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Changes in quality of life in patients with acromegaly after surgical remission — A prospective study using SF-36 questionnaire

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Abstract. Patients with acromegaly have a compromised quality of life (QOL). Modern surgical techniques have improved the surgical cure rate. However, there are no prospective studies reporting postoperative changes in QOL among patients cured solely by surgery. The aim of the present study was to determine the effect of surgery on QOL using the 36-item short form health survey (SF-36) questionnaire. SF-36 scores comprise 3 components: the physical component summary (PCS), the mental component summary (MCS) and role-social component summary (RCS). Included in this prospective cohort were 41 patients with acromegaly who underwent surgery alone and achieved postoperative normalization of insulin-like growth factor-1. All participants completed the SF-36 preoperatively and 1 year postoperatively. Preoperatively, RCS and 4 subscale scores (role physical, social functioning, role emotional, mental health) were below the set standards for the normal population. Postoperatively, the PCS and RCS scores did not change significantly, but the MCS score improved significantly (from 48.1 ± 11.3 to 51.7 ± 8.9, p=0.03). Further we compared the QOL of 26 patients whose nadir GH level was < 0.4 μg/L during postoperative oral glucose tolerance testing (complete remission group) with that of 15 patients whose nadir GH level was ≥ 0.4 μg/L (partial remission group). There were no significant differences between these groups in terms of PCS, MCS, RCS, or any subscale scores. In conclusion, surgical remission mostly improved the participants' mental condition. There was no difference in QOL between patients who achieved the new remission criteria and those who did not.

Key words: Acromegaly, Growth hormone deficiency, Quality of life, SF-36, Transsphenoidal surgery

GROWTH HORMONE (GH) has a wide variety of effects on the physical and mental health [1, 2]. Acromegaly is caused by the hypersecretion of GH and insulin like growth factor-1 (IGF-1), most commonly caused by a GH-secreting pituitary adenoma (GHoma). Patients with acromegaly frequently complain of changes in their facial and acral appearance, and the excessive secretion of GH can also cause serious metabolic disruptions, neoplastic complications, and concurrent illnesses [2]. However, disease control can improve metabolic function, reduce morbidity, and restore life expectancy to normal [3-5].

The introduction of endoscopic and advanced surgical techniques has improved the surgical cure rate of acromegaly [6-8]. However, a new consensus guideline recommends a stricter definition of remission based on normal age- and sex-adjusted IGF-1 levels and GH suppression to < 0.4 μg/L during an oral glucose tolerance test (OGTT) [9]. Nevertheless, we do not know the clinical benefits of these stricter remission criteria, especially regarding patient quality of life (QOL). The present study aimed to assess the effect of surgical treatment on QOL using the 36-item short form health survey (SF-36) questionnaire in a prospec-

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tive cohort comprising patients with acromegaly who underwent surgery alone. We also aimed to compare the postoperative QOL in patients who had achieved remission based on these new criteria with those who had not.

Methods

Ethical considerations

This study's prospective design was approved by the ethical committee of Kagoshima University Hospital (reference no. 402). All data were routinely obtained and essential for the proper management of the patient's pituitary disease. These data were collected and anonymized in a linkable fashion prior to analysis, in order to protect patient privacy.

Patients

Between 2008 and 2015, 66 patients with newly diagnosed acromegaly were treated using transsphenoidal surgery performed by a senior neurosurgeon (K.A.). The surgery was mainly performed using microscopic view and was aided by endoscopic observation. Among these 66 cases, IGF-1 normalization (age- and sex-adjusted IGF-1 standard deviation [SD] < 2.0) was achieved in 54 patients (81.8%). Of these 54 patients, 48 had pre- and post-surgical hormonal levels measured, and 6 were lost to follow-up. Seven patients were excluded from the study: 4 had medication-treated dementia or depression, 1 was from another country, and 2 received preoperative medical treatment for acromegaly. Thus, the study included 41 patients (16 men and 25 women) with an average age of 51.4 ± 14.2 (range: 18–73) years. Hypertension, diabetes mellitus, and hyperlipidemia were defined based on the use of medication(s) to treat these diseases.

Survey methods

Clinical and biochemical examinations were performed pre- and 1-year post- surgery (follow-up visits were completed at 343.2 ± 102.2 days). All 41 patients completed the second Japanese version of SF-36 questionnaire [10] at the assessment. The Japanese SF-36 questionnaire evaluates 36 items regarding a patient's general well-being, and all items have 3–5 possible answers that are scored on a scale of 1–5. The items are scored in 8 subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Based on these 8 subscales, QOL can be evaluated in 3 components: the physical component summary (PCS), the mental component summary (MCS), and the role-social component summary (RCS). The PCS, based primarily on the physical functioning subscale, is derived from the role physical, bodily pain, general health, vitality, and social functioning subscales. The MCS, based primarily on the mental health subscale, is derived from the bodily pain, general health, vitality, and role emotional subscales. The RCS, based primarily on role physical, social functioning, and role emotional subscales, can be derived from four subscales including general health [11, 12]. Higher scores are associated with a better QOL. Data were converted to norm-based scoring in which the scores have a mean of 50 and SD of 10. Norms were derived from a Japanese national survey conducted in 2007 [12]. Because some responses were not given, in 1 case the PCS, MCS, RCS, bodily pain, and social functioning scores and in another case the PCS, MCS, RCS, and general health scores could not be calculated.

We compared the pre- and post- operative SF-36 scores with standardized scores. Then, we evaluated the postoperative changes in SF-36 results. Further, we evaluated the correlation of preoperative PCS, MCS, and RCS scores with age and preoperative IGF-1 SD score (SDS), as well as the correlation between postoperative PCS, MCS, and RCS scores with age, postoperative IGF-1 SDS, and the reduction in IGF-1 SDS. We also evaluated the correlation between postoperative changes in PCS, MCS, and RCS scores and the reduction in IGF-1 SDS.

A preoperative questionnaire was completed by 34 of the 41 participants. In this questionnaire, responses to questions around physical symptoms — headache, joint pain, excessive sweating, and general fatigue — could be given as "not experienced", "mild", "moderate", or "severe". We also assessed the severity of sleep apnea with polysomnography or apnomonitor. The severity of sleep apnea syndrome is shown by the apnea hypopnea index (AHI): the higher the AHI, the greater the severity. The relationship between physical symptoms, the AHI, and the PCS, MCS, RCS scores before surgery was evaluated.

All participants underwent an OGTT 3 months after surgery. Based on that nadir GH level, the patients were divided into 2 groups: the complete remission group or the partial remission group. Cases with complete remission were identified based on a postopera-

tive nadir GH level during the OGTT of < 0.4 μg/L, and those with partial remission were identified based on a postoperative nadir GH level during the OGTT of ≥ 0.4 μg/L. Then, we compared the clinical and biochemical characteristics, and postoperative SF-36 scores between those groups.

Of the 41 cases being investigated, 38 met the old consensus criteria (nadir GH level during OGTT < 1 μg/L and normal levels of IGF-1) [13]. The cases that met the new consensus criteria (nadir GH level during OGTT < 0.4 μg/L) were labeled the "new consensus group" (n = 26) and the cases that met the old consensus criteria but not the new consensus criteria (0.4 μg/L ≤ nadir GH level during OGTT < 1 μg/L) were labeled the "old consensus group" (n = 12). We compared the clinical and biochemical characteristics and postoperative SF-36 scores between these groups.

Assays

The concentration of GH was measured using an electrochemiluminescence immunoassay (Immulite 2000 hGH; Siemens, Erlangen, Germany), with recombinant human GH as the internal standard. The sensitivity of this assay is 0.1 μg/L. The concentration of IGF-1 was measured using an immunoradiometric assay (IGF-1 IRMA "Daiichi"; TFB, Tokyo, Japan), and the raw IGF-1 concentration was assessed according to the IGF-1 SDSs that were calculated based on the Japanese standard IGF-1 values for each sex and age group [14].

Statistical analysis

All statistical analyses were performed using Starflex software (version 6.0; Artech Co. Ltd., Osaka, Japan). The data were analyzed using Wilcoxon signed-rank test, Mann-Whitney's U test, Welch's *t* test, and the chi-squared test or Fisher's exact test, based on the characteristics of the dataset. The correlations of the QOL metrics (PCS, MCS, RCS) with the other factors were evaluated using Spearman's rank-correlation coefficient. Differences with a *p*-value of < 0.05 were considered statistically significant.

Results

Patient preoperative and postoperative clinical and biochemical characteristics are shown in Table 1. All patients were treated with surgery alone to achieve IGF-1 normalization. None of the patients developed overt central hypothyroidism, hypocortisolism, or diabetes insipidus requiring replacement therapy. One patient experienced a spinal fluid leak that required surgical repair, and another experienced a transient abducens nerve palsy that resolved within 3 months.

The preoperative IGF-1 levels ranged from 262.0 μg/L to 1,420.0 μg/L (mean: 611.0 ± 236.2 μg/L), and the preoperative IGF-1 SDSs ranged from 3.0 to 10.63 (mean: 6.62 ± 1.86). There was a significant reduction in postoperative serum IGF-1 levels (from 611.0 ± 236.2 μg/L to 162.9 ± 66.9 μg/L, $p < 0.01$) and IGF-1 SDSs (from 6.62 ± 1.86 to 0.30 ± 0.97, $p < 0.01$). There was no significant change between the pre- and post-operative proportion of patients with hypertension, diabetes mellitus, or hyperlipidemia.

Fig. 1 shows the results of PCS, MCS, and RCS. The preoperative RCS score was below the national standard ($p < 0.01$), as was the MCS score, but the difference in MCS score was not statistically significant ($p = 0.31$). The postoperative PCS and RCS scores were below the national standard, but those differences did not achieve statistical significance ($p = 0.88$ and $p = 0.06$, respectively). The PCS and RCS scores did not change significantly after surgery (50.2 ± 10.6 *vs*. 49.7 ± 11.0, $p = 0.97$ and 44.6 ± 11.7 *vs*. 47.3 ± 8.9, $p = 0.14$, respectively), but the MCS score significantly improved (48.1 ± 11.3 *vs*. 51.7 ± 8.9, $p = 0.03$).

Table 1 Patient preoperative and postoperative clinical and biochemical characteristics

	Preoperative	Postoperative	*p*-value
IGF-1 (μg/L)	611.0 ± 236.2	162.9 ± 66.9	<0.01 [a]
SD score for IGF-1	6.62 ± 1.86	0.30 ± 0.97	<0.01 [a]
Hormone replacement (yes/no)	0/41	0/41	—
Hypertension (yes/no)	15/26	16/25	0.82 [b]
Diabetes (yes/no)	11/30	7/34	0.29 [b]
Hyperlipidemia (yes/no)	3/38	2/39	1 [c]

Data are presented as mean ± standard deviation or number. [a] Wilcoxon signed-rank test; [b] Chi-squared test; [c] Fisher's exact test. IGF-I, insulin-like growth factor-1; SD, standard deviation.

Fig. 2 show the results of the subscales. Preoperatively, the scores for four subscales — role physical, social functioning, role emotional, and mental health — were significantly below the national standard ($p = 0.01$, $p < 0.01$, $p = 0.01$, and $p = 0.03$, respectively). Postoperatively, the physical functioning, role physical, and role emotional subscale scores tended to be lower than the national standard, but the differences were not statistically significant ($p = 0.33$, $p = 0.38$, and $p = 0.14$, respectively). Significant improvements were observed for role physical (45.1 ± 12.0 *vs*. 48.9 ± 9.3, $p = 0.02$), general health (47.5 ± 9.0 *vs*. 50.3 ± 7.8, $p = 0.04$), social functioning (44.6 ± 10.6 *vs*. 50.1 ± 10.0, $p < 0.01$), and mental health subscale scores (45.7 ± 11.5 *vs*. 51.9 ± 10.0, $p < 0.01$).

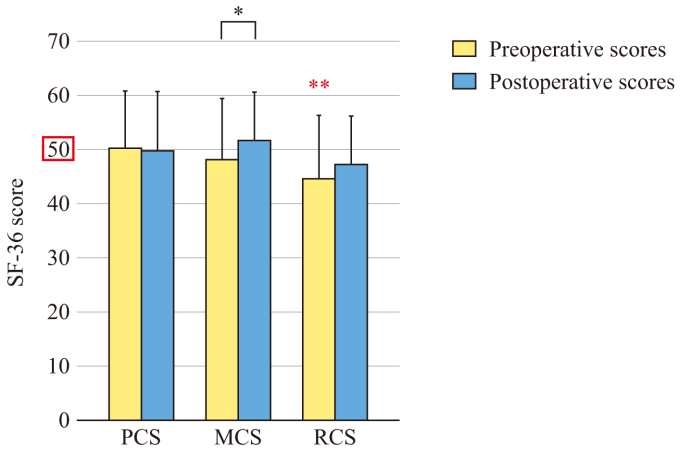


Fig. 1 Preoperative and postoperative physical component summary, mental component summary, and role-social component summary scores

Data are reported as mean ± standard deviation. Preoperative role-social component summary (RCS) score was below the national standard (red asterisk). After surgery, the mental component summary (MCS) score improved significantly (black asterisk). * $p < 0.05$, ** $p < 0.01$. The national standard value is 50, and indicated by the boxed value. PCS, physical component summary.

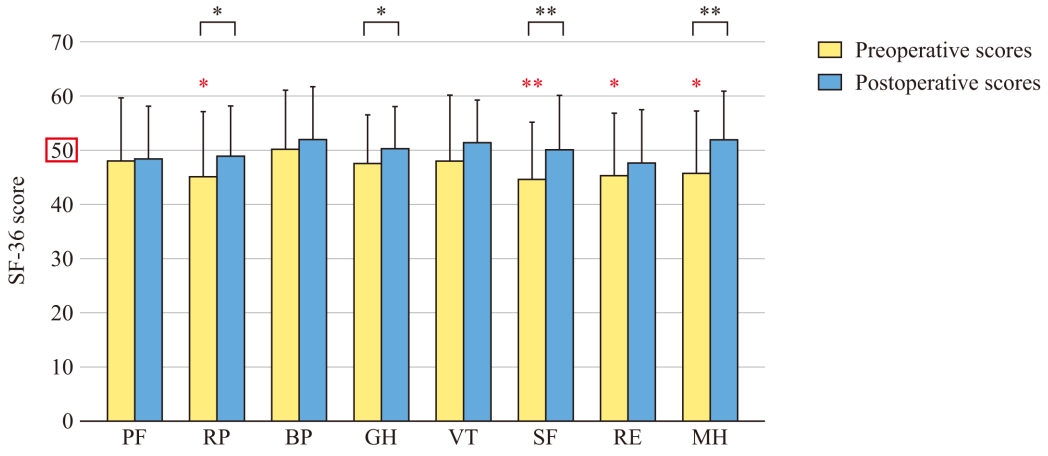


Fig. 2 Preoperative and postoperative subscale scores

Data are reported as mean ± standard deviation. Preoperative role physical (RP), social functioning (SF), role emotional (RE), and mental health (MH) scores were below the national standard values (red asterisk). Postoperatively, physical functioning (PF), RP, and RE subscale scores tended to be lower than the national standard, but the differences were not statistically significant. Significant postoperative improvements were observed for the RP, general health (GH), SF, and MH scores (black asterisk). * $p < 0.05$, ** $p < 0.01$. The national standard value is 50, as indicated by the boxed value. BP, bodily pain; VT, vitality.

There was a negative correlation between the preoperative PCS score and age (r_s = -0.34, p = 0.04) and between the postoperative PCS score and age (r_s = -0.47, p < 0.01). However, there was no correlation between the pre- or post-operative MCS or RCS scores and age. There was no correlation between the preoperative PCS, MCS, and RCS scores and preoperative IGF-1 SDS. Further, there was no correlation between the postoperative PCS, MCS, and RCS scores and postoperative IGF-1 SDS, or the reduction in IGF-1 SDS. There was no correlation between the postoperative changes in PCS, MCS, and RCS scores and the reduction in IGF-1 SDS. In addition, there were no sex-specific differences in the preoperative PCS, MCS, and RCS scores (p = 0.12, p = 0.63, and p = 0.80, respectively) or in the postoperative PCS, MCS, and RCS scores (p = 0.19, p = 0.71, p = 0.69, respectively). The results of the preoperative questionnaire regarding physical symptoms and AHI of the 34 cases are shown in Table 2. If the patients had headache and joint pain, the PCS score decreased (r_s = -0.40, p = 0.02 *vs*. r_s = -0.41, p = 0.01, respectively). Also, in severe malaise cases, a decrease in MCS score was shown (r_s = -0.54, p < 0.01). Conversely, a positive correlation between severe headache and RCS score was identified (r_s = 0.41, p = 0.01).

Table 2 Patient preoperative scores of physical symptom, apnea hypopnea index, physical component summary, mental component summary and role-social component summary

	Age	Sex	Headache	Joint pain	Excessive sweating	General fatigue	AHI	PCS	MCS	RCS
Case 1	18	M	3	0	2	0	3.8	46.0	35.1	57.3
Case 2	20	M	1	0	2	0	2.8	57.8	48.2	33.4
Case 3	26	M	1	0	2	0	4.8	56.4	50.4	53.2
Case 4	29	F	1	0	0	1	5.9	44.5	51.1	47.1
Case 5	31	F	2	2	2	2	2.7	26.6	36.4	40.3
Case 6	32	F	0	0	2	1	8.2	54.9	47.3	42.5
Case 7	33	M	0	0	3	2	3.3	70.5	39.7	26.7
Case 8	35	M	0	0	2	0	8.8	67.3	56.9	37.8
Case 9	37	F	0	0	2	3	5.9	56.5	26.2	52.2
Case 10	39	F	0	0	3	0	19.0	50.0	58.2	44.9
Case 11	40	F	0	0	1	1	73.2	56.4	35.7	25.3
Case 12	47	F	2	2	2	3	11.1	43.2	50.5	63.1
Case 13	49	M	2	3	3	2	5.9	41.2	51.4	58.0
Case 14	51	F	0	0	3	0	2.3	58.2	56.3	50.6
Case 15	53	F	0	0	3	0	46.2	61.3	65.1	40.0
Case 16	53	F	0	2	2	2	35.9	50.1	34.1	23.4
Case 17	54	F	1	0	2	0	18.8	52.0	56.6	56.3
Case 18	55	M	1	2	3	0	7.2	55.1	49.4	43.5
Case 19	55	F	1	0	3	0	48.2	47.2	53.3	51.9
Case 20	56	F	1	2	3	2	30.4	54.9	39.6	53.9
Case 21	57	F	0	1	3	2	7.0	56.2	48.5	55.8
Case 22	57	M	2	1	2	2	2.8	65.5	21.4	37.2
Case 23	58	F	0	0	0	0	16.1	62.8	56.7	48.5
Case 24	58	F	1	0	3	0	45.1	51.6	59.0	52.3
Case 25	60	F	1	3	0	2	17.8	42.2	42.5	48.2
Case 26	60	M	1	0	3	0	43.8	46.3	46.3	60.6
Case 27	62	M	0	0	1	0	25.4	66.5	50.0	20.2
Case 28	63	F	1	1	3	0	5.3	45.4	23.4	54.4
Case 29	63	F	0	1	1	0	25.0	50.1	52.7	52.4
Case 30	63	F	1	0	2	2	4.7	36.1	51.7	28.9
Case 31	66	M	0	1	0	0	9.7	50.1	63.3	54.0
Case 32	67	F	0	2	0	1	45.5	24.3	52.7	35.1
Case 33	71	M	0	0	0	0	49.8	48.2	50.5	30.0
Case 34	73	F	0	0	0	0	7.8	35.7	62.5	35.7

Degree of severity of headache, joint pain, excessive sweating, and general fatigue were represented as number: Non-experienced, 0; Mild, 1; Moderate, 2; Severe, 3. AHI, apnea hypopnea index; MCS, mental component summary; PCS, physical component summary; RCS, role-social component summary; M, male; F, female.

The baseline and postoperative characteristics of the 26 patients who achieved complete remission and the 15 patients who achieved partial remission are shown in Table 3. There were no significant differences between the 2 groups in terms of age, sex, postoperative IGF-1, IGF-1 SDS, and postoperative proportion of patients with hypertension, diabetes mellitus, or hyperlipidemia. There were no significant differences in the PCS, MCS, RCS, or any subscale scores between the 2 groups (Figs. 3 and 4).

Baseline and postoperative characteristics of patients in the "new consensus group" *vs*. "old consensus group" are shown in Table 4. There were no significant differences between the 2 groups regarding their age, sex, postoperative IGF-1, IGF-1 SDS, or the postoperative proportion of patients with hypertension, diabetes mellitus, or hyperlipidemia. There were no significant differences in the PCS, MCS, RCS, or any subscale score between the 2 groups (Figs. 5 and 6).

Discussion

Acromegaly is a chronic disease that can cause various disabilities and premature mortality [2] and can also affect QOL [15, 16]. In the present study, we found that the preoperative SF-36 scores of patients with acromegaly were lower than that of the general Japanese population in RCS and in 4 subscales, including role physical, social functioning, role emotional, and mental health. These results indicate that acromegaly can affect patient's participation as well physical condition and self-perception. Preoperatively, PCS score had a negative correlation with patient age, consistent with findings from a national survey of Japan conducted in 2007 that showed that PCS scores decreased with age [12]. Thus, PCS scores depend on not only physical condition but also on age.

If headache and joint pain were severe, the PCS score before surgery decreased. When severe malaise was present, the MCS score decreased. However, unexpectedly, a positive correlation between severe headache and RCS score was found. This relationship should be re-evaluated using a classification of type of headache and a quantitative severity scale in a larger number of cases.

The effect of treatment on the QOL of patients with acromegaly remains unknown. Gilbert *et al.* reported improvements in health perception and fatigue during medical treatment among 9 patients newly-diagnosed with acromegaly [17]. In addition, Sardella *et al*. used the Acromegaly Quality of Life Questionnaire (AcroQoL) to evaluate patients with controlled disease after a 6-month course of a somatostatin analog and observed improvements in their psychological and appearance domains, but not in their physical domains [18]. To the best of our knowledge, there are no prospective studies reporting postoperative changes in QOL among patients cured solely by surgery.

Similar to the findings of Sardella *et al*., we found that surgical cure mostly resulted in significant improvements in the mental components of the SF-36, but not in the physical or role-social components. Furthermore, Matta *et al*. reported that patients with controlled acromegaly had higher AcroQoL psychological subscale scores compared to patients with uncontrolled disease [19]. Yoshida *et al*. also reported that patients who had achieved disease control with surgery alone exhibited higher psychological scores, but not physical scores, compared with patients who had received pharmaceutical therapy [20]. Rapid and perceptible postoperative improvements in the external symptoms of acromegaly (*e.g.*, excessive sweating, sleep apnea, and diabetes mellitus) may improve a patient's perception of their general mental health.

Biermasz *et al*. reported that surgically cured patients had better physical function compared to patients who were cured using a somatostatin analog, radiotherapy, and/or hypopituitarism treatment [21]. In the present study, however, PCS and some physical domain subscale scores did not significantly improve after surgery, although all of our patients achieved IGF-1 normalization by surgery alone, and none required postoperative hormone replacement therapy. The lack of improvement in physical condition may be related to the fact that some patients with acromegaly suffer from several comorbidities, such as joint pain and hypertension, even after achievement of postoperative cure [22].

Most of the suppressed subscale scores improved after surgery, but the role emotional subscale score did not. In the United States and in Western European countries, scores on the role emotional subscale are loaded strongly on the mental component, whereas in Japan they are loaded strongly on the physical component [11]. As described before, even when patients with acromegaly achieved remission post-surgery, because their physical condition remained unchanged, no substantial improvement was observed in the role emotional subscale score.

Table 3 Baseline and postoperative characteristics of patients with complete remission group *vs*. partial remission group

	Complete remission group (nadir GH < 0.4 μg/L)	Partial remission group (nadir GH ≥ 0.4 μg/L)	*p*-value
Age (years)	53.4 ± 12.3	48.0 ± 16.9	0.23 [a]
Sex (male/female)	11/15	5/10	0.57 [b]
IGF-1 (μg/L)	152.6 ± 43.0	180.8 ± 94.6	0.57 [a]
SD score for IGF-1	0.31 ± 0.90	0.28 ± 1.10	0.82 [a]
Hypertension (yes/no)	12/14	4/11	0.22 [b]
Diabetes (yes/no)	5/21	2/13	0.7 [c]
Hyperlipidemia (yes/no)	2/24	0/15	0.52 [c]

Data are presented as mean ± standard deviation or number. [a] Mann-Whitney U test; [b] Chi-squared test; [c] Fisher's exact test. GH, growth hormone; IGF-I, insulin-like growth factor-1; SD, standard deviation.

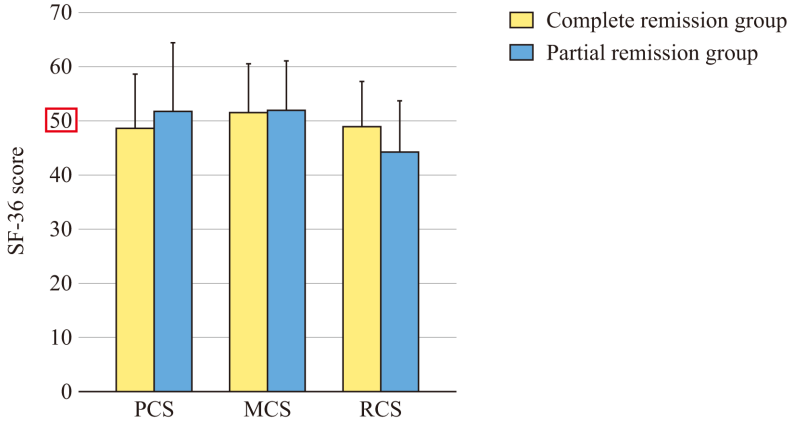


Fig. 3 Postoperative physical component summary, mental component summary, and role-social component summary scores for the complete remission and partial remission groups

Data are reported as mean ± standard deviation. The complete remission group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L, and the partial remission group included patients whose postoperative nadir growth hormone levels during the OGTT were ≥ 0.4 μg/L. No significant differences in the physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS) scores were observed between the two groups. The national standard value is 50, as indicated by the boxed value.

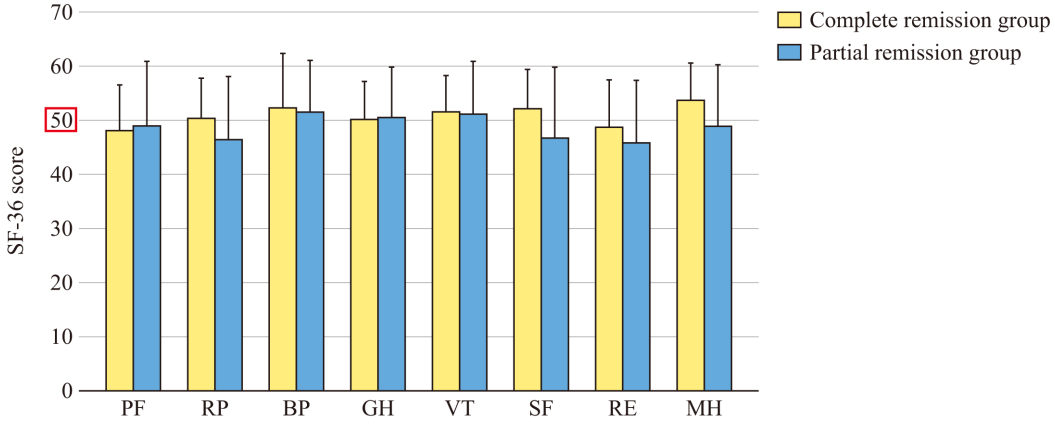


Fig. 4 Postoperative subscale scores for the complete remission and partial remission groups

Data are reported as mean ± standard deviation. The complete remission group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L, and the partial remission group included patients whose postoperative nadir growth hormone levels during the OGTT were ≥ 0.4 μg/L. No significant differences in the subscale scores were observed when we compared the two groups. The national standard value is 50, as indicated by the boxed value. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Table 4 Baseline and postoperative characteristics of patients with new consensus group (n=26) *vs*. old consensus group (n=12)

	New consensus group (nadir GH < 0.4 μg/L)	Old consensus group (0.4 μg/L ≤ nadir GH < 1 μg/L)	*p*-value
Age (years)	53.4 ± 12.3	49.8 ± 17.7	0.51 [a]
Sex (male/female)	11/15	5/7	0.97 [b]
IGF-1 (μg/L)	152.6 ± 43.0	181.5 ± 105.4	0.85 [a]
SD score for IGF-1	0.31 ± 0.90	0.28 ± 0.95	0.90 [a]
Hypertension (yes/no)	12/14	2/10	0.15 [c]
Diabetes (yes/no)	5/21	2/10	1.0 [c]
Hyperlipidemia (yes/no)	2/24	0/12	0.56 [c]

Data are presented as mean ± standard deviation or number. [a] Mann-Whitney U test; [b] Chi-squared test; [c] Fisher's exact test. GH, growth hormone; IGF-I, insulin-like growth factor-1; SD, standard deviation.

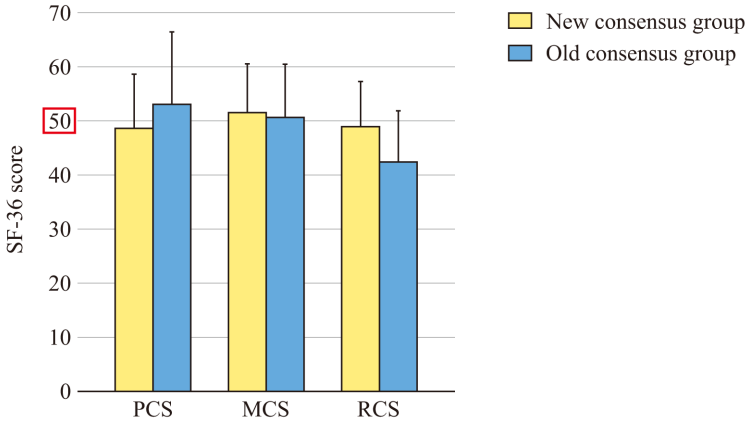


Fig. 5 Postoperative physical component summary, mental component summary, and role-social component summary scores for the new consensus and old consensus groups

Data are reported as mean ± standard deviation. The new consensus group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L, and the old consensus group included patients whose postoperative nadir growth hormone levels during the OGTT were < 1.0 μg/L and ≥ 0.4 μg/L. No significant differences in the physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS) scores were observed between the two groups. The national standard value is 50, as indicated by the boxed value.

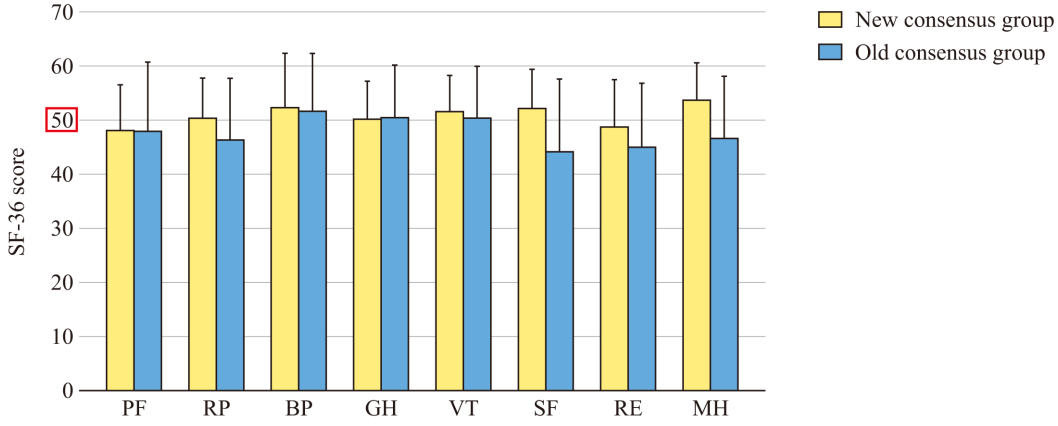


Fig. 6 Postoperative subscale scores for the new consensus and old consensus groups

Data are reported as mean ± standard deviation. The new consensus group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L, and the old consensus group included patients whose postoperative nadir growth hormone levels during the OGTT were < 1.0 μg/L and ≥ 0.4 μg/L. No significant differences in the subscale scores were observed when we compared the two groups. The national standard value is 50, as indicated by the boxed value. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Postoperatively, too, the PCS score was negatively correlated with patient's age. PCS scores depend on not only physical condition but also on age, even postoperatively.

Stricter biochemical criteria for remission have recently been proposed [9], although it is not clear how these criteria affect a patient's QOL. Kauppinen-Mäkelin *et al*. reported that the best QOL was achieved by targeting a post OGTT nadir GH level in the 0.3–1.0 μg/L range, but not < 0.3 μg/L [23]. The authors suggested that patients with treated acromegaly and post-OGTT nadir GH levels of < 0.3 μg/L might have GH deficiency. GH deficiency has adverse effects on QOL, even if cure is achieved [24]. In our previous study, we found that the GH deficiency rate among patients with postoperative remission was not high [25]. We also evaluated GH secretory function using the stimulation test in 34 of the 41 patients in the present study (data not shown). An insulin tolerance test (ITT) was performed in 28 patients, an arginine infusion test was performed in 4 patients, and a growth hormone-releasing peptide-2 (GHRP-2) test was performed in 2 patients. Only 2 patients (1 with complete- and 1 with partial-remission) in the present study exhibited severe GH deficiency (criteria: peak GH ≤ 1.8 μg/L in ITT and arginine test, or peak GH ≤ 9.0 μg/L in GHRP-2 test). Moreover, there was no significant difference between the QOL scores of the 26 patients who achieved complete remission and the 15 patients in partial remission. Further, there was no significant difference between the QOL scores of the 26 patients who achieved new consensus criteria and the 12 patients who achieved only the old consensus criteria. Although the small sample size of our study limits the value of the statistical analyses, we can suggest that the new stricter criteria for remission do not increase the frequency of GH deficiency or significantly reduce patients' postoperative QOL. Nevertheless, larger studies are needed to confirm the effects of the new criteria on the postoperative QOL of patients with acromegaly.

The proportion of patients with diabetes mellitus and hyperlipidemia decreased after surgery, whereas the proportion of patients with hypertension increased. This is likely due to our decision to define these conditions based on the use of relevant oral medications. In untreated hypertensive patients, antihypertensive medication was started post-surgery. This caused the impression of an increase of the proportion of patients with hypertension. However, the dose of antihypertensive medication decreased in some cases post-surgery, although in no case could antihypertensives be withdrawn.

Our study has some limitations. First, we chose the SF-36 questionnaire to evaluate QOL because it is the most widely used questionnaire for evaluating QOL and because it allowed us to compare patients with acromegaly to the general population. However, generic questionnaires (*e.g.*, the SF-36 questionnaire) may be less sensitive than disease-specific questionnaires, such as the AcroQoL questionnaire [1], as those questionnaires evaluate dimensions that are most affected by the disease. The AcroQoL was recently translated into Japanese, and Yoshida *et al*. found significant correlations between the AcroQoL and SF-36 scores in post-treatment patients with acromegaly [20]. We are currently accumulating AcroQoL scores of patients with acromegaly pre- and post-operatively, to determine the effect of surgery on disease-specific QOL.

Second, we performed OGTT 3 months postoperatively. The nadir GH level during the OGTT has been reported to change depending on the period of measurement [26]. If the OGTT had been performed 1 year after the surgery, when we had administered the questionnaires postoperatively, we may have observed a difference in the SF-36 scores between complete remission group and partial remission group, new consensus group and old consensus group. However, we conducted a SF-36 questionnaire survey in 30 out of 41 patients 3 months after the surgery, when we performed the OGTT. There was no significant difference between the QOL scores of patients who achieved complete remission and of those who were in partial remission (Supplemental Figs. 1 and 2). Additionally, there was no significant difference between the QOL scores of the new and old consensus groups (Supplemental Figs. 3 and 4). Therefore, we suppose that there is no difference in the QOL scores between these two set of two groups, at least during 3–12 months after the surgery.

Third, we cannot deny the possibility of underestimation of a postoperative improvement in QOL, because there were at least 2 patients who had severe GH deficiency in the cohort. In a future study, we will gather information regarding more cases of GH deficiency among patients with postoperative remission in order to evaluate the impact of GH deficiency on postoperative QOL.

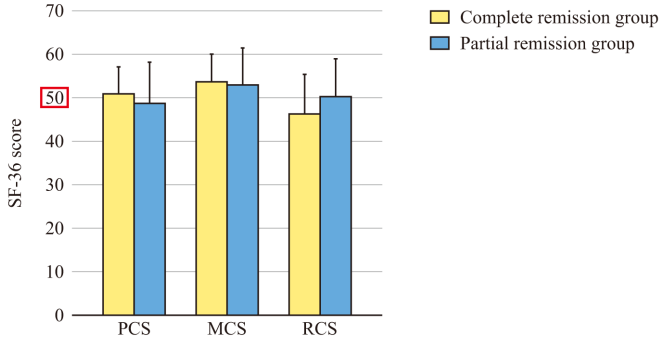
Finally, the present study compared QOL scores at baseline and 1 year after surgery, although a patient's QOL can change at any time. Therefore, future studies with an extended follow-up period are needed to confirm the long-term effects of surgery.

Conclusion

The present study revealed that patients with acromegaly exhibited low preoperative SF-36 QOL scores in the role-social domain compared to the general Japanese population. Surgically-achieved remission provided an improvement in the mental QOL. Nevertheless, there were no significant differences in scores of QOL when we compared patients who achieved complete remission to those who achieved partial remission, using a postoperative nadir GH cut-off level during OGTT of < 0.4 μg/L to define complete remission. Future large-scale long-term studies are needed to evaluate the prolonged effects of surgery as well as stricter remission criteria on QOL.

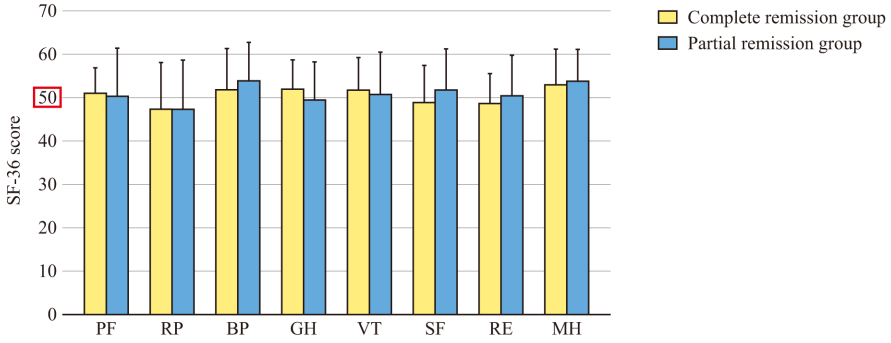
Disclosures

The authors declare that there are no conflicts of interest regarding the publication of this report.



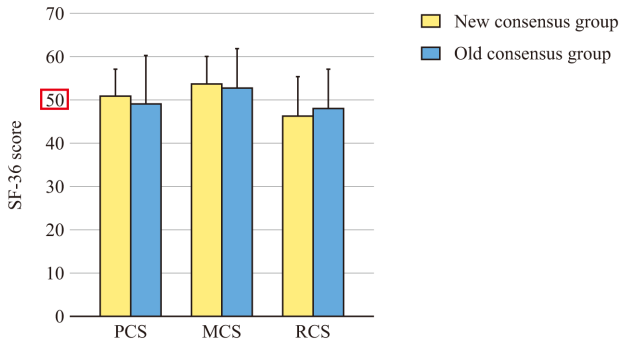
Supplemental Fig. 1 Physical component summary, mental component summary, and role-social component summary scores for the complete remission and partial remission groups at 3 months after surgery

Data are reported as mean ± standard deviation. The complete remission group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L (n = 19), and the partial remission group included patients whose postoperative nadir growth hormone levels during the OGTT were ≥ 0.4 μg/L (n = 11). No significant differences in the physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS) scores were observed between the two groups. The national standard value is 50, as indicated by the boxed value.



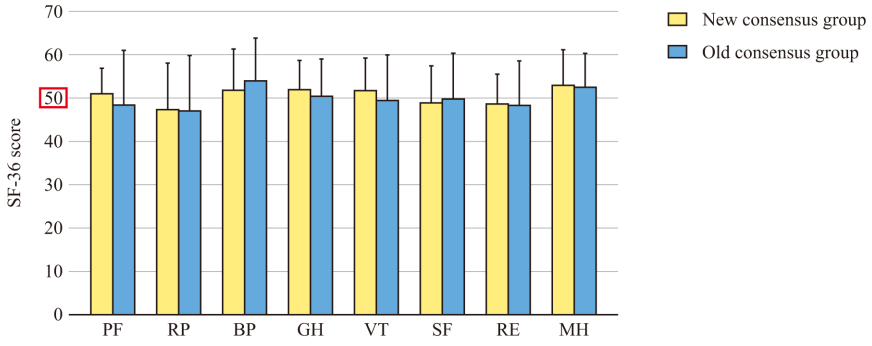
Supplemental Fig. 2 Subscale scores for the complete remission and partial remission groups at 3 months after surgery

Data are reported as mean ± standard deviation. The complete remission group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L (n = 19), and the partial remission group included patients whose postoperative nadir growth hormone levels during the OGTT were ≥ 0.4 μg/L (n = 11). No significant differences in the subscale scores were observed when we compared the two groups. The national standard value is 50, as indicated by the boxed value. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH: mental health.



Supplemental Fig. 3 Physical component summary, mental component summary, and role-social component summary scores for the new consensus and old consensus groups at 3 months after surgery

Data are reported as mean ± standard deviation. The new consensus group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L (n = 19), and the old consensus group included patients whose postoperative nadir growth hormone levels during the OGTT were < 1.0 μg/L and ≥ 0.4 μg/L (n = 8). No significant differences in the physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS) scores were observed between the two groups. The national standard value is 50, as indicated by the boxed value.



Supplemental Fig. 4 Subscale scores for the new consensus and old consensus groups at 3 months after surgery

Data are reported as mean ± standard deviation. The new consensus group included patients whose postoperative nadir growth hormone levels during the oral glucose tolerance test (OGTT) were < 0.4 μg/L (n = 19), and the old consensus group included patients whose postoperative nadir growth hormone levels during the OGTT were < 1.0 μg/L and ≥ 0.4 μg/L (n = 8). No significant differences in the subscale scores were observed when we compared the two groups. The national standard value is 50, as indicated by the boxed value. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

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