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KEYWORDS

• Acromegaly • Somatotropinoma • Comorbidities • Quality of life
• Patient-reported outcomes

KEY POINTS

- Although metabolic alterations, hypertension, and the early stages of cardiomyopathy may be reversible after cure or disease control, many other complications such as musculoskeletal disorders can persist even when the disease is controlled. Consequently, the clinical burden due to acromegaly-associated comorbidities may adversely affect the quality of life (QoL).
- Patient-reported outcome measures (PROMs) are pivotal in the evaluation of disease activity. PROMs have added value in guiding treatment decisions, in particular when growth hormone (GH) and insulin-like growth factor I (IGF-1) levels are discrepant, when patients are only partial responders to treatment, or in patients with discrepant results between PROMs and conventional biochemical outcomes.
- A patient-centered approach should be considered in treatment decisions, integrating conventional biochemical outcomes, tumor control, comorbidities, treatment complications, and PROMs, including QoL measures.

INTRODUCTION

Excess levels of circulating GH and IGF-1 in acromegaly have deleterious effects on a wide range of physiologic processes and tissues. GH levels directly reflect somatotroph tumor secretory activity, and IGF-1 levels reflect peripheral disease activity. Unfortunately, there is often a delay in treatment, as it can take several years of symptoms for a patient to be diagnosed with acromegaly.[1] During this delay, irreversible acromegaly-associated comorbidities may develop, including malignant

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neoplasm and cancer, cardiovascular disorders, type 2 diabetes mellitus, hypopituitarism, arthropathy, vertebral fractures, and psychological morbidity, all of which may affect mortality risk and/or well-being.[2–8]

Recent advances in acromegaly disease control, as well as improved management of comorbidities, have led to lower mortality rates, approaching those of the general population.[9,10] This is usually achieved by multimodality treatment (eg, a combination of surgery, chronic medical treatment, and radiotherapy). In the last two decades, however, it has become apparent that despite normalization of GH and IGF-1 levels and establishing tumor control, musculoskeletal disorders and several other persistent comorbidities may persist. As a consequence, both active and controlled patients with acromegaly report impairments in quality of life (QoL), and the clinical burden due to acromegaly-associated comorbidities adversely affects QoL.[11–15]

Although effective treatment of acromegaly improves QoL and patients' symptoms, biochemical control does not necessarily correlate with clinical well-being, and QoL impairments often persist despite biochemical control.[11] Therefore, a more patient-centered approach, including conventional biochemical outcomes, comorbidities, treatment complications, and the patient perspective by using patient-reported outcome measures (PROMs), should all be considered in treatment decisions. PROMs can assess any component of a patient's health status that comes directly from the patient, without the interpretation of clinicians or anyone else.[16] PROMs can be used to measure purely somatic or psychological symptoms (eg, pain, weight gain, and depressive thoughts), functional problems (eg, carrying out daily activities such as work and family life), and more complex general health perceptions and QoL. PROMs can be generic assessments of QoL in general (eg, Short Form 36 [SF-36]), domain-specific (ie, Hospital Anxiety and Depression Scale [HADS]), or disease-specific (eg, *Acromegaly Quality of Life questionnaire*[AcroQoL]). When interpreting PROMs, it is important to acknowledge the biopsychosocial character of well-being, as conceptualized by the Wilson and Cleary model.17 To effectively use PROMs for decision-making, it is important to understand the paradigm of how well-being is conceptualized. Following the Wilson and Cleary model, health can be seen as a continuum of increasing biological, psychological, and social complexity, ranging from pure biological factors, symptoms, and functional impairments to general health perceptions, all taking into account the influence of individual and environmental characteristics.

This review aims to discuss the impact of acromegaly on QoL from the clinical perspective as well as from the patient perspective. Furthermore, it aims to evaluate the use of PROMs in acromegaly and how PROMs aid decision-making. The recommendations presented in this review are based on recent clinical evidence on the impact of acromegaly on QoL combined with authors' own clinical experience treating patients with acromegaly.

CLINICAL BURDEN

Patients receiving treatment for acromegaly often experience a significant clinical disease burden. Local mass effects and treatment of the tumor may result in side effects and complications, such as hypopituitarism, visual symptoms, and headache. Furthermore, hormone excess results in specific somatic symptoms (eg, changes in facial appearance, acral growth, fatigue, sweating, and pain) and acromegaly-associated comorbidities (eg, type 2 diabetes mellitus, heart failure, arthropathy, and obstructive sleep apnea [OSA]). The risk of developing one of these characteristic comorbidities is greater relative to that of the general population, with a higher risk for comorbidities observed in patients with biochemically uncontrolled

acromegaly.[15,18,19] Although metabolic alterations, hypertension, and early stages of cardiomyopathy may be reversible after early cure or disease control,[20,21] many other complications (eg, musculoskeletal disorders or OSA) may persist or even show progression.[22–25]

Malignant Neoplasm and Cancer

Other neoplasms apart from the pituitary, specifically the prevalence of colon cancer and differentiated thyroid carcinomas, appear to be increased among patients with acromegaly.[26] Cancer is currently the leading cause of mortality,[27–29] although cancer-specific mortality rates in acromegaly are generally similar to those observed in the general population.[27] In addition, increased life expectancy in acromegaly has been associated with more deaths resulting from malignancies that are not typically related to GH or IGF-1 excess. With this in mind, cancer incidence in acromegaly seems to be more related to age than to GH excess, and patients in the modern era may live long enough to reach the age of increased cancer risk.[30] Finally, it should be borne in mind that the increased number of diagnoses of cancer could happen in these patients because they are examined more accurately and more frequently before diagnosis (ie, surveillance bias).

As colonoscopy screening for colonic neoplasia is recommended every 10 years and more frequently in those with persistently elevated IGF-1, having polyps at previous colonoscopies, or in case of a positive family history of colon cancer,[4] it should be kept in mind that screening methods for early cancer detection might lead to significant psychological distress in patients.[31,32]

Cardiovascular Disorders

Cardiovascular events are responsible for increased mortality rates in acromegaly; however, those with well-controlled acromegaly are now closely approximating that of the general population.[27,28]

Subclinical cardiomyopathy with left ventricular hypertrophy is a frequent finding (up to 80% of patients) and is characterized by concentric hypertrophy, progressive systolic deficiency, and diastolic dysfunction. Congestive heart failure may ensue that it is associated with substantial complaints (including loss of energy, reduced exercise tolerance, shortness of breath), functional limitations, and a worse prognosis.

Arterial hypertension is a common finding in up to 60% of acromegaly patients.[8,33] Multifactorial pathogenesis must be assumed in which GH- and IGF-1-mediated sodium and water retention and sympathetic dysfunction seem to play an important role, but hyperinsulinemia and cardiovascular disorder must also be considered.

Endocrine and Metabolic Disorders

Type 2 diabetes mellitus

The most frequent metabolic comorbidities are impaired glucose tolerance and type 2 diabetes mellitus, which are present at diagnosis in up to 50% of patients.[34,35] Owing to GH excess, patients develop insulin resistance, and in the long term, insulin insufficiency with impaired glucose tolerance may occur.[36] Although there are no available studies evaluating the outcome of diabetes complications in acromegaly, microangiopathic complications occur relatively early in the disease course, suggesting a role of GH. As acromegaly patients with diabetes have a higher prevalence of dyslipidemia and hypertension but are also at increased risk of hypertrophic cardiomyopathy with severe diastolic dysfunction, mortality is increased in this subset of patients.[37,38] Previous studies showed that having diabetes mellitus affects QoL adversely in patients with acromegaly.[39,40]

As nearly all patients at diagnosis undergo oral glucose tolerance test, the required information to evaluate the glycemic status is available. Accordingly, if type 2 diabetes is diagnosed, it should be managed for the general population.

Hypopituitarism

Hypopituitarism has been observed in more than 40% of patients with acromegaly, especially among patients treated with conventional radiation therapy. Although hormonal substitution therapy has been extremely successful in improving morbidity and mortality, many patients treated for endocrine insufficiencies still suffer from "vague" complaints and experience impairment in QoL.[41] Glucocorticoid replacement is specifically important to mention, because both under-supplementation and over-supplementation are associated with significant morbidity (including adrenal crisis vs dyslipidemia, cardiovascular risk, and further impairment of bone quality) and mortality.[42] Moreover, it is known from previous studies that glucocorticoid replacement therapy is taxing for patients, with the need for several lifestyle adaptations, concerns about side effects of their medication, fear of adrenal crisis, and often suboptimal care at the emergency department.[43]

The development of GH deficiency following acromegaly treatment is also clearly associated with a compromised QoL.[14,39,44] Hypogonadotropic hypogonadism occurs in more than 50% of patients, either caused by hypopituitarism from tumor mass effect or hyperprolactinemia.[45] On acromegaly treatment, semen quality and androgen levels (total testosterone, sex hormone-binding globulin) do not always fully recover, which has not only substantial consequences for the sexual and reproductive ability but also affects body composition, glucose homeostasis, and energy level. Therefore, regular evaluation of the gonadal axis is needed, and testosterone supplementation should be considered on an individual basis.

Long-term monitoring for the development of hormonal deficit and signs of under-supplementation and over-supplementation is recommended annually, particularly in those who have received radiotherapy, with a clear need for optimization and individualization of supplementation regimens.[19]

Obstructive sleep apnea

Up to 80% of patients suffer from OSA as a result of macroglossia and soft-tissue pharyngeal swelling,[23,35,46–49] but some patients also present with central sleep apnea. Although the soft tissue swelling improves after adequate treatment of GH excess, there is an irreversible remodeling of the upper airways in acromegaly with the persistence of OSA after biochemical cure in most patients. OSA results in headaches, poor sleep quality, daily somnolence, and impaired neurocognitive function in acromegaly patients. Moreover, in observational studies, OSA is related to insulin resistance, hypertension, heart failure, arrhythmias, and cerebrovascular disease.[50] Thereby, OSA has a major negative impact on physical, social, and psychological functioning and predisposes to morbidity and mortality.[51–53]

Owing to the high prevalence of OSA in acromegaly, thorough history taking, questioning of spouse/partner, and potentially use of a PROM (ie, Epworth sleepiness scale [ESS][54]) is necessary. In cases of strong suspicion, polysomnography may be performed, even before transsphenoidal surgery.

Musculoskeletal Disorders

Arthropathy

Arthropathy is one of the most frequent complications of acromegaly, and arthropathy pain is one of the most prominent symptoms negatively affecting QoL.[55] GH and IGF-1 excess induces cartilage hypertrophy and osteophyte formation that contribute to

joint space narrowing, with generally degenerative but no inflammatory changes. One of the difficulties in the diagnostics of acromegalic arthropathy is the unexplained mismatch between radiologic changes and clinical symptoms, which is well-known in primary osteoarthritis. The knees and spine are particularly affected, but other functionally important joints such as the hands, hips, and shoulders are often involved too. Our recent prospective studies demonstrated that a large subset of patients show the clinical and radiographic progression of the joint disease over time, even after long-term disease control.[56,57] Although treatment of GH and IGF-1 excess is able to improve symptoms in most patients and is thereby the cornerstone in the management of joint symptoms, good biochemical control of acromegaly alone is insufficient to stabilize this chronic, partially irreversible complication in many patients. In some cases, physiotherapy may be beneficial, and in late-stage disease, individual joints may benefit from replacement surgery, but there is only anecdotal evidence of its effectiveness. There is a clear need for optimization of treatment strategies, and we recommend the development of multidisciplinary care for severe joint disease beyond endocrine care only.

Vertebral fractures

GH and IGF-1 excess in acromegaly leads to high bone turnover, deterioration of the cortical and trabecular bone structure, and increased risk of vertebral fractures. More than 50% of individuals with fractures have multiple or severe vertebral fractures, predisposing patients to have back pain, progressive thoracal kyphosis, sagittal imbalance, and thereby functional impairments. In addition, cardiopulmonary complications have a potentially worse outcome in acromegalic patients with (severe) vertebral fractures/deformities.[58] The presence of vertebral fractures is related to increased pain scores and impairments in QoL in patients with acromegaly.[59,60]

Accordingly, fracture risk is highest in patients with long-standing active acromegaly, especially in patients with hypogonadism. However, vertebral fractures can also occur in a later phase of the disease, with a persistently high prevalence and even progression in patients with disease control.[57,61] In the absence of reliable tools to predict the fracture risk in acromegaly patients, we recommend screening all patients for osteoporosis and vertebral fractures by dual-energy x-ray absorptiometry and plain radiographs, respectively, regardless of disease status. Other risk factors, including hypogonadism, vitamin D deficiency, and glucocorticoid over substitution, should be identified and corrected. Although the literature on the efficacy and safety of bone-modifying drugs in acromegaly is limited,[62,63] patients with low bone mineral density values and progressive vertebral fractures are likely to benefit from antiresorptive drugs, especially early in the disease course when bone turnover is high.

Changes in Physical Appearance

Acromegaly is typically associated with excessive sweating and morphometric changes, including enlarged extremities and facial abnormalities, such as furrowing of the forehead, enlargement of the nose and ears, thickening of the lips, and mandibular prognathism. These features significantly improve after the reversal of GH excess but do not always completely normalize.[64–66] Morphometric changes significantly correlate with poor psychological outcomes in acromegaly patients, and it is extremely important to address this subject during consultation.[40,67] GH-induced vocal changes are also frequently reported during active disease, although mucosal edema and hypertrophy largely resolve during treatment with the improvement of symptoms, voice complaints persist in a subset of patients. This also negatively influences QoL, and consultation with a speech therapist could be beneficial.[68]

Issues in Psychosocial Functioning

Even after optimal medical treatment, acromegaly is associated with an increased prevalence of psychopathology and maladaptive personality traits.[13,69] According to Pertichetti *and colleagues*, 63% of acromegalic patients suffer from psychiatric disorders, mostly attributed to depression, followed by psychosis and anxiety.[70] Impairments in cognitive functioning were absent in some studies,[69] whereas others did observe impairments in cognitive functioning, in particular attention deficits, with the occurrence of alterations in brain volume.[71–73]

A recent quantitative study of our research group examined work disability among patients treated for a pituitary tumor. It was shown that a substantial part of pituitary patients had no paid job (28%). Patients with acromegaly or Cushing's disease were more often without a paid job than patients with prolactinoma or nonfunctioning adenoma. Of the pituitary patients who had a paid job, 41% reported health-related absenteeism in the previous year. Most of that impacted work productivity was of mental or social origin.[74] This is in line with the results of a focus group study where patients treated for a pituitary tumor reported work-related problems because of diminished ability to function, concentration problems, and issues with collaborating with others.[75] Besides the psychosocial burden perceived by patients, their partners/spouses also reported a negative impact of the consequences of the disease on their psychosocial well-being.[76]

Furthermore, patients with acromegaly reported more problems with sexual functioning compared with healthy controls, including inability to achieve orgasm and decreased libido. In accordance with the multifactorial nature of sexual functioning, issues in sexual functioning were related to higher IGF-I levels, more depressive symptoms, and older age.[75,77] In focus group conversations with patients with acromegaly, patients attributed their decreased libido to the disease as well as to aging, a negative self-image, shame, physical pain, and as a side effect of their medical therapy.[75]

In the examination of how patients perceive their illness, it was shown that patients with acromegaly report affected illness perceptions,[69] with acromegalic patients receiving medical treatment tending to perceive a more chronic timeline of their disease compared with patients in remission without medical treatment.[78] In patients using medication for acromegaly, negative beliefs about their medication were related to more negative illness perceptions and more impairments in acromegaly-specific QoL (ie, AcroQoL).[78] Moreover, patients reported less effective coping strategies.[79] Clinicians should be aware of these persistent psychosocial issues and potential impairments in cognitive functioning that can be supported by the use of PROMs.

PATIENT-REPORTED OUTCOME MEASURES

A substantial number of clinical trials among patients with acromegaly use PROMs alongside biochemical outcomes.[16] PROMs are now contemplated by health administrators and regulating agencies when considering health-related decisions, such as authorizing reimbursement of new drugs.[4,80] However, no clear criteria nor consensus exists for the use of PROMs in trials of patients with acromegaly. In addition, comparability between trials is limited due to a great variety of validated and unvalidated generic and disease-specific PROMs that are currently being used. Recently, in a large meta-analysis of 53 intervention and cohort studies, the authors showed that of the 14 PROMs that were used in acromegaly patients, only one, the AcroQoL, has been validated in patients with acromegaly.[81]

Generic-specific, domain-specific, and acromegaly-specific QoL measures can help identify specific factors for follow-up. The following is a list of the most commonly used PROMs in acromegaly:

Disease-Specific/Acromegaly-Specific Patient-Reported Outcome Measures

- *AcroQoL Questionnaire:* A disease-specific, self-rating questionnaire that comprises 22 items, with each having five possible answers scoring 1 to 5. The questions are divided into two main categories: physical (8 items) and psychological function (14 items, subdivided into appearance and personal relationships). The score of 110 (100%) represents optimal QoL.[82]
- *Patient-Assessed Acromegaly Symptom Questionnaire (PASQ)*: A disease-specific, self-rating questionnaire that comprises 6 items, with each having nine possible answers scoring 0 to 8. These questions evaluate symptoms and signs of acromegaly, such as headache, excessive perspiration, osteoarthralgia, fatigue, soft-tissue swelling, and paresthesia. The seventh question addresses the overall health status, based on the other six questions, scoring 0 to 10. The maximum score is 48 and represents the greatest symptom burden.[83]
- *Leiden Bother and Needs Questionnaire for patients with pituitary disease*: A self-rating questionnaire that compromises 26 items, scoring 0 to 4, and covering five domains (mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, and issues in social functioning).[84]

Domain-specific Patient-Reported Outcome Measures Relevant to Acromegaly

PROMs originally developed in other patient populations that measure specific dimensions are also relevant for patients with acromegaly, such as anxiety and depression symptoms (eg, HADS[85]), joint complaints (eg, Australian/Canadian Osteoarthritis Hand Index[86]), fatigue (eg, Multidimensional Fatigue Inventory-20[87]), cognitive functioning (eg, Cognitive Failure Questionnaire[88]), sleeping problems (eg, Epworth Sleepiness Scale[89]), sexual function (eg, Female Sexual Function Index[90]), or social situation (eg, Social Adjustment Scale[91,92]). These domain-specific PROMs assess domains at the level of symptom status and functional status as per the Wilson–Cleary model. One can also use domain-specific PROMs at the level of individual characteristics (eg, Beliefs about Medicine Questionnaire,[93] Brief Illness Perception Questionnaire,[94] or environmental characteristics [work role functioning questionnaire 2.0[95]]).

Generic Patient-Reported Outcome Measures

- *EuroQol 5 dimensions:* A self-rating questionnaire that compromises 6 items (5 multiple choice questions, scoring 1–3 and one visual analog scale, scoring 0–100) and covers five domains to assess the utility and health-related QoL.[96]
- *Short Form-36:* A non-disease-specific, self-rating questionnaire that compromises 36 items and covers eight domains (general health, vitality, physical functioning, bodily pain, physical role functioning, emotional role functioning, social role functioning, and mental health) which yield a physical component score and mental component score to assess health-related QoL. The ninth domain is the role–social component and is sometimes reported as well.[97]

Standardized Outcome Measures for Acromegaly

Scoring tools such as ACROmegaly Disease Activity Tool[98] and combining Signs and symptoms, Associated comorbidities, Growth hormone levels, IGF-1 levels, and Tumor profile[99] are useful instruments to assess overall disease activity. Both

instruments combine clinician-observed outcomes (IGF-1 and GH levels, tumor status, associated comorbidities symptoms) with PROMs (patient-perceived health status). However, comprehensive PROMs are still lacking, especially to evaluate the efficacy of personalized medicine, which is receiving increasing attention in the treatment of acromegaly.[4,100] For example, the HADS, by paying attention to—and evaluating the treatment of psychopathological comorbidities (by either psychological or pharmaceutical approaches), may provide added value to the chronic care of patients with acromegaly with depressive symptoms or anxiety.

DETERMINANTS OF QUALITY OF LIFE

As previously described, determinants of general health perception and QoL can be categorized following the conceptual model of Wilson and Claery.[17] Based on the previous literature overview, we adapted this model for acromegaly with main causal relationships and mediating factors (**Fig. 1**). Factors contributing to impairments in QoL include higher GH and IGF-1 levels, GH deficiency after treatment, and having undergone conventional radiotherapy (biological and physiologic factors); pain (mainly arthropathy pain), anxiety, and depressive symptoms (symptom status); and impairments in cognitive functioning (functional status), and individual characteristics including older age at onset, female gender, and higher body mass index (BMI).[11–14,44,100,101]

The Contribution of Biochemical Outcome to Quality of Life

Following the Wilson and Cleary model, a cascade of improvement can be induced by the normalization of biological and physiologic variables.[17] In acromegaly, this could, for instance, be induced by controlling excess GH and/or IGF-1 levels. In a recent meta-analysis, including 53 intervention and cohort studies and 3667 acromegaly patients, it was reported that in most studies (n = 34, 64%), the improvement of PROMs was accompanied by a significant decrease in IGF-1 levels, both in the intervention

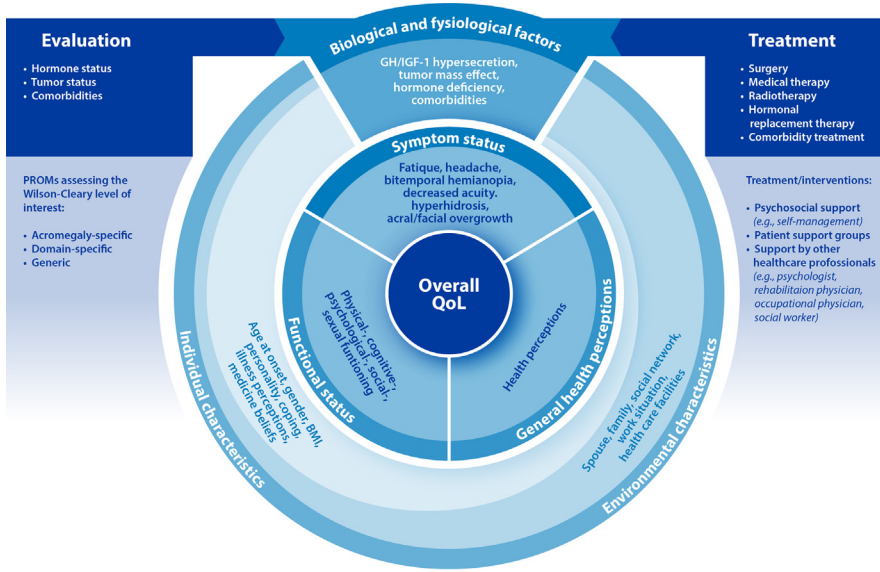

Fig. 1. A conceptual model for acromegaly including diagnostic and therapeutic interventions and the use of PROM based on the Wilson and Cleary model.[17]

(mean difference: −292 g/L, 95% CI -372 – −211) and cohort studies (mean difference: −326 g/L, 95% CI -496 – −157).[81] In 28 intervention studies, the improvement of PROMs was accompanied by a significant decrease in GH levels (mean difference: −10.7, 95% CI -13.2 – −8.3); however, this was not observed in cohort studies (mean difference: −1·6 g/L, 95% CI -4.7–1.5).[81]

Nevertheless, in the evaluation of the contribution of biochemical outcomes to QoL, one should take into account that the discrepancy between biochemical outcome and symptomatology in acromegaly is not straightforward, including the biopsychosocial factors mentioned above, and variable and tissue-specific GH and/or IGF-1 sensitivity.[100–109] In the same meta-analysis,[81] the authors also studied the differences between PROMs and conventional biochemical outcomes. In a third of the studies among patients with acromegaly (n = 18, 34%), discrepancies exist between PROMs and conventional biochemical outcomes (ie, both changed in opposite directions). The percentage of discrepant results was slightly higher among studies measuring QoL (38%) compared with studies measuring patients' symptoms (32%). In half of the studies with discrepant results (n = 10, 56%), biochemical outcomes overall improved with treatment, although QoL and patients' symptoms remained the same across most domains. No clear determinants of this dissociation were identified.

Next, the phenomenon called "extrahepatic acromegaly" may play a role in medically treated patients.[110] In addition to the suppression of GH secretion from the somatotroph tumor, somatostatin receptor ligands (SRLs) also suppress insulin secretion in the portal vein, which by itself downregulates hepatic IGF-1 production via GH receptors. Nevertheless, the GH action in the peripheral tissues (eg, white adipose tissue, bone, and kidney) remains unaltered and might still have acromegaly-inducing effects.[110] To put it another way, extrahepatic GH activity may remain elevated despite normal IGF-1 levels. If the addition of the GH-receptor antagonist pegvisomant could antagonize these extrahepatic GH actions in patients using first-generation or second-generation SRLs, one might observe an improvement of QoL in comparison with SRL monotherapy. Indeed, it has been shown previously that the addition of pegvisomant to the first-generation long-acting SRL therapy in acromegaly patients can improve GH-dependent parameters of QoL and patients' symptoms (eg, headache and soft-tissue swelling),[111] irrespective of the improved IGF-1 control. Data from intervention studies on other medical therapies were too limited to draw conclusions on the effects of these modalities on QoL.

RECOMMENDATIONS FOR THE MANAGEMENT OF ACROMEGALY

Optimal management of acromegaly by achieving biochemical control correlates with improvements in QoL, morbidity, functional outcome and health care-related costs, and reduced mortality risk, albeit not to the levels seen in the general population.[15] Although some comorbidities may be reversible after cure or disease control, many other complications could persist or even progress when the disease is controlled. In light of the incomplete reversibility of some comorbidities, optimal disease management seems to be crucial to prevent major side effects that may, in turn, lead to these premature comorbidities and impaired QoL. Therefore, in addition to normalizing GH and IGF-1 and achieving tumor volume control, if possible with preserving pituitary function, prompt diagnosis and treatment of acromegaly-associated comorbidities are critical to pursuing a good functional status, optimal QoL, and ensuring the best long-term outcome for this chronic illness.[4,80] There is a need to consider both IGF-1 and GH levels and PROMs to judge the status of control. Next, the model of Wilson

and Cleary can be used to offer a holistic individualized approach and better understand variability in the outcome and other determinants of QoL.[17]

The patient perspective on their symptoms, functional status, and QoL is important to address during the care process and is ideally measured longitudinally and used for shared decision-making. Although the AcroQoL and the PASQ are acromegaly-specific and frequently used PROMs, the PASQ has not been validated (yet) in acromegaly or any other patient populations. Therefore, in accordance with the current consensus criteria, it is recommended to assess disease-specific QoL via the AcroQoL annually.[4] For clinical trials in patients with acromegaly, it is advised to use a disease-specific PROM (eg, AcroQoL or PASQ if validated for acromegaly), in combination with a generic QoL measure (eg, SF-36 if validated for acromegaly) and depending on the specific study aim, a domain-specific PROM.

A patient-centered approach, accounting for conventional biochemical outcomes, tumor control, comorbidities, treatment complications, and PROMs, should all be considered in treatment decisions.[9] PROMs have added value in guiding treatment decisions, in particular when patients are only partial responders to treatment. In patients with discrepant results between PROMs and conventional biochemical outcomes, PROMs have incremental value and should be incorporated in the evaluation of treatment efficacy.[112] Better markers of disease activity are still warranted to decrease this clinical burden. In general, it remains difficult to judge an effective treatment of acromegaly on biochemical outcome parameters alone, partly because every patient has an individual optimal hormonal setpoint[113] but also impairment in QoL may be caused by permanent damage, that is, unresponsive to treatment. In addition, extrahepatic GH activity[110] and hormonal oversubstitution or undersubstitution could be identified and corrected with PROMs. Therefore, both conventional biochemical outcomes and PROMs are pivotal to obtain a comprehensive view of disease activity.

Acromegaly is a rare condition with severe chronic multiorgan and multisystemic morbidities requiring life-long complex multidisciplinary treatment. The Pituitary Tumor Centers of Excellence[114] provides this multimodal management to achieve biochemical and tumor control as well as providing access for patients to a wide range of health care providers to diagnose, monitor, and treat acromegaly-associated comorbidities. A more integrated approach seems effective in treating comorbidities and improving patient-reported outcomes and is critical, as many patients do not achieve biochemical or tumor control and comorbidities, impairment in QoL may not remit even when full biochemical control is achieved.[114,115]

SUMMARY

Acromegaly has a substantial negative impact on QoL. A patient-centered approach should be considered in treatment decisions, integrating conventional biochemical outcomes, tumor control, comorbidities, treatment complications, and PROMs, including QoL measures.

CLINICS CARE POINTS

Recommendations for evaluating the effect of acromegaly on quality of life (QoL)

- A patient-centered approach, accounting for conventional biochemical outcomes, tumor control, comorbidities, treatment complications, and patient-reported outcome measures (PROMs), should all be considered in treatment decisions.

- The patient's perspective on their symptoms, functional status, and QoL is important to address during the care process and is ideally measured longitudinally and used for shared decision-making.
- In the light of the incomplete reversibility of some comorbidities, optimal disease management is crucial to prevent major side effects that may, in turn, lead to premature comorbidities and impaired QoL.

Areas where further research is needed

- Better markers of disease activity are still warranted to guide management decisions (eg, interventions and dose titration) to ultimately decrease the clinical burden in patients with acromegaly.
- Proper reporting of the use, analysis, and outcomes of validated and unvalidated generic and disease-specific PROMs in publications is needed to facilitate translation of the PROMs into clinical practice.
- Development of comprehensive PROMs in research, including a disease-specific PROM, in combination with a generic QoL measure, and depending on the specific study aim, a domain-specific PROM is needed. Likewise, further development of effective PROMs for use in clinical practice is needed.

DECLARATION OF INTEREST

The authors report no conflict of interest.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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