in combination with disproportionate or reduced ACTH, central hypogonadism with regard to low testosterone levels combined with disproportionate or reduced LH in men, oligo-menorrhea in premenopausal women, and FSH lower than normal in postmenopausal women (normal menopause was defined by FSH > 30 mIU/mL) was considered as central hypogonadism. In the next step, a suitable hormone replacement therapy was performed for cases with laboratory and clinical symptoms of hypopituitarism.

## Quality of Life Assessment

For the first time in Iran, the AcroQoL questionnaire was used in this study to assess QoL in patients with acromegaly. The Acromegaly Quality of Life Questionnaire (ACROQOL) is the first acromegaly-specific HRQOL measure to be designed. This questionnaire includes 22 items, mostly evaluating three dimensions: patients' physical function, appearance, and personal relationships. Each item is scored on a 1–5 Likert scale (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree). The maximum score is 110 (100%), corresponding to the best QoL, while the minimum score is 22 (0%), corresponding to the worst condition (results are quoted as a percentage) [10, 11]. To localize the AcroQoL questionnaire in assessing the quality of life of patients with acromegaly disease, first, the English version of this questionnaire was translated into Persian by three translators using the forward-backward method. Then, its face and content validity were calculated. Content validity was evaluated using the Lawshe model. The questionnaire was sent to six specialists, comprising neurosurgeons, an endocrinologist, and a social medicine specialist, who expressed their opinions in three areas of necessity, clarity, and simplicity of questions. Then, the votes of the panel members were quantified by calculating the content validity ratio (CVR), and by placing in the content validity index (CVI) calculation formula, a final index number of 0.97 was obtained. After confirming the content validity, the face validity was determined by giving the final version of the questionnaire to 15 patients and asking them to rate the relevance, simplicity, and clarity of the questions on a four-point scale, as follows: 1) Completely relevant, simple, clear; 2) relevant, simple, clear but requires minor revisions; 3) Requires major revision; 4) Completely irrelevant. Each question was confirmed when either 50% of patients chose the first option, or 70% of them chose the first two options. Therefore, the face validity of the questionnaire was also confirmed [12, 13]. The Guttman split-half coefficient was used to evaluate the reliability, and a correlation coefficient of  $r = 0.9$  was estimated. The AcroQoL questionnaire was completed by patients before surgery and 6 months after surgery. Surgeries were performed by four skilled neurosurgeons with at least five years of surgical experience. All patients provided signed informed consent at the beginning of the study. If for any reason a patient was unavailable after surgery, that person was excluded from the study. All information which obtained from patients remained confidential. This

study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.RETECH.REC.1398.337).

**Statistics**

Values are presented as mean±SD (standard deviation) for continuous variables and as numbers (percentage) for categorical data. Normality of data distribution was evaluated by Kolmogorov–Smirnov’s test. Researchers used the chi square or Fisher’s exact test to analyze categorical data in the two groups of remission and non-remission. We also used the parametric independent test to compare the means of continuous data with normal distribution, and the non-parametric Mann–Whitney test was used to compare the means of non-normally distributed continuous data to compare QoL scores in the two groups of remission and non-remission. The paired-t and Wilcoxon tests were performed to compare the mean QoL scores before and after the study. Significance level was set at P<0.05. All statistical analyses were performed by SPSS version 18.0 (SPSS, Inc.). The cluster bar chart of changes in the hypothalamic-pituitary axis in the remission and non-remission groups of acromegaly patients before and after surgery is shown in Figure 1.

**Results**

In this study, 90 patients with acromegaly underwent surgery sometime during the 4 years from 2016 to 2020. Ten patients who, for whatever reason, did not return to follow-up within 6 months after surgery were excluded. A total of 80 patients were studied, and their symptoms, laboratory tests, and QoL scores in each dimension before and after surgery were assessed using an AcroQoL questionnaire. Participants were assigned to the remission group (52 patients; 42 immediately post-surgery and 10 after adding medication or radiotherapy) or the non-

remission group (n=28) according to the control criteria. Overall, the mean±SD age of patients with acromegaly was 40.05±12.22 years, and 46 (57.5%) of patients were female. The basic characteristics of patients in both groups are detailed in Table 1. There was no difference in age and remission frequency (P=0.1) between the groups, but 36 (69.2) patients in the remission phase were female, which is a statistically significant difference (P=0.004). We also found a significant difference between groups in the remission phase and GH level (P=0.04) and in IGF1 levels after surgery (P=0.02). Table 2 shows a comparison of QoL score according to the AcroQoL questionnaire before and after surgery. There was a statistically significant difference in both the total AcroQoL score and its subgroups before and after surgery. In this longitudinal survey, significant differences between the remission and non-remission phases of acromegaly disease after treatment were seen in the total AcroQoL score (P=0.03), psychological scale (P<0.001), psychological sub-scale “appearance “after treatment (P<0.001), psychological sub-scale “personal relationships “after treatment (P=0.003). In the same analysis, however, no difference between the remission and non-remission groups was seen in the physical scale after treatment (P=0.3) (Table 3). Figure 1 shows the changes in the hypothalamic-pituitary axis in the remission and non-remission groups before and after surgery.

**Discussion**

In this longitudinal before - after study, 65% of patients entered the remission phase within 6 months. Patients with acromegaly before and after surgery with or without other treatment (radiotherapy or medication intake) during the 6 months had scores of 35.22±11.35% and 63.17±11.19%, respectively, on the AcroQoL questionnaire. This result

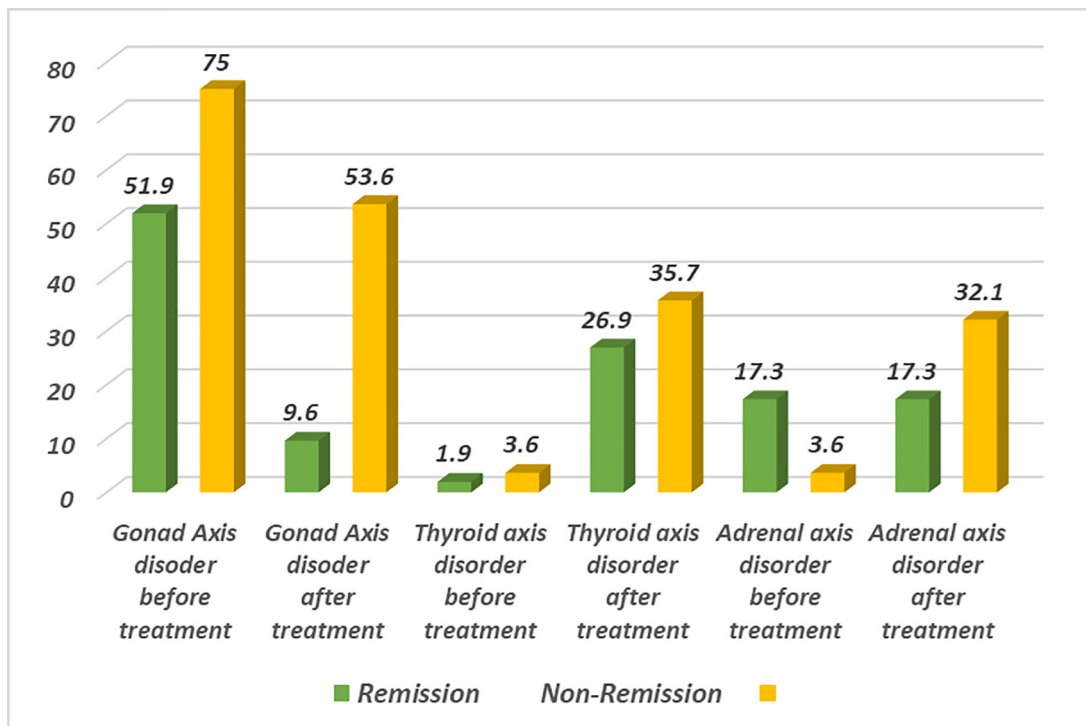


Figure 1: Hypothalamic-pituitary axis changes in acromegaly patients in the remission and non-remission groups before and after treatment

**Table 1:** Comparison of the basic characteristics of acromegaly patients by remission and non-remission group

Variables	Remission 52(65%)	Non-Remission 28(35%)	P value
Age(Years)	40±12.61	39.89±11.68	0.1
Sex			0.004*
Male	16(30.8)	18(64.3)	
Female	36(69.2)	10(35.7)	
BMI	29.37±6.09	31.05±8.36	0.3
Diabetes			0.5
Yes	12(23.1)	8(28.6)	
No	40(76.9)	20(71.4)	
Hypertension			0.5
Yes	13(25)	8(28.6)	
No	39(75)	20(71.4)	
Sleep Apnea Syndrome			0.1
Yes	9(17.3)	19(67.9)	
No	43(82.7)	9(32.1)	
GH(ng/ml) before surgery	16.18±8.11	15.79±9.09	0.9
GH(ng/ml) after surgery	1.17±0.62	3.40±0.84	0.04*
IGF1(ng/ml)before surgery	729.22±60.54	591.55±150.28	0.1
IGF1(ng/ml)after surgery	190.68±94.67	421.65±83.39	0.02*
Gonadal disorder before treatment			0.04*
Yes	27(51.9)	21(75)	
No	25(48.1)	7(25)	
Gonadal axis disorder after treatment			<0.001*
Yes	5(9.6)	15(53.6)	
No	47(90.4)	13(46.4)	
Thyroid axis disorder before treatment			0.9
Yes	1(1.9)	1(3.6)	
No	51(98.1)	27(96.4)	
Thyroid axis disorder after treatment			0.4
Yes	14(26.9)	10(35.7)	
No	36(73.1)	18(64.3)	
Adrenal axis disorder before treatment			0.06
Yes	9(17.3)	1(3.6)	
No	43(82.7)	27(96.4)	
Adrenal axis disorder after treatment			0.1
Yes	9(17.3)	9(32.1)	
No	43(82.7)	19(67.9)	

\*Statistical significance is shown; GH: Growth hormone; IGF1: Insulin like growth Factor-I

**Table 2:** Comparison of quality of life (QoL) scores before and 6 months after treatment

Variables	Before treatment	After treatment	P value
Total AcroQoL score	35.22±11.35	63.17±11.19	<0.001*
Physical scale	31.48±11.54	72.49±7.80	<0.001*
Psychological scale	34.01±8.13	70.59±6.80	<0.001*
Psychological sub-scale “appearance “	38.08±9.95	75.53±6.35	<0.001*
Psychological sub-scale “personal relationships	33.40±10.07	74.28±5.97	<0.001*

QoL: quality of life; AcroQoL: Acromegaly quality of life

**Table 3:** Comparison of quality of life (QoL) scores in remission and non-remission groups after treatment

Variables	Remission	Non-remission	P value
Total AcroQoL score	70.89±11.25	62.52±11.23	0.03*
Physical scale	73.35±7.80	71.72±7.83	0.3
Psychological scale	73.05±5.80	67.88±6.86	<0.001*
Psychological sub-scale “appearance “	78.05±5.61	72.73±6.01	<0.001*
Psychological sub-scale “personal relationships “	76.18±4.64	72.17±6.6	0.003*

AcroQoL: Acromegaly quality of life

confirmed that QoL score was severely impaired in some patients before treatment. Six months after treatment, the total QoL score improved and was obviously higher in the remission group. The QoL score in the non-remission group also increased, although the increase was significantly lower than that of the remission group. Two studies also reported that the biochemical uncontrolled group had a lower HR-QoL score than the controlled

group using the same criteria for defining remission status of acromegaly [14, 15]. However, in another study conducted by Webb and Badia, biochemical control did not necessarily correlate with the patient's perception of a normal quality of life [16]. We found that 69.2% of patients who entered the remission phase were women (P=0.004), which is the same as the result obtained by Matta [4]. Why women show greater improvement than

men entering the remission phase is not known. Perhaps females had fewer hormonal disorders before treatment or presented in an earlier phase of acromegaly. Moreover, GH and IGF-1 levels after treatment were significantly lower in the remission group. Gonadal axis disorder after treatment was higher in the non-remission group, which was related to less improvement in the QoL score in the non-remission group. In a survey by Webb SM, delayed diagnosis of acromegaly was associated with a lower QoL score in the non-remission group compared to the remission group (60±18% vs 78±16%) [16]. In 2014, Fathalla Hin revealed no significant effect of endocrine remission, gross total resection, preoperative tumor size, cavernous sinus invasion, or repeated surgery on any of the QoL total or subscale scores [17]. Although the total QoL score in the remission phase in this survey showed a significant increase compared to the non-remission group, there was no statistically significant difference between the two groups in the physical dimension. Webb SM conducted another study in 2016 in which they demonstrated that the physical dimensions of the AcroQoL score were correlated with weight loss, suggesting that despite being within reference IGF-1 concentrations, some body tissues of patients were “still acromegalic” and benefitted from the addition of GH receptor blockers [18]. In an article published in 2020, Gu J indicated the median overall AcroQoL score increased to 74.5% at 3 months and 77.3% at 6 months ( $P < 0.001$ ) after surgery. At 6-month follow-up, median scores were still less than 70% in appearance, vitality, and mental health dimensions [19]. In the current study, no association was found between diabetes, hypertension, sleep apnea, and rate of remission, while Biermasz NR demonstrated treated and well-controlled patients with persisting co-morbidities had reduced QoL scores [20]. The most prevalent morbidity was joint-related complaints, with about 39-45% of patients reporting them. Another report showed that sleep apnea syndrome affected 60-70% of acromegalic patients and reduced QoL scores in patients [21]. Findings indicate that lower IGF-1 levels have a beneficial effect on upper airway soft tissue [22]. Furthermore, patients in the non-remission phase of acromegaly who had undergone tumor excision by TSS surgery due to lower IGF1 levels and thus lower disease activity showed the better psychological subscale appearance than those who were treated medically only [22, 23]. Despite the results of research, it is not yet known whether a decrease in hypothalamic-pituitary-axis hormone levels after treatment improves quality of life in patients with acromegaly. Because of the low prevalence of this disorder and the small number of patients who have it, studies about the QoL of people with acromegaly should be done with longer time intervals so as to evaluate more patients from different angles. Furthermore, this study represents the first time the Persian version of the AcroQoL questionnaire has been used; therefore, further research with this questionnaire is needed.

## Conclusion

According to the practical AcroQoL questionnaire for

measuring the quality of life of acromegaly patients, it is recommended that further studies be performed with longer follow-up periods and more factors related to improving the quality of life of acromegaly patients.

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**Conflict of Interest:** None declared.

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