CLINICAL STUDY

The 'bio-assay' quality of life might be a better marker of disease activity in acromegalic patients than serum total IGF-I concentrations

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Abstract

Objectives: To investigate the quality of life (QoL) in acromegalic patients in relation to biochemical parameters.

Design and methods: Single-center, open label study in 14 acromegalic patients (eight woman and six men, age 33–77 years), with normal serum IGF-I levels during long-term treatment with monthly injections of 20 mg of long-acting octreotide. We investigated which biochemical parameter might reflect optimal QoL, using the SF-36 questionnaire.

Results: We observed that six patients had a low QoL score at baseline in the same range as observed in cancer patients. The other eight patients had a normal QoL. GH, IGF-I nor free IGF-I could discriminate these two subgroups at baseline. After skipping one monthly injection, all six subjects with the low QoL escaped in their free IGF-I concentrations. Also total IGF-I concentrations escaped in four of these six. In the subjects with normal QoL, free IGF-I levels remained normal in all, while total IGF-I levels only escaped in one.

Conclusions: This study tells us that the currently used biochemical criteria for disease control in acromegaly might be sufficient in assessing long-term mortality and morbidity, but they are insufficient in addressing the most important parameter from the patient's perspective – QoL.

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Introduction

Physicians involved in the treatment of acromegalic patients know that biochemical control of the disease does not necessarily stop a patient complaining. To address these issues, Sonino and co-workers (1) studied with several symptom questionnaires the effects on quality of life (QoL) of the slow-release somatostatin analogue, lanreotide. Together with a significant decrease in growth hormone (GH) and insulin-like growth factor-I (IGF-I), treatment with lanreotide significantly improved psychological distress, well-being and social fears (1). In a another study on the efficacy of the novel GH receptor antagonist pegvisomant to lower serum IGF-I concentrations, a questionnaire evaluating five clinical signs and symptoms of acromegaly showed significant dose dependent differences from placebo (2). Recently, Webb and co-workers reported the successful development of a disease-specific questionnaire suitable to measure health-related QoL in acromegaly (ACROQOL) (3).

Another QoL measure, the MOS 36-Item Short-Form Health Survey (SF-36), was used to assess patients'

perception of the impact of a pituitary adenoma, prior to treatment, on his or her physical and mental functioning in 270 new patients evaluated for pituitary disease at the University of Virginia Pituitary Clinic (4). They clearly found that patients with a pituitary adenoma do have an impaired QoL that should be routinely assessed in conjunction with endocrine and anatomic studies before and after treatment (4).

However, no clear biochemical parameter appears to be available that correlates well with disease activity-related QoL (5). At the same time, serum GH concentrations and serum total IGF-I levels, but not QoL, are used as parameters to determine dosing of Sandostatin LAR, or any of the available medical therapies for acromegaly (6–9).

As no data from the literature are available that use the patient's own opinion as a parameter for dosing, we designed a double blind study, in which self-assessment of the patient was correlated with the known biochemical disease parameters. We only investigated patients sensitive to long-acting somatostatin receptor agonists (Sandostatin LAR), which meant that IGF-I levels

were normalized in all these patients during long-term LAR treatment. Sandostatin LAR, a synthetic octapeptide-somatostatin analogue, is a long-acting release formulation of octreotide, in which the drug has been incorporated into microspheres of a biodegradable polymer. It is administered as an intramuscular injection every 4 weeks. The usual starting dose is 20 mg, and the dose may be adjusted up to 30 mg if there is insufficient suppression of GH and IGF-I (8–14).

Self-assessment of the patient in this study was obtained with the Medical Outcomes Study (MOS)-36-Item Short-Form Health Survey (SF-36). The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments, constructed as an alternative to longer measures included in MOS questionnaires. The MOS is a longitudinal investigation of variations in health status from the point of view of patients with chronic conditions (15). Eight of the most useful scales of the MOS health concepts are included in the SF-36 and presented in Table 1 with the number of items used to score each scale (16–21). The generic nature of the SF-36 allows comparisons to be made of the relative benefit of different treatments, and in this setting, results from clinical studies have largely supported the validity of the SF-36 scales (22).

A 5-point (0–8 rating scale) questionnaire evaluating five clinical symptoms of acromegaly (soft tissue swelling, arthralgia, headache, excessive perspiration and fatigue) (2), was also used in order to measure the frequency and impact of disease-specific symptoms.

Subjects

Fourteen subjects (eight woman and six men; age 33–77 years) were included in the study (Table 2). Acromegaly was previously diagnosed based on the clinical presentation, GH levels unsuppressed during an oral glucose tolerance test, elevated age- and gender-matched IGF-I levels (and radiological detection of a pituitary tumor). Twelve patients had a macroadenoma of the pituitary gland. Eleven patients were primarily treated with pituitary surgery, followed in ten patients by radiotherapy. Surgery was at least 2 years, with a maximum of 21 years, before the start of the study and radiotherapy was at least 4 years, with a maximum of 21 years, prior to the start of the study.

Before the study all subjects were treated monthly with Sandostatin LAR 20 mg, at least 1 year and 3 months, with a maximum of 7 years, and all subjects had total serum IGF-I levels within the normal age- and gender-adjusted range.

Normal anterior pituitary functions (apart from GH secretion) were present in seven patients, of which three woman were receiving primary medical therapy. Panhypopituitarism was present in three patients and deficiency of one or two pituitary axes was present in four patients. All patients were on stable pituitary replacement therapy. None of the subjects had abnormal renal or liver functions or a history of cancer. Seven patients received anti-hypertensive medication, two of which had a history of a transient ischemic attack. Two patients received medication for hyperlipidemia and two other patients received oral anti-hyperglycemics medication for type 2 diabetes mellitus.

Methods

According to their QoL score at baseline, i.e. during long-term 20 mg Sandostatin LAR treatment, patients were stratified into two groups: one group with low QoL ($n = 6$; the unhappy patients) and one group

Table 1 Definition of health concepts using the SF-36 questionnaire.

Concepts	No. of items	Definition
Physical functioning	10	Extent to which health interferes with a variety of activities, such as sports, carrying groceries, climbing stairs and walking
Role limitations due to physical problems	4	Extent to which health interferes with usual daily activities, such as work, housework, or school
Role limitations due to emotional problems	3	Extent to which health interferes with usual daily social activities, for example accomplished less than would like
Mental health	5	General mood of affect, including depression, anxiety and psychological well-being during the past week
Vitality	4	Energy or fatigue
Social functioning	2	Extent to which health interferes with normal social activities, such as visiting with friends during the past week
Bodily pain	2	Extent to bodily pain in past week
General health perceptions	6	Overall rating of current health in general
Total score	36	

Taken from references 20; 21; 23.

Table 2 Patient characteristics of happy vs unhappy acromegalic patients, using the SF-36 QoL questionnaire, while under long-term long-acting octreotide therapy of 20 mg, which decreased serum total IGF-I levels down to within the age and sex adjusted normal ranges. Baseline values are scored at the first visit (wk-4). *P*-values denote statistical differences between octreotide sensitive and non-sensitive subjects. Most patients had received more than one type of previous therapy.

Characteristic	Happy	Unhappy	<i>P</i> -value
No. of patients	8	6	
Age (mean $\pm$ S.E.M. in yr)	50 $\pm$ 5.2	63 $\pm$ 4.8	0.1017
Sex (no. M/F)	4/4	2/4	
Body-mass index (mean $\pm$ S.E.M. in kg/m ²)	27.0 $\pm$ 0.7	27.3 $\pm$ 1.0	0.8129
Duration of disease (mean $\pm$ S.E.M. in yr (range))	13.3 $\pm$ 3.5 (2–28)	11.7 $\pm$ 3.4 (5–26)	0.7496
No. of macroadenoma (%)	6 (75)	6 (100)	
Previous therapy no. (%)			
Surgery	6 (75)	5 (83)	
Radiotherapy	5 (63)	5 (83)	
No. of deficiency SAI (%)	1 (13)	4 (67)	
No. of deficiency SHT (%)	3 (38)	4 (67)	
No. of deficiency SHG (%)	1 (13)	5 (83)	
No. of patients with DM (%)	0 (0)	2 (33)	

SAI, secondary adrenal insufficiency; SHT, secondary hypothyroidism; SHG, secondary hypogonadism; DM, diabetes mellitus (type II); M, male; F, female.

with a normal QoL ($n = 8$; the happy patients) (Fig. 1). After a wash-out period of 4 weeks, so 8 weeks off Sandostatin LAR 20 mg medication, both the happy and unhappy patients received again their monthly 20 mg Sandostatin LAR for 3 months, followed by another wash-out period of 4 weeks. The study ended with another treatment period of 3 months with Sandostatin LAR. Clinical and laboratory assessments were conducted at each visit. Only the happy group of patients was followed during an extra wash-out period of 3 months to investigate their QoL and serum total

IGF-I levels without the presence of clinically significant octreotide levels. Routine hematological, serum and urine chemistry parameters were collected, as well as serum GH, total and free serum IGF-I and IGFBP3. At each visit, a Bio-electrical Impedance Analysis (BIA) was performed with the Holtain Body Composition Analyser (Crymych, UK) and all subjects completed the SF-36 Physical and Mental health summary scales and the symptoms questionnaires. Adverse effects were recorded at each visit.

Study procedure

The study was approved by the Medical Ethics Committee. Subjects were included after their written informed consents were obtained. All blood samples were obtained, after an overnight fast and immediately centrifuged and stored at -20°C . BIA for assessment of body composition was performed. Psychometric evaluation was obtained by means of two self-rating scales questionnaires filled in by the patients at each visit.

The SF-36 contains 36 questions measuring both positive and negative health status, of which the validated Dutch translated version was used (23) (Maximal score is 100, which indicates the most optimal QoL). Item scores were coded and summed into scale scores and transformed into a scale from 0 (worst health) to 100 (best health). The 5-point (0–8 rating scale) symptoms questionnaire evaluates five clinical symptoms of acromegaly (headache, excessive perspiration, arthralgia, fatigue, soft tissue swelling). The scores denote a scale from 0 (no symptoms) to 40 (severe, incapacitating symptoms) (2).

Hormonal assays

GH (Diagnostic Products Corporation, Los Angeles, USA) and total IGF-I, free IGF-I, IGFBP-3 were assayed by radioimmunoassay (total IGF-I: non-extraction)

Figure 1 QoL scores (SF-36, total items $\pm$ S.E.M.; % of score and 100% indicating optimal QoL, showing the scores of the happy patients with a normal QoL ($\blacktriangle$) and unhappy acromegalic patients ($\blacksquare$). The arrows indicate intramuscular injections of 20 mg Sandostatin LAR. The difference between the two groups in QoL was highly significant. The trend of decreasing QoL during the 8 week wash-out of Sandostatin LAR injections in the unhappy group was not significant, while that over the 3 months wash-out was significant.

Table 3 Baseline fasting hormone concentrations of happy vs unhappy subjects, using the SF-36 QoL questionnaire, while under long-term long-acting octreotide therapy of 20 mg, which decreased serum total IGF-I levels down to within the age and sex adjusted normal ranges.

Baseline fasting hormone levels	Happy	Unhappy	P-value
No. of patients	8	6	
Serum GH (ng/ml)			
median	0.85	0.85	
mean $\pm$ S.E.M.	1.05 $\pm$ 0.2	1.44 $\pm$ 0.6	
range	0.4–1.9	0.4–4.7	
Serum total IGF-I (ng/ml)			
median	29.2	22.3	
mean $\pm$ S.E.M.	28.1 $\pm$ 3.1	24.6 $\pm$ 3.4	0.47
range	9.6–37.5	17.2–39.8	
Serum free IGF-I (pmol/l)			
median	92.6	125.7	
mean $\pm$ S.E.M.	105.4 $\pm$ 20.6	181.3 $\pm$ 43.9	0.54
range	20.8–180	79.5–334.3	
Serum IGFBP3 (ng/ml)			
median	4.40	3.80	
mean $\pm$ S.E.M.	4.53 $\pm$ 0.45	4.37 $\pm$ 0.53	
range	2.60–6.50	2.90–6.50	

Data are shown as the median, mean $\pm$ S.E.M. and range. GH, growth hormone; IGF-I, insulin-like growth factor I; IGFBP3, insulin-like growth factor binding protein 3.

(Diagnostic Systems Laboratories, Inc., Webster, Texas, USA). We used the reported results of free-IGF-I as determined by Juul and co-workers (24) as reference values of age- and gender-matched free IGF-I levels. The assay sensitivity was 0.01 ng/ml for GH, 2.06 ng/ml for total IGF-I, 0.03 ng/ml for free IGF-I and 0.5 ng/ml for IGFBP-3. The intra- and inter-assay coefficients of variation for the low and high points of the curve were 5.3%–6.5% and 5.7%–6.1% for GH, 7.0%–3.9% and 7.4%–4.2% for total IGF-I, 10.3%–3.3% and 7.7%–10.7% for free IGF-I, 1.8–3.9% and 1.9–0.6% for IGFBP-3. Age-related reference ranges ($\pm$ S.D.) for total IGF-I are 100–494 (88.3) ng/ml in patients 30–39 years old, 101–303 (48.3) ng/ml in patients 40–49 years old, 78–258 (49.3) ng/ml in patients older than 50 years old, for IGFBP-3 are 1730–7260 (900) ng/ml ($\times$ 0.035 for nmol/l) in patients 30–39 years old 2080–4310 (497) in patients 40–49 years old and 2020–3990 (439) in patients older than 50 years (Table 3).

Data analysis

Continuous variables, including the primary efficacy end point (decrease from baseline of serum concentrations of GH, IGF-I, IGFBP3 and free IGF-I) were compared with the use of analysis of variance. For statistical analysis, two group (unpaired) student's *t*-test, and unpaired *t*-test with Welch's correction, SPSS 11.0 (SPSS, Inc., Chicago, IL, USA).

For the SF-36 scales, factor analyses were performed to evaluate construct validity in light of what is known about the factor structure of the SF-36 from previous studies (17, 25). There were no missing data for the Symptoms questionnaire or for the SF-36.

Results

Baseline characteristics and hormone concentrations of happy vs unhappy patient groups during long-term treatment with monthly injections of 20 mg of Sandostatin LAR and 4 weeks after the last Sandostatin LAR injection were not significantly different (wk-4; Table 2). Mean age was 56 ± 13 years (minimum 33 and maximum 77 years) and the mean duration of acromegaly was 11 ± 8 years (minimum 1 and maximum 28 years). All subjects had normal age- and gender-adjusted total and free IGF-I levels at baseline (Table 3). None of the patients withdrew from the study.

We observed that only the unhappy group (Fig. 1) had free IGF-I concentrations above their age- and gender adjusted normal range within the 8 weeks after the last injection of Sandostatin LAR (so after skipping one injection; Fig. 2). Also they tended to rise above the normal range in their total IGF-I levels (Fig. 3) unlike those of the happy group after skipping one injection of LAR. The total IGF-I levels of the unhappy group seemed to be more stable during wash-out of LAR (Fig. 3). The data obtained from the first wash-out period gave the same information as those obtained from the last wash-out period, as data analyses revealed no extra differences that were significant, nor showed that significance was lost for some parameters after the second wash-out. We therefore only provide the data from the first wash-out period in the following parts of the manuscript. After the study, a third wash-out period of 3 months was performed in those six subjects in whom no rise in total and free IGF-I was observed. After these extra three months without treatment with Sandostatin LAR, all of these patients showed an increase above the normal levels of total IGF-I, which was accompanied

Figure 2 Serum free IGF-I levels (pmol/l) in happy and unhappy acromegalic subjects. Each group shows data on free IGF-I levels during long-term treatment with 20 mg long-acting octreotide and at 8 weeks after the last injection, i.e. after skipping one monthly injection. Note that only the unhappy subjects had serum free IGF-I concentrations above the normal range. (Upper level of normality 205 pmol/l is indicated as solid line.)

by a recurrence in signs and symptoms of active acromegaly, indicating that they were not cured.

Significantly higher serum GH values at all visits were found in the unhappy subjects compared with the happy subjects when the area under the curves (AUC) over the entire study were used ($P = 0.0035$). When individual data are shown (Fig. 4), this difference in AUC can be explained by the two unhappy subjects who escaped the normal range in their GH levels during the first wash-out. The same is true for the difference between AUC for the age- and gender adjusted free IGF-I values at all visits between the happy and unhappy group ($P < 0.0001$; Fig. 2). However, the patients who did escape normal range in their free IGF-I with the highest wash-out levels were the patients that had the highest GH levels, both before and after the wash-out. There were no significant differences in total IGF-I ($P = 0.99$).

The difference between the happy and unhappy subjects in QoL in the total SF-36 (mean unhappy QoL score, mean $\pm$ S.E.M. for whole period was 54.3 ± 1.2 versus 75.7 ± 1.1 for the happy group; $P < 0.001$) was based on the observed significant differences in 'physical functioning', 'role limitations due to physical functioning' and 'role limitations due to emotional functioning' scores (all $P < 0.05$). There was also a significantly better score for symptoms of acromegaly for perspiration, arthralgia, and fatigue (all $P < 0.05$), but not in headache and soft tissue swelling

Figure 3 Serum total IGF-I levels (nmol/l) in happy and unhappy acromegalic subjects. Each group shows data on total IGF-I levels during long-term treatment with 20 mg long-acting octreotide and at 8 weeks after the last injection, i.e. after skipping one monthly injection. Note that all the unhappy subjects had serum total IGF-I concentrations above the normal range. (Upper level of normality 45 nmol/l is indicated as solid line.) For the happy group, also the total IGF-I levels after 12 weeks of wash-out are provided, showing that all happy patients did escape after a longer period of time without octreotide therapy.

of the symptoms questionnaire comparing the same subjects.

Safety

Sandostatin LAR was well tolerated. A mild and transient redness at the injection-site was reported by two patients after receiving one of the Sandostatin LAR injections. Mild gastro-intestinal discomfort was observed by three patients, while dizziness and headache were reported by four patients. No significant changes in safety laboratory were recorded during the study period.

Discussion

Both GH and IGF-I are reported as factors that might affect long-term morbidity and mortality in acromegalic patients (9, 26–34). However, in this study we assess a different parameter in acromegalic patients whom we assume to have an optimized metabolic situation by medical intervention and have decreased IGF-I levels to within what we call the normal range – patients that are 'adequately controlled'. The most important

message of our study is that in these biochemically controlled patients, we are not able to predict their own most important parameter – QoL. The observed difference in total SF-36 scores that we came across is an important one in the validation study of the SF-36 in the Netherlands, the score of the unhappy acromegalic patients was in the same range as was observed in cancer patients undergoing active anti-neoplastic treatment (23), while the happy acromegalic subjects in our study had the same SF-36 scores as the Dutch control population (23). This suggests that the data of our study indicate that when we use serum total IGF-I levels to define well controlled patients under long-term treatment with at least long-acting somatostatin analogs, we are not able to discriminate between patients that feel so bad that they have the same QoL as cancer patients following chemotherapy regimes, from acromegalic patients that feel good. From the patient's perspective, this implies that physicians are not able to address their complaints in QoL adequately, as they tend to be more or less convinced that they 'cured' these patients, because they brought back their serum IGF-I levels down to within the normal range. Apparently, acromegalic patients are very capable at observing whether or not they are well-controlled, as they can foresee that when they skip one injection of 20 mg of long-acting octreotide, they will escape biochemically in at least their free IGF-I levels and sometimes in their total IGF-I as well. Physicians can apparently not foresee that, as our study shows that happy and unhappy patients have exactly the same total and free IGF-I levels during treatment. Although the difference in QoL might be the result of the difference in GH activity, it is noteworthy that the unhappy patients were more likely to have hypopituitarism (especially hypogonadism and likely infertility and diabetes, although these differences were not significant). Also, cosmetic disfigurement, persistent joint aches etc. may plague even the perfectly 'controlled' patient and impair his/her QoL. This by itself might have affected their perception of well-being.

Our results also give the impression that GH levels might be more important for the patient's QoL, as mean GH levels in the unhappy group were always higher at any time point, compared with the happy patients. However, this increased mean GH level in the unhappy group was caused by relatively high GH levels in only two subjects, while the other unhappy subjects had GH levels that completely overlapped GH concentrations in the happy group (Fig. 4).

To be sure that the so-called happy patients still had active acromegaly, we took all those subjects who did not have levels outside the normal range biochemically off octreotide medication for 3 months. All of them showed an escape in their total IGF-I and showed a recurrence in signs and symptoms of active acromegaly and a clear reduction in their QoL SF-36 scores, indicating that they indeed were not cured. We have not

Figure 4 Serum GH levels ($\mu\text{g/l}$) in happy and unhappy acromegalic subjects. Each group shows data on GH levels during long-term treatment with 20 mg long-acting octreotide and at 8 weeks after the last injection, so after skipping one monthly injection. Note that only two unhappy subjects show largely increased serum GH concentrations.

studied potential differences between the happy versus the unhappy subgroup in e.g. octreotide levels or clearance rates of octreotide, as apparently, these potential differences did not result in different serum IGF-I levels under chronic octreotide LAR treatment.

If we may consider QoL as a bio-assay itself, our study indicates that QoL might be superior to serum IGF-I levels in assessing 'poor' control of disease activity according to patients.

In conclusion, we report the outcome of a study in 14 acromegalic patients in whom adequate biochemical control was obtained by long-term long-acting octreotide therapy. Six of these patients had a very low QoL score in the SF-36 questionnaire that was comparable to cancer patients, receiving chemotherapy. The other eight patients had a normal QoL, comparable to the normal population. No biochemical parameter such as GH, IGF-I or free IGF-I could discriminate between these two subgroups. After skipping one injection of the monthly administrations, all six subjects with the low QoL had increased serum free IGF-I concentrations to levels above the normal range. Also total IGF-I concentrations in four of these six increased to levels above the normal range, while in the subjects with normal QoL, serum total and free IGF-I levels remained normal in all but one, who only showed an increase in total IGF-I to just above the normal range.

This study tells us that the currently used biochemical criteria for disease control in acromegaly patients, although potentially sufficient in assessing mortality

and morbidity in the long run, are insufficient in addressing the most important parameter from the patient's perspective – QoL. In other words, normalization of serum IGF-I concentrations in acromegalic patients by whatever therapy might impress physicians, but not necessarily the patients involved.

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