

## Improving Quality of Life in Patients with Pituitary Tumours

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### Abstract

Evaluation of health-related quality of life (QoL) in people with pituitary tumours 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 tumours 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 tumours

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Pituitary tumours 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.<sup>1</sup>

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 tumours are the Nottingham Health Profile (NHP),<sup>2</sup> Short-Form 36 (SF-36),<sup>3</sup> the EuroQoL<sup>4–6</sup> or the Psychological General Wellbeing Scale (PGWBS)<sup>7</sup> (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,<sup>8</sup> CushingQoL for Cushing's syndrome (CS)<sup>9,10</sup> and Adult Growth Hormone Deficiency Assessment (AGHDA)<sup>11</sup> or Questions on Life Satisfaction-Hypopituitarism (QLS-H) for growth hormone (GH) deficiency<sup>12,13</sup> (see *Table 1*).

The following section reviews what is known about QoL in patients with pituitary tumours, 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.<sup>14–18</sup>

When 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.<sup>19</sup> 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 normalisation 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.<sup>20,21</sup> The availability of a questionnaire, specifically designed to evaluate the problems typical of acromegaly (AcroQoL), has favoured 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.<sup>22</sup>

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.<sup>23–26</sup> 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.<sup>27</sup>

**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) <i>Higher: Worse QoL</i>	It has six 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, interest and hobbies and vacations)	2
	Short-Form 36 (SF-36) <i>Higher: Better QoL</i>	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 – <i>Higher: Better QoL</i> 5D – <i>Higher: Worse QoL</i>	It has a VAS to assess general wellbeing (similar to a thermometer) and 5D: mobility, self-care, usual activities, pain/discomfort and anxiety/depression	4–6
	Psychological General Wellbeing Scale (PGWBS) <i>Higher: Better QoL</i>	It has six subscales: anxiety, depressed mood, positive wellbeing, self-control, general health and vitality	7
Specific questionnaires	<i>Acromegaly</i> AcroQoL <i>Higher: Better QoL</i>	It includes 22 questions, can be scored globally or in two scales (physical and psychological). The psychological scale is subdivided into two further subscales: appearance and personal relations	8
	<i>Growth-hormone deficiency</i> AGHDA <i>Higher: Worse QoL</i>	It is unidimensional, with 24 questions with Yes/No possibility	11
	Questions on Life Satisfaction-Hypopituitarism (QLS-H) <i>Higher: Better QoL</i>	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
	<i>Cushing's syndrome</i> Cushing QoL <i>Higher: Better QoL</i>	It is unidimensional, with 12 questions	9,10

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

Pharmacological treatment (either monotherapy or combination therapy) lower GH and IGF-1, and improve both acromegaly comorbidities and QoL.<sup>22,24,28–32</sup> A double-blind study in acromegalic patients controlled on somatostatin analogue therapy showed how the addition of pegvisomant improved the AcroQoL score, without changes in IGF-1 levels.<sup>22</sup> This highlighted the importance of including patient-reported outcome measures such as QoL assessment in clinical practice,<sup>22</sup> 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 of monthly injections of somatostatin analogues to control the disease has also been shown to impair AcroQoL scores.<sup>33</sup> 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.<sup>14,34,35</sup> Disease duration, active disease, older age, female gender and presence of joint pain are also negatively correlated with the AcroQoL scores.<sup>14,34,36</sup> Multidisciplinary teams with specific experience in pituitary disease, including experienced

dedicated pituitary neurosurgeons have higher success rates<sup>37–41</sup> in long-term outcome and this may improve QoL. The possibility to personalise 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 behaviour and impulsivity, compared with non-functioning adenomas, which may affect QoL, treatment adherence and patient–doctor contact.<sup>42</sup> 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 tumours 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.<sup>43</sup> 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),<sup>44</sup> 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).<sup>45</sup> However, this was not found in older patients with a mean age of 56 years.<sup>46</sup>

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 maladaptive 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 analogue 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.<sup>19,47–50</sup> Several investigators have demonstrated greater impairment of QoL in active CS patients than in 'cured' patients.<sup>10,47,48</sup> However, cured CS patients failed to normalise their QoL, even long term after control of hypercortisolism.<sup>48,50,51</sup> The degree of initial hypercortisolism is not associated with subsequent level of decreased QoL. Complex pharmacological treatments, need for frequent medical check-ups and concerns about future health deterioration due to comorbidity, also negatively affect QoL.<sup>51,52</sup> Therefore, CS patients show more emotional problems (depression and anxiety) and slower recovery after surgery than other patients with pituitary adenomas.<sup>19,53</sup>

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 %).<sup>54</sup> These problems in CS patients cause negative effects on family life, partner relations and work/school performance.<sup>54</sup> Furthermore, a retrospective report showed low scores in questions regarding employment status and work capacity in CS patients both before and after treatment.<sup>55</sup> 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.<sup>55</sup>

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.<sup>9,49,51</sup> An European-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.<sup>56</sup> Most CS patients have depression or emotional lability especially if they are older, female and have severe hypercortisolism.<sup>57,58</sup> Psychopathology (mainly atypical depression) was more prevalent before cure (66.7 %) than at three months (53.6 %), six months (36 %) and 12 months (24.1 %) after successful treatment.<sup>59</sup>

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,<sup>51</sup> but this observation was not confirmed with the CushingQoL questionnaire (a disease-specific questionnaire for measuring QoL in CS patients).<sup>9,10</sup> Wagenmakers et al.<sup>50</sup> 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.<sup>9,10</sup> 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,<sup>9,10,50,56,60</sup> 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 [ACTH], 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.<sup>61,62</sup> 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.<sup>63</sup> 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.<sup>64</sup> 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 one year before surgery, and 68 % reported no problems with moderate activities.<sup>64</sup> Moreover, another report demonstrated that in CS patients, improvement of health-status perception is detectable a few months after surgery ( $4 \pm 1.5$  months), using the CushingQoL questionnaire.<sup>10</sup> 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 wellbeing 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,<sup>19,43,65</sup> in contrast with others showing that successful treatment led to normalisation of QoL compared with healthy population.<sup>66–68</sup> NFA are usually macroadenomas causing visual field defects and hypopituitarism. Visual field deficiencies were associated with reduced interest in leisure activities,<sup>66</sup> without affecting the global QoL score.<sup>65,66</sup> However, post-operative hypopituitarism is a strong predictor of reduced QoL.<sup>43,65</sup> 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.<sup>65,66</sup> On the other hand, several studies have found that QoL is impaired in patients suffering GH deficiency,<sup>69–72</sup> and impairment is worse if other pituitary deficits are present.<sup>73</sup> NFA patients with GH deficiency showed impaired body pain, mental health and general health perception compared with GH-deficient patients,<sup>66</sup> which improved after correct replacement with GH.<sup>74</sup> Once treated, improvements can be found in QoL, cardiac function, body composition and lipid profile.<sup>13,75–79</sup> Furthermore, patients also have improvements in sexual arousal and body shape after treatment, and have a very prompt improvement in dimensions of socialising and tenseness.<sup>80,81</sup> 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.<sup>82</sup> Disturbed sleep was associated with fatigue during the day and poor QoL.<sup>82</sup> Reduced energy, fatigue (mental and physical), physical problems, lower activity and motivation were previously reported in another study on operated NFA patients.<sup>65</sup> Thus, regulating patient's sleep-wake cycle is recommendable in order to ameliorate QoL.<sup>82</sup>

In NFA patients, as well as in normal population, gender and age seem to be determinants of QoL.<sup>43</sup> NFA patients are older than patients with other pituitary adenomas,<sup>19</sup> 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.<sup>66</sup> Moreover, NFA patients with tumour recurrence have abnormal scores in physical ability, energy and anxiety.<sup>66</sup> Therefore, because 20 % of tumours relapse 10 years after the first intervention, long-term post-operative monitoring is highly recommended.<sup>83</sup>

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

In conclusion, specific characteristics of NFA patients, such as female gender, hypopituitarism (especially hypogonadism and GH deficiency) or tumour 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.<sup>19,85–87</sup> 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.<sup>88,89</sup> In women, hyperprolactinaemia causes amenorrhoea, galactorrhoea, vaginal dryness, dyspareunia and decreased libido, which can lead to infertility.<sup>88</sup> These reproductive impairments have a great influence on patient's QoL, especially in women.<sup>86</sup> To treat these reproductive impairments is important because they can impact on patients' QoL even after correction of hyperprolactinaemia.

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

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.<sup>87</sup> Moreover, it has been shown that women treated for microprolactinomas were more vulnerable to anxiety and depression symptoms than control subjects.<sup>86</sup> 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 normalise 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 tumours. 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 co-morbidities occur, should impact HRQoL positively. In larger tumours with a mass effect on surrounding structures (i.e., causing visual impairment or hypopituitarism), QoL may be impaired by these complications. ■

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