Improving Quality of Life in Patients with Pituitary Tumors

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Abstract

Evaluation of health-related quality of life (QoL) in people with pituitary tumors has received much attention over the last 10–15 years. Most of them show impaired QoL, but little is known about how to prevent impairment or how to improve QoL. Our aim is to review what is known about QoL in pituitary tumors patients and to highlight the areas worth improving, for the patient's well-being. The article has four sections: acromegaly, Cushing's syndrome, prolactinomas, and non-functioning adenomas. Control of comorbidities is usually an important factor to prevent QoL impairment; however, each disease has specific characteristics that should be properly addressed in order to obtain full patient recovery after successful therapy.

Keywords

Quality of life, acromegaly, Cushing's syndrome, prolactinomas, non-functioning adenomas, pituitary tumors

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Pituitary tumors are associated with pituitary dysfunction, either hypersecretion (mainly prolactinomas, acromegaly, or Cushing's disease [CD]) or hypopituitarism, due to compression or destruction of normal pituitary cells. They may also cause headache or visual disturbances due to pressure on surrounding structures.

Health-related quality of life (QoL) is a concept that refers to individual wellbeing. It is based on how a particular individual feels, responds, and functions in daily life. Subjects will value their QoL, taking into account their expectations, standards, and goals, as well as the emotional, physical, and social aspects of their lives, which may be affected if a disease is present.[1]

There are two kinds of tools normally used to measure QoL: generic and specific questionnaires. In both, patients answer questions related to their perception of their health status. Answers can be rated in yes/no questions, a Likert scale (i.e. always, often, sometimes, rarely, never), or in a range (i.e. 0–100). Generic questionnaires are useful in different populations, including healthy subjects. They can help to compare QoL in different diseases, for instance. Examples of generic questionnaires used in pituitary tumors are the Nottingham Health Profile (NHP),[2] Short-Form 36 (SF-36),[3] the EuroQoL[4–6] or the Psychological General Wellbeing Scale (PGWBS)[7] (see *Table 1*).

However, they are often not sensitive enough to appreciate particular problems that may be related to a certain disease. That is why disease-specific questionnaires have been developed, more sensitive to detect subtle changes in QoL in a determined disease (for instance, improvement after treatment). For pituitary adenomas, questionnaires often used are AcroQoL for acromegaly,[8] CushingQoL for Cushing's syndrome (CS),[9,10] and Adult Growth Hormone Deficiency Assessment (AGHDA)[11] or Questions on Life Satisfaction-Hypopituitarism (QLS-H) for growth hormone (GH) deficiency[12,13] (see *Table 1*).

The following section reviews what is known about QoL in patients with pituitary tumors, both at diagnosis and after treatment, highlighting what may be helpful to improve QoL.

Acromegaly

Acromegaly is a syndrome caused by chronic exposure to elevated levels of GH and peripheral insulin-like growth factor 1 (IGF-I). It is associated with morphological changes (including soft tissue swelling, excessive sweating, and change in patients' voice), often not completely reversible, with physical and psychological limitations (including joint pains, headache, low energy, and libido). Due to the insidious nature of the disease, the diagnosis of acromegaly is significantly delayed, being undiagnosed for years, despite the presence of signs and symptoms, thus, the impact of the disease and its treatment on the patients' QoL can be great.[14–18]

Compared with the general population, SF-36 questionnaire scores are lower in acromegaly, reflecting impairment of perceived QoL in physical function dimensions, but not in the mental ones.[19] Successful surgery or medical treatment may be followed by marked improvement in the patient's overall health, often, but not always, accompanied by improvement or normalization of biochemical parameters such as GH and IGF-I. Since comorbidities occur after many years of exposure to excessive GH, an earlier diagnosis would benefit patients' perceived health and QoL.[20,21] The availability of a questionnaire, specifically designed to evaluate the problems typical of acromegaly (AcroQoL),

Table 1: Generic and Disease-specific Questionnaires to Assess Health-related Quality of Life

		Name and Interpretation	Characteristics	Reference
Generic questionnaires		Nottingham Health Profile (NHP) *Higher: Worse QoL*	It has 6 subscales: energy level, pain, emotional reaction, sleep, social isolation, and physical abilities. Furthermore, it gives information on affected life areas (work, looking after home, social life, home life, sex life, interests and hobbies, and vacations)	2
		Short-Form 36 (SF-36) *Higher: Better QoL*	It has 8 scales divided into physical health (physical functioning, role-physical, bodily pain, and general health) and mental health (vitality, social functioning, role-emotional, and mental health)	3
		EuroQoL *VAS – Higher: Better QoL* *5D – Higher: Worse QoL*	It has a VAS to assess general well-being (similar to a thermometer) and 5D: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	4–6
		Psychological General Wellbeing Scale (PGWBS) *Higher: Better QoL*	It has 6 subscales: anxiety, depressed mood, positive well-being, self-control, general health, and vitality	7
Specific questionnaires	*Acromegaly*	AcroQoL *Higher: Better QoL*	It includes 22 questions, can be scored globally or in 2 scales (physical and psychological). The psychological scale is subdivided into 2 further subscales: appearance and personal relations	8
	Growth-hormone deficiency	AGHDA *Higher: Worse QoL*	It is unidimensional, with 24 questions with Yes/No possibility	11
		Questions on Life Satisfaction-Hypopituitarism (QLS-H) *Higher: Better QoL*	It is unidimensional with parts: the first presents the degree of agreement with the items; the second, the importance given by the individual to of each of the items	12,13
	Cushing's syndrome	Cushing QoL *Higher: Better QoL*	It is unidimensional, with 12 questions	9,10

5D = five dimensions; AGHDA = Adult Growth Hormone Deficiency Assessment; QoL = quality of life; VAS = visual analog scale.

has favored research in this area. This is particularly important in consideration of the fact that GH and IGF-I do not always correlate with subjective and clinical improvements experienced by patients and physicians after treatment.[22]

With AcroQoL, lower scores in active disease have persistently been observed in different countries, compared with patients in remission after successful therapy, with appearance being the most affected dimension and the personal relations area the least affected.[23–26] However, impairments in QoL, as assessed by the generic questionnaire PGWBS, persist in 'cured' acromegaly compared with the normal population and patients treated for a non-functioning pituitary adenoma, mainly in the domains of general health and vitality, and similarly bad or worse than adults with GH deficiency.[27]

Pharmacologic treatment (either monotherapy or combination therapy) lower GH and IGF-1, and improve both acromegaly comorbidities and QoL.[22,24,28–32] A double-blind study in acromegalic patients controlled on somatostatin analog therapy showed how the addition of pegvisomant improved the AcroQoL score, without changes in IGF-1 levels.[22] This highlighted the importance of including patient-reported outcome measures such as QoL assessment in clinical practice,[22] since evaluation of perceived QoL and clinical improvement with these questionnaires could be more sensitive than IGF-I measurement. The AcroQoL results have questioned the current recommendations on assessment of disease activity in acromegaly with GH and IGF-I and highlighted the importance of including QoL assessment in daily practice. The chronic need for monthly injections of somatostatin analogs to control the disease has also been shown to impair AcroQoL scores.[33] Patients treated with radiotherapy had low QoL scores, although it is unknown whether this relates to the more aggressive nature of the disease, which remains active after surgery and medical therapy.[14,34,35] Disease duration, active disease, older age, female gender, and presence of joint pain are also negatively correlated with the AcroQoL scores.[14,34,36] Multidisciplinary teams with specific experience in pituitary disease, including experienced dedicated pituitary neurosurgeons have higher success rates[37–41] in long-term outcome and this may improve QoL. The possibility to personalize therapeutic options on patients' individual clinical and biochemical characteristics would determine better long-term prognosis and have a positive impact on patients QoL. Nevertheless, it is important to be aware of the persistent adverse effects of pituitary disease on QoL. Discussions with the patient could prevent inappropriate expectations in terms of the long-term results of treatment.

Among the factors affecting QoL, psychological status seems to be one of the most relevant. Acromegaly is associated with higher anxiety-related traits

and reduced novelty-seeking behavior and impulsivity, compared with non-functioning adenomas, which may affect QoL, treatment adherence, and patient–doctor contact.[42] Patients described themselves as more harm avoidant and neurotic and showed a high social conformity. All these psychological aspects may be benefited by a proper treatment, which may also improve QoL.

When QoL is compared in different pituitary tumors using Z-scores (or standard deviation scores) for different generic questionnaires, differences in age and gender (two determinants of QoL) are accounted for, and comparisons with reference populations are possible.[43] Total QoL score and all subscales of the questionnaires are worse in acromegaly compared with controls, demonstrating impairment of QoL during long-term follow up after treatment. More impairment for physical ability and functioning and more bodily pain were seen than in patients treated for non-functioning pituitary adenomas (NFA) or prolactinomas. Hypopituitarism further impaired multiple aspects of QoL.

Development of GH deficiency after treatment for acromegaly also affects QoL negatively. In fact, the patients least affected were those who attained a normal GH after treatment (i.e. between 0.3–1 mcg/l), while if GH was higher (reflecting active disease), or lower (indicating that these patients had become GH deficient),[44] more impairment ensued. With the AGHDA score, young adult patients who became GH deficient due to prior treatment of acromegaly (with surgery and/or radiotherapy) improved their QoL after substitution therapy with recombinant human GH (rhGH).[45] However, this was not found in older patients with a mean age of 56 years.[46]

In summary, the availability of a disease-specific questionnaire as AcroQoL has confirmed that QoL is impaired in acromegaly, especially in active disease, if medical therapy is provided (with greatest impact on the appearance dimension), and if musculoskeletal symptoms (mainly pain) are present. Patients with acromegaly experience maladaptative personality traits, which may impact QoL. The physical dimensions of the AcroQoL questionnaire have been shown to be more sensitive than circulating IGF-I to detect patient's improvement after adding pegvisomant to somatostatin analog treatment in 'controlled' patients. In conclusion, an earlier diagnosis in order to prevent long-term complications, good disease control, specific approach to comorbidities, and patient education on the disease and its consequences tend to be helpful to improve QoL in acromegaly. However, awareness of the incomplete reversibility of some QoL dimensions is important to prevent unrealistic expectations of the outcome of therapy.

Cushing's Syndrome

The clinical features associated with hypercortisolism in patients with CS seem to be a strong determinant for wellbeing and QoL. QoL questionnaires used together with specific evaluations of cognitive functioning or depression have shown impaired QoL in CS.[19,47–50] Several investigators have demonstrated greater impairment of QoL in active CS patients than in 'cured' patients.[10,47,48] However, cured CS patients failed to normalize their QoL, even long term after control of hypercortisolism.[48,50,51] The degree of initial hypercortisolism is not associated with subsequent level of decreased QoL. Complex pharmacologic treatments, need for frequent medical check-ups and concerns about future health deterioration due to comorbidity, also negatively affect QoL.[51,52] Therefore, CS patients show more emotional problems (depression and anxiety) and slower recovery after surgery than other patients with pituitary adenomas.[19,53]

Patients with CS most often complain of fatigue/weakness (85 %), changes in physical appearance (63 %), emotional instability (61 %), cognitive problems (49 %), depression (32 %), and sleeping difficulties (12 %).[54] These problems in CS patients cause negative effects on family life, partner relations, and work/school performance.[54] Furthermore, a retrospective report showed low scores in questions regarding employment status and work capacity in CS patients both before and after treatment.[55] Although after treatment, 81 % of CS patients were working, 11 % were retired because of disability, 5 % were retired because of age, and 3 % were on sick-leave at the time of answering the questionnaire.[55]

The mechanism through which CS determines impairment of QoL is probably multifactorial, involving physical, medical, and psychological factors. Impaired QoL has not been found to correlate with modality of treatment (pituitary or adrenal surgery or pituitary irradiation), duration of follow up after biochemical remission, disease duration, or severity of hypercortisolism.[9,49,51] An Europe-wide study demonstrated that depression was the only negative predictor of QoL score (using the disease-specific CushingQoL questionnaire), whereas other variables such as delay to diagnosis, diabetes or hypertension did not significantly influence it.[56] Most CS patients have depression or emotional lability especially if they are older, female, and have severe hypercortisolism.[57,58] Psychopathology (mainly atypical depression) was more prevalent before cure (66.7 %) than at 3 months (53.6 %), 6 months (36 %) and 12 months (24.1 %) after successful treatment.[59]

Some studies using generic questionnaires (NHP, SF-36, Multidimensional Fatigue Inventory-20 [MFI-20], Hospital Anxiety and Depression Inventory [HADS]) showed that pituitary radiotherapy led to greater QoL impairment in CS patients compared with those who had not been irradiated,[51] but this observation was not confirmed with the CushingQoL questionnaire (a disease-specific questionnaire for measuring QoL in CS patients).[9,10] Wagenmakers et al.[50] showed that hormonal deficiencies in patients in long-term remission of CS was associated with impaired QoL. Others have not found differences in the CushingQoL score in relation to the presence or not of hypopituitarism, although they described that longer duration of adrenal insufficiency did affect QoL negatively.[9,10] Therefore, assessment of adrenal insufficiency is important in monitoring of patients, and to start on effective replacement as early as possible is fundamental for QoL of CS patients.

Studies seem to agree that there are no differences in QoL between patients with CS of pituitary or adrenal origin,[9,10,50,56,60] suggesting that persistent QoL deficits after biochemical cure of CD are driven by the disease process and hypercortisolism itself, and not by the origin or eventual mode of curative therapy. QoL evaluation after uni- or bilateral adrenalectomy for CS has shown symptomatic improvement in all patients regardless of their primary diagnosis (adrenal adenoma, ectopic adrenocorticotropic hormone, macronodular hyperplasia, CD, adrenocortical cancer, and pigmented micronodular hyperplasia) and independently of the surgical procedure performed (laparoscopic or open bilateral adrenalectomy), similar to that found in patients treated with pituitary surgery or radiotherapy.[61,62] When CD patients were asked to value the effect of adrenalectomy on QoL, 78 % (28/36) answered they had improved and 68 % (19/28) claimed a dramatic improvement, but 14 % (5/36) experienced no change and 8 % (3/36) stated that their QoL had

worsened.[63] Limited data comparing pre- and post-treatment QoL in CD patients are currently available. Vitality/Fatigue and General Health in the treated group scored better than in the active, pre-treatment group, but to a lower degree than seen for the other scales.[64] Fatigue was still present in 46 % of treated CD patients. However, the majority of these patients (86 %) felt that their health status was good to excellent, compared with 1 year before surgery, and 68 % reported no problems with moderate activities.[64] Moreover, another report demonstrated that in CS patients, improvement of health-status perception is detectable a few months after surgery (4±1.5 months), using the CushingQoL questionnaire.[10] These data indicate that significant improvement of QoL is time dependent after therapy.

In conclusion, despite successful treatment of CS, long-term residual effects on QoL persist. Handling physicians should advise patients that QoL recovery is progressive and slower than biochemical correction, independently of the cause of CS (adrenal or pituitary), and the modality of treatment. Patients should be warned that complete reversal of physical and psychological comorbidities does not occur immediately after surgery and poor well-being may be associated with persistent depression. Thus, appropriate treatment to reduce depressive symptoms is necessary to improve QoL in CS patients.

Non-functioning Pituitary Adenomas

Few and conflicting data on QoL on NFA have been published. Some studies demonstrated that QoL was reduced in treated NFA patients,[19,43,65] in contrast with others showing that successful treatment led to normalization of QoL compared with healthy population.[66–68] NFA are usually macroadenomas causing visual field defects and hypopituitarism. Visual field deficiencies were associated with reduced interest in leisure activities,[66] without affecting the global QoL score.[65,66] However, post-operative hypopituitarism is a strong predictor of reduced QoL.[43,65] In particular, NFA patients with hypogonadism showed worse social life and reduced daily activity in comparison to those having normal gonadotropin function or on correct hormone replacement.[65,66] On the other hand, several studies have found that QoL is impaired in patients suffering GH deficiency,[69–72] and impairment is worse if other pituitary deficits are present.[73] NFA patients with GH deficiency showed impaired body pain, mental health, and general health perception compared with GH-deficient patients,[66] which improved after correct replacement with GH.[74] Once treated, improvements can be found in QoL, cardiac function, body composition, and lipid profile.[13,75–79] Furthermore, patients also have improvements in sexual arousal and body shape after treatment, and have a very prompt improvement in dimensions of socializing and tenseness.[80,81] This information gives more support to the idea that patients could benefit from GH-substitution therapy.

Altered sleep characteristics have been described in 17 patients after surgical removal of NFA.[82] Disturbed sleep was associated with fatigue during the day and poor QoL.[82] Reduced energy, fatigue (mental and physical), physical problems, lower activity, and motivation were previously reported in another study on operated NFA patients.[65] Thus, regulating patient's sleep–wake cycle is recommended in order to ameliorate QoL.[82]

In NFA patients, as well as in normal population, gender, and age seem to be determinants of QoL.[43] NFA patients are older than patients with other pituitary adenomas,[19] and recent data indicated that female NFA patients have physical and emotional problems, reduced energy, and poorer health perception in comparison to their male counterparts.[66] Moreover, NFA patients with tumor recurrence have abnormal scores in physical ability, energy, and anxiety.[66] Therefore, because 20 % of tumors relapse 10 years after the first intervention, long-term post-operative monitoring is highly recommended.[83]

Another important aspect negatively impacting on QoL in pituitary adenomas is radiotherapy. Some studies demonstrated that having received radiotherapy can impair mental health[67] or energy levels of NFA patients,[66] without affecting their general health perception.[43,65,84]

In conclusion, specific characteristics of NFA patients, such as female gender, hypopituitarism (especially hypogonadism and GH deficiency), or tumor recurrence seem to be related with impaired QoL. Radiological and clinical monitoring, hormone replacement, and better sleep quality will ameliorate the perception of health status.

Prolactinomas

Patients with prolactinomas present poor QoL as evaluated by different generic questionnaires.[19,85–87] Gonadal dysfunction is one of the most important problems in these patients. In men, decreased libido, erectile dysfunction, and poor seminal fluid quality are frequent consequences of prolactin hypersecretion.[88,89] In women, hyperprolactinemia causes amenorrhea, galactorrhea, vaginal dryness, dyspareunia, and decreased libido, which can lead to infertility.[88] These reproductive impairments have a great influence on patient's QoL, especially in women.[86] To treat these reproductive impairments is important because they can impact on patients' QoL even after correction of hyperprolactinemia.

The first-line treatment for prolactinomas, dopamine agonists, are able to reduce tumor size, normalize prolactin levels, and relieve symptoms in these patients,[88] but impaired QoL may persist after successful treatment.[86] Female patients with treated microprolactinoma showed lower scores in physical problems, vitality, emotional aspects, and social isolation compared with control subjects.[85,86] These results were independent of prolactin serum values, current or previous intake of dopamine agonists, and dosage or formulation of this treatment.[86]

Mental health and psychological function measures have been described to be impaired in prolactinoma patients. Altered personality profiles have been evidenced in these patients in comparison to the normal population. In particular, prolactinoma patients presented minor extraversion, lesser novelty seeking, increased shyness and neuroticism compared with healthy controls.[87] Moreover, it has been shown that women treated for microprolactinomas were more vulnerable to anxiety and depression symptoms than control subjects.[86] Psychological support and psychiatric treatment may prevent and resolve these problems, since mental health is a major factor in perception of QoL.

In summary, prolactinoma patients (particularly women) show emotional and psychological problems that negatively impact QoL. It is important to normalize sexual/reproductive function and to treat psychopathology symptoms, in order to achieve significant improvement of QoL in these patients. Globally, QoL is impaired in pituitary tumors. As in healthy subjects, women tend to have worse QoL than men. Specific psychological and physical limitations are present in secreting adenomas (i.e., acromegaly, Cushing's syndrome—both of pituitary and other origins—and prolactinomas), often not completely reversible even after endocrine cure. Thus, an earlier diagnosis, before irreversible comorbidities occur, should impact HRQoL positively. In larger tumors with a mass effect on surrounding structures (i.e. causing visual impairment or hypopituitarism), QoL may be impaired by these complications. ■

1. Webb SM, Resmini E, Santos A, et al., Quality of Life in acromegaly and Growth Hormone Deficiency. In: Ken Ho (ed.), *Growth Hormone Related Diseases and Therapy: A Molecular and Physiological Perspective for the Clinician*, New York City: Humana Press, 2011;201;237–50.
2. Hunt SM, McKenna SP, McEwen J, et al., The Nottingham Health profile: Subjective health status and medical consultations, *Soc Sci Med*, 1981;15A:221–9.
3. Ware JE, Snow KK, Kosinski M, et al., *SF-36 Health Survey. Manual and Interpretation Guide*. Boston: The Health Institute, New England Medical Center, 1993.
4. Dolan P, Modelling valuations for EuroQol health states, *Medical Care*, 1997;35(11):1095–108.
5. Badia X, Herdman M, Schiaffino A, A determining correspondence between scores on the EQ-5D "thermometer" and a 5-point categorical rating scale, *Medical Care*, 1999;37(1):671–7.
6. Brooks R, EuroQol: the current state of play, *Health Policy*, 1996;37:53–7.
7. Gray LC, Goldsmith HF, Livieratos BB, et al., Individual and contextual social-status contributions to psychological wellbeing, *Soc & Soc Res,* 1983;68(1):78–95.
8. Webb SM, Prieto L, Badia X, et al., Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties, *Clin Endocrinol*, 2002;57(2):251–8.
9. Webb SM, Badia X, Barahona MJ, et al., Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire, *Eur J Endocrinol*, 2008;158(5):623–30.
10. Santos A, Resmini E, Martínez-Momblán MA, et al., Psychometric performance of the CushingQoL questionnaire in conditions of clinical practice, *Eur J Endocrinol*, 2012;167(3):337–42.
11. McKenna SP, Doward LC, Alonso J, et al., The QoL.AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency, *Qual Life Res*, 1999;8(4):373–83.
12. Blum WF, Shavrikova EP, Edwards DJ, et al., Decreased quality of life in adult patients with growth hormone deficiency compared with general populations using the new, validated, self-weighted questionnaire, questions on life satisfaction hypopituitarism module, *J Clin Endocrinol Metab*, 2003;88:4158–67.
13. Rosilio M, Blum WF, Edwards DJ, et al., Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by QLS-H, *J Clin Endocrinol Metab*, 2004;89(9):1684–93.
14. Biermasz NR, Pereira AM, Smit JW,et al., Morbidity after long-term remission for acromegaly: Persisting joint-related complaints cause reduced quality of life, *J Clin Endocrinol Metab*, 2005;90(5):2731–9.
15. Cappola A, Disorders of the Anterior Pituitary and Hipothalamus. In: Kasper DL, Braunwald E, Fauci AS, et al., (eds), *Harrison's Manual of Medicine*, New York City: McGraw-Hill, 2005; 807–13.
16. Melmed S, Acromegaly pathogenesis and treatment, *J Clin Invest*, 2009;119(5):3189–202.
17. Vannucci L, Luciani P, Gagliardi E, et al., Assessment of sleep apnea syndrome in treated acromegalic patients and correlation of its severity with clinical and laboratory parameters, *J Endocrinol Invest*, 2013;36(4):237–42.
18. Unubol M, Eryilmaz U, Guney E, et al., QT dispersion in patients with acromegaly, *Endocrine*, 2013;43(2):419–23.
19. Johnson MD, Woodburn CJ, Vance ML, Quality of life in patients with a pituitary adenoma, *Pituitary*, 2003;6(2):81–7.
20. Melikoglu MA, Sezer I, Kocabas H, et al., Acromegalic arthropathy of the hip: a case report, *Acta Rumatol Port*, 2008;33(3):357–9.
21. Siegel S, Streetz-van der Werf C, Schott JS, et al., Diagnostic delay is associated with psychosocial impairment in acromegaly, *Pituitary*, 2013;16(4):507–14.
22. Neggers SJ, van Aken MO, de Herder WW, et al., Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant, *J Clin Endocrinol Metab*, 2008;93(10):3853–9.
23. Webb SM, Badia X, Surinach NL, et al., Validity and clinical applicability of the acromegaly quality of life questionnaire AcroQoL: a 6-month prospective study, *Eur J Endocrinol*, 2006;155(2):269–77.
24. Matta MP, Couture E, Cazals L, et al., Impaired quality of life of patients with acromegaly: control of GH/IGF-1 excess improves psychological subscale appearance, *Eur J Endocrinol*, 2008;158(3):305–10.
25. Trepp R, Everts R, Stettler C, et al., Assessment of quality of life in patients with uncontrolled versus controlled acromegaly using the acromegaly quality of life questionnaire (AcroQoL), *Clin Endocrinol*, 2005;63(1):103–10.
26. Deyneli O, Yavuz D, Gozu H, et al. Evaluation of quality of life in Turkish patients with acromegaly (abstract P3-508). In: Programs and abstracts of the 84th Annual Meeting of the Endocrine Society, Philadelphia, 2003.
27. Rowles SV, Prieto L, Badia X, et al., 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(6):3337–41.
28. Galdiero M, Pivonello R, Grasso LF, et al., Growth hormone, prolactin, and sexuality, *J Endocrinol Invest*, 2012;35(8):782–94.
29. Ruchala M, Stangierska I, Gurgul E, et al., The effect of octreotide treatment on somatic and psychological symptoms of acromegaly, *Neuro Endocrinol Lett*, 2010;31(2):265–9.
30. Sardella C, Lombardi M, Rossi G, et al., Short and long-term changes of quality of life in patients with acromegaly, results from a prospective study, *J Endocrinol Invest*, 2010;33(1):20–25.
31. Sievers C, Brübach K, Saller B, et al., Change of symptoms and perceived health in acromegalic patients on pegvisomant therapy: a retrospective cohort study within the German Pegvisomant Observational Study (GPOS), *Clin Endocrinol (Oxf)*, 2010;73(1):89–94.
32. Lombardi G, Minuto F, Tamburrano G, et al., Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in somatostatin analogue-naive patients with acromegaly, *J Endocrinol Invest*, 2009;32(3):202–9.
33. Postma MR, Netea-Maiter RT, Van den Berg G, et al., Quality of life is impaired in association with the need for prolenged postoperative therapy by somatostatin analogs in patients with acromegaly, *Eur J Endocrinol*, 2012;166(4):585–92.
34. Biermasz NK, Van Thiel SW, Pereira AM, et al., Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess, *J Clin Endocrinol Metab*, 2004;89(11):5369–76.
35. Van der Klaauw AA, Biermasz NR, Hoftijzer HC, et al., Previous radiotherapy negatively influences quality of life during 4 years of follow-up in patients cured from acromegaly, *Clin Endocrinol (Oxf)*, 2008;69(1):123–8.
36. Miller A, Doll H, David J, Wass J, Impact of musculoskeletal disease on quality of life in long-standing acromegaly, *Eur J Endocrinol*, 2008;158(5):587–93.
37. Melmed S, Colao A, Barkan A, et al., Guidelines for acromegaly management: an update, *J Clin Endocrinol Metab*, 2009;94(5):1509–17.
38. Ciric I, Ragin A, Baumgartner C, et al., Complications of transsphenoidal surgery: results of a national survey, review of the literature and personal experience, *Neurosurgery*, 1997;40(2):225–36.
39. Ahmed E, Stratton P, Adams W, Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience, *Clin Endocrinol (Oxf)*, 1999;50(5):561–67.
40. Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM, Outcome of surgery for acromegaly-the experience of a dedicated pituitary surgeon, *QJM*, 1999;92(12):741–5.
41. Bates PR, Carson MN, Trainer PJ, et al., Wide variation in surgical outcomes for acromegaly in the UK, *Clin Endocrinol (Oxf)*, 2008;68(1):136–42.
42. Sievers C, Ising M, Pfister H, et al., Personality in patients with pituitary adenomas is characterised by increased anxiety related traits: comparison of 70 acromegalic patients to patients with non-functioning pituitary adenomas and age and gender matched controls, *Eur J Endocrinol*, 2009;160:367–73.
43. Van der Klaauw AA, Kars M, Biermasz NR, et al., Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas, *Clin Endocrinol*, 2008;69(5):775–84.
44. Kauppinen-Mäkelin R, Sane T, Sintonen H, et al., Quality of life in treated patients with acromegaly, *J Clin Endocrinol Metab*, 2006;91:3891–6.
45. Wexler T, Gunnell L, Omer Z, et al., Growth hormone deficiency is associated with decreased quality of life in patients with prior acromegaly, *J Clin Endocrinol Metab*, 2009;94:2471–7.
46. Van der Klaauw AA, Bax JJ, Roelfsema F, et al., Limited effects of growth hormone replacement in patients with GH deficiency during long-term cure of acromegaly, *Pituitary*, 2009;12(4):339–46.
47. Lindsay JR, Nansel T, Baid S, et al., Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission, *J Clin Endocrinol Metab*, 2006;91:447–53.
48. Lindholm J, Juul S, Jorgensen JO, et al., Incidence and late prognosis of Cushing's syndrome: a population-based study, *J Clin Endocrinol Metab*, 2001;86:117–23.
49. Hawn MT, Cook D, Deveney C, et al., Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease, *Surgery*, 2002;132(6):1064–8.
50. Wagenmakers MA, Netea-Maier RT, Prins JB, et al., Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism? *Eur J Endocrinol*, 2012;167(5):687–95.
51. Van Aken MO, Pereira AM, Biermasz NR, et al., Quality of life in patients after long-term biochemical cure of Cushing's disease, *J Clin Endocrinol Metab*, 2002;90(6):3279–86.
52. Heald AH, Ghosh S, Bray S, et al., Long-term negative impact on quality of life in patients with successfully treated Cushing's disease, *Clin Endocrinol*, 2004;61:458–65.
53. Sonino N, Navarrini C, Ruini C, et al., Persistent psychological distress in patients treated for endocrine disease, *Psychother Psychosom*, 2004;73:(4)78–83.
54. Gotch PM, Cushing's syndrome from the patient's perspective, *Endocrinol Metab Clin North Am*, 1994;23(3):607–17
55. Pikkarainen L, Sane T, Reunanen A, The survival and wellbeing of patients treated for Cushing's syndrome, *J Intern Med*, 1999;245(5):463–8.
56. Valassi E, Santos A, Yaneva M, et al., The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics, *Eur J Endocrinol*, 2011;165(3):383–92.
57. Sonino N, Fava GA, Psychosomatic aspects of Cushing's disease, *Psychother Psychosom*, 1998;67(3):140–46.
58. Bourdeau I, Bard C, Noel B, et al., A loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism, *J Clin Endocrinol Metab*, 2002;87(5):1949–54.
59. Dorn LD, Burgess ES, Friedman TC, et al., The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism, *J Clin Endocrinol Metab,* 1997;82:(3)912–9.
60. O'Riordain DS, Farley DR, Young WF Jr, et al., Long-term outcome of bilateral adrenalectomy in patients with Cushing's syndrome, *Surgery*, 1994;116(6):1088–94.
61. Nagesser SK, van Seters AP, Kievit J, et al., Long-term results of total adrenalectomy for Cushing's disease, *World J Surg*, 2000;24(1):108–13.
62. Thompson SK, Hayman AV, Ludlam WH, et al., Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience, *Ann Surg*, 2007;245(5):790–94
63. Sippel RS, Elaraj DM, Kebebew E, et al., Waiting for change: Symptom resolution after adrenalectomy for Cushing's syndrome, *Surgery*, 2008;144(6):1054–61.
64. Smith PW, Turza KC, Carter CO, et al., Bilateral adrenalectomy for refractory Cushing's disease: A safe and definitive therapy, *J Am Coll Surg*, 2009;208(6):1059–64.
65. Dekkers OM, van der Klaauw AA, Pereira AM, et al., Quality of life is decreased after treatment for nonfunctioning pituitary macroadenomas, *J Clin Endocrinol Metab*, 2006;91:3364–69.
66. Capatina C, Christodoulides C, Fernandez A, et al., Current treatment protocols can offer a normal or near normal quality of life in the majority of patients with non-functioning pituitary adenomas, *Clin Endocrinol*, 2013;78(1):86–93.
67. Page RC, Hammersley MS, Burke CW, et al., An account of the quality of life of patients after treatment for non-functioning pituitary tumours, *Clin Endocrinol*, 1997;46(4):401–6.
68. Nielsen EH, Lindholm J, Laurberg P, et al., Non-functioning pituitary adenomas: incidence, causes of death and quality of life in relation to pituitary function, *Pituitary*, 2007;10(1):67–73.
69. Degerblad M, Grunditz R, Hall K, et al., Substitution therapy with recombinant growth hormone (Somatrem) in adults with growth hormone deficiency, *Acta Paediatr Scand*, 1987;337(Suppl.):170–1.
70. Salomon F, Cuneo R, Hesp R, et al., The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency, *N Engl J Med*, 1989;321(26):1797–803.
71. Cuneo R, Salomon F, McGauley G, et al., The growth hormone deficiency syndrome in adults, *Clin Endocrinol*, 1992;37(5):387–97.
72. McGauley GA, Cuneo RC, Salomon F, et al., Psychological wellbeing before and after growth hormone treatment in adults with growth hormone deficiency, *Horm Res*, 1990;33(Suppl. 4):52–4.
73. Koltowska-Häggström M, Kind P, Monson, et al., Growth hormone (GH) replacement in hypopituitary adults with GH deficiency evaluated by a utility-weighted quality of life index: a precursor to cost–utility analysis, *Clin Endocrinol*, 2008;68:122–9.
74. Höybye C, Ragnarsson O, Jönsson PJ, et al., Clinical features of GH deficiency and effects of 3 years of GH replacement in adults with controlled Cushing's disease, *Eur J Endocrinol*, 2010;162(4):677–84.
75. Miller KK, Wexler T, Fazeli P, et al., Growth hormone deficiency after treatment of acromegaly: a randomised, placebo-controlled study of growth hormone replacement, *J Clin Endocrinol Metab*, 2010;95:567–77.
76. Lombardi G, di Somma C, Grasso LF, et al., The cardiovascular system in GH excess and GH deficiency, *J Encocrinol Invest*, 2012;35(11):1021–9.
77. Giavoli C, Profka E, Verrua E, et al., GH replacement improves quality of life and metabolic parameters in cured acromegalic patients with growth hormone deficiency, *J Clin Endocrinol Metab*, 2012;97(11):3983–8.
78. Spielhagen C, Schwahn C, Möller K, et al., The benefit of long-term growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency: results of the German KIMS database, *Growth Horm IGF Res*, 2011;21(1);1–10.
79. Kann PH, Growth Hormone therapy in adult patients: a review, *Wien Klin Wochenschr*, 2011;123(9–10):259–67.
80. Koltowska-Häggström M, Mattsson AF, Shalet SM, Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations, *Eur J Endocrinol*, 2009;161(Suppl. 1):S51–64.
81. Attanasio AF, Shavrikova EP, Blum WF, et al., Quality of life in childhood onset growth hormone-deficient patients in the transition phase from childhood to adulthood, *J Clin Endocrinol Metab*, 2005;90:4525–9.
82. Biermasz NR, Joustra SD, Donga E, et al., Patients previously treated for non-functioning pituitary macroadenomas have disturbed sleep characteristics, circadian movement rhythm and subjective sleep quality, *J Clin Endocrinol Metab*, 2011;96(5):1524–32.
83. Reddy R, Cudlip S, Byrne JV, et al., Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma? *Eur J Endocrinol*, 2011;165(5):739–44.
84. Van Beek AP, van den Bergh AC, van den Berg LM, et al., Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for non-functioning pituitary adenoma, *Int J Radiat Oncol Biol Phys*, 2007;68:986–91.
85. Cesar de Oliveira Naliato E, Dutra Violante AH, Caldas D, et al., Quality of life in women with microprolactinoma treated with dopamine agonists, *Pituitary*, 2008;11(3):247–54.
86. Kars M, van der Klaauw AA, Onstein CS, et al., Quality of life is decreased in female patients treated for microprolactinoma, *Eur J Endocrinol*, 2007;157(2):133–9.
87. Athanasoulia AP, Ising M, Pfister H, et al., Distinct dopaminergic personality patterns in patients with prolactinomas: A comparison with non-functioning pituitary adenoma patients and age- and gender-matched controls, *Neuroendocrinology*, 2012;96(3):204–11.
88. Kars M, Dekkers OM, Pereira AM, et al., Update in prolactinomas, *Neth J Med*, 2010;68(3):104–12.
89. Ciccarelli A, Guerra E, De Rosa M, et al., PRL secreting adenomas in male patients, *Pituitary*, 2005;8:39–42.