Reviews in Endocrine and Metabolic Disorders (2019) 20:365–381
https://doi.org/10.1007/s11154-019-09506-y

Current perspectives on the impact of clinical disease and biochemical control on comorbidities and quality of life in acromegaly

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Published online: 24 July 2019

Abstract
Acromegaly is a rare chronic, systemic disorder caused by excessive growth hormone (GH) secretion from a somatotroph pituitary adenoma. GH hypersecretion leads to overproduction of insulin-like growth factor-1 (IGF-1), which contributes to the somatic overgrowth, physical disfigurement, onset of multiple systemic comorbidities, reduced quality of life (QoL) and premature mortality of uncontrolled patients. Somatostatin receptor ligands, dopamine agonists and a GH receptor antagonist are currently available for medical therapy of acromegaly. The main aim of treatment is biochemical normalisation, defined as age-normalised serum IGF-1 values and random GH levels <1.0 μg/L. However, there is an increasing evidence suggesting that achieving biochemical control does not always decrease the burden of disease-related comorbidities and/or improve patients' QoL. This lack of correlation between biochemical and clinical control can be due to both disease duration (late diagnosis) or to the peculiarity of a given comorbidity. Herein we conducted ad hoc literature searches in order to find the most recent and relevant reports on biochemical and clinical disease control during medical treatment of acromegaly. Particularly, we analyse and describe the relationship between biochemical, as well as clinical disease control in patients with acromegaly receiving medical therapy, with a focus on comorbidities and QoL. In conclusion, we found that current literature data seem to indicate that clinical disease control (besides biochemical control), encompassing clinical signs and symptoms, comorbidities and QoL, emerge as a primary focus of acromegaly patient management.

Keywords Acromegaly · Biochemical control · Clinical control · Comorbidities · Medical therapy

1 Introduction

Acromegaly is a rare chronic disorder caused by excessive growth hormone (GH) secretion, arising predominantly from a benign pituitary adenoma (>95% of cases) [1]. In patients with acromegaly, GH hypersecretion leads to overproduction of insulin-like growth factor-1 (IGF-1) thus resulting in a multitude of clinical manifestations, including somatic overgrowth, physical disfigurement, multisystem comorbidities, reduced quality of life (QoL) and premature mortality (Fig. 1) [2–4]. In line with this complex scenario, a recent Statement by the Pituitary Society strongly recommend to refer acromegaly patients to selected Centres of Excellence, identified based on clinicians' expertise and health care provider facilities [5].

Acromegaly-related comorbidities mainly include cardiovascular, metabolic and respiratory disorders, rheumatological and orthopaedic issues, hypopituitarism and sexual dysfunction, as well as malignancies [3, 6, 7]. Patients without typical features of acromegaly, affected, however, by several of these comorbidities should raise the suspicion of acromegaly in physicians [2]. Measurement of IGF-1 levels is the recommended biochemical screening. However, in patients with elevated or equivocal serum IGF-1 levels, failure of GH to

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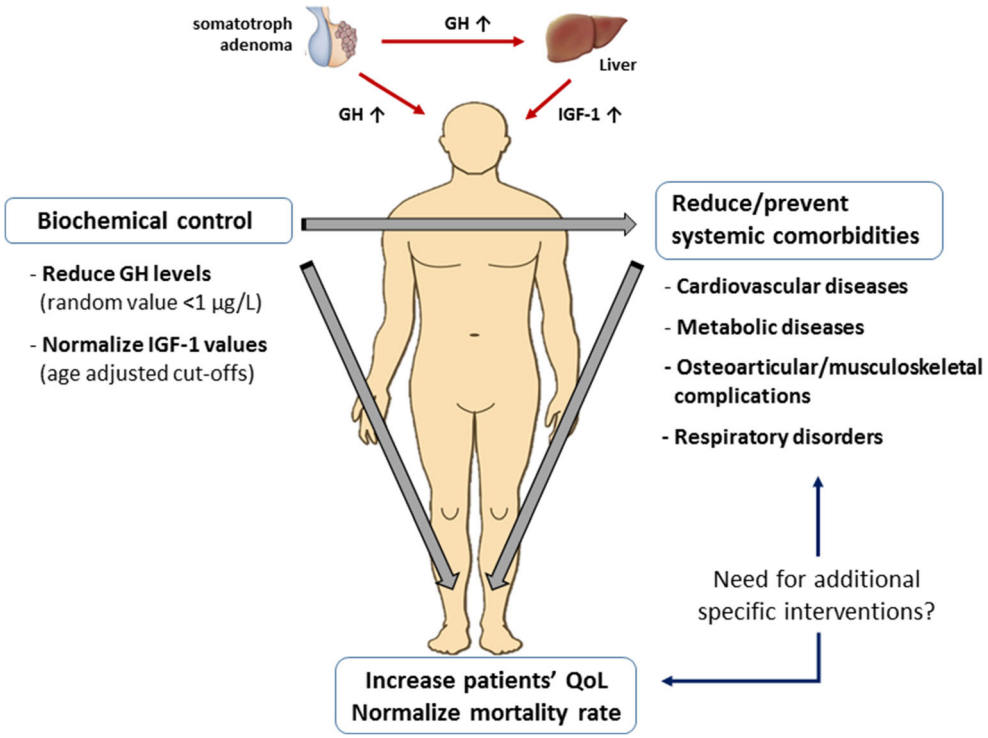

Fig. 1 The normalization of mortality risk and the improvement of patients' quality of life (QoL) represent the final goal of acromegaly treatment. These targets can be achieved only through the control of hormone hypersecretion (primary target of current available medical treatments) and the reduction/prevention of disease related comorbidities. However, biochemical control does not always results in the complete resolution of comorbidities, with an impact on QoL and mortality. Therefore, in such cases, additional treatments, directly directed on specific comorbidities (i.e. anti-hypertensive drugs, anti-diabetic-agents, psychological support, etc.) need to be promptly started in order to pursue a general clinical improvement of patient's health status

decrease <1 μg/L following an oral glucose load should be used to confirm the diagnosis [2].

Current treatment modalities include surgery, radiotherapy and medical (pharmacological) therapy [2, 8, 9]. The Endocrine Society Clinical Practice Guidelines and the Consensus Statement of 2018 recommend transsphenoidal surgery as the primary therapy in most patients [2, 9]. Medical therapy with first generation somatostatin receptor ligands (SRLs) is recommended as adjuvant therapy in patients with persistent disease following surgery and as first-line treatment for those ineligible for surgery, while its role in a neo-adjuvant setting is still debated [2, 10, 11]. To date three different classes of drugs (alone or in combination) are available for the medical treatment of acromegaly [namely, SRLs, dopamine agonists (DAs) and GH receptor antagonist (GHRA)] (Table 1) [2, 8, 12].

The aim of treatment is the biochemical control, with current treatment targets being age-normalised serum IGF-1 (for all the drugs), and random GH levels <1.0 μg/L for only SRLs and DAs [2, 8]. Biochemical criteria have changed over time, with current recommendations being more rigorous [13, 14]. In a comprehensive meta-analysis, GH or IGF-1 control was achieved in approximately 55% of patients by use of SRLs [13]. In this light, a puzzling discordance in biochemical disease activity has been observed in clinical practice, where patients exhibit normalised GH but elevated IGF-1 levels and vice versa [15–18]. The exact mechanisms underlying this discordance [15] and its clinical significance remain to be established [9].

Beyond biochemical control, the goals of treatment for acromegaly include reduction of mortality risk, management of comorbidities, minimising clinical signs and symptoms of the disease, as well as control of tumour mass and maintenance of the remaining pituitary function [2]. Another significant consideration in the management of acromegaly is health-related QoL [8], which is significantly impaired by comorbidities [19].

The management of comorbidities and the improvement of patients' QoL are often considered secondary endpoints in the treatment of acromegaly. Although biochemical control leads to a significant improvement in a number of comorbidities, this is not always the case. Full biochemical control cannot reverse some of the pathological changes associated with acromegaly, while partial control can still produce significant improvements in a patient's clinical status.

2 Objectives and methodology

The aim of this review is to describe the relationship between biochemical and clinical disease control in patients with acromegaly who are receiving medical therapy (mainly SRLs and GHRA), with a focus on comorbidities and QoL. Discussion of control of tumour burden is beyond the scope of this review.

Ad hoc literature searches were carried out in order to find the most recent and relevant reports on the correlation between pharmacological treatment of acromegaly, normalization of biochemical parameters and clinical disease control.

Table 1 Currently available drugs for the management of acromegaly

Agent	Available formulations	Recommended dosage/schedule	Therapeutic indication
SRLs			
Lanreotide	Slow-release (SR); 30 mg; powder for suspension for intramuscular injection	Starting dose: 30 mg/14 days Subsequently, injections may be given every 7 to 10 days, depending on response	First-line medical therapy in patients with persistent disease after surgery; first line treatment in patients ineligible for surgery or which refuse it
	Autogel; 60 mg, 90 mg and 120 mg; solution for deep subcutaneous injection in a prefilled syringe	Starting dose: 60 mg–90 mg/4 weeks Maximum dose: 120 mg/4 weeks Dose interval can be reduced up to 21 days	First-line medical therapy in patients with persistent disease after surgery; first line treatment in patients ineligible for surgery or which refuse it
Octreotide	Long-acting release (LAR); 10 mg, 20 mg and 30 mg; powder and solvent for suspension for deep intramuscular injection	Starting dose: 20 mg/4 weeks Maximum dose: 40 mg (20 + 20 mg)/4 weeks	First-line medical therapy in patients with persistent disease after surgery; first line treatment in patients ineligible for surgery or which refuse it
Pasireotide	Long-acting release (LAR) 20 mg, 40 mg and 60 mg; powder and solvent for suspension for deep intramuscular injection	Starting dose: 40 mg/4 weeks Maximum dose: 60 mg/4 weeks The dose should to be adjusted according to response and tolerability	Second-line medical therapy when patients are inadequately controlled with first-generation SRLs (octreotide and lanreotide) Suggested in case of concomitant tumor concern
GHRA			
Pegvisomant	10 mg, 15 mg, 20 mg, 25 mg and 30 mg; powder and solvent, to make a solution for subcutaneous injection	Loading dose: 80 mg. Following, 10 mg/day Maximum dose: 30 mg/day (240 mg/week) The dose should to be adjusted according to response and tolerability	Second-line medical therapy when patients are inadequately controlled with first-generation SRLs (octreotide and lanreotide) Suggested in presence of impaired glucose metabolism
DA[a]			
Cabergoline	0.5 mg; oral tablet	Dose: 0.5–7 mg/week (titration needed)	First-line medical therapy (same indications than SRLs) in patients with mild disease activity (IGF-1 levels <2.5 times the upper limit of normal (ULN))

Legend: *SRL* somatostatin receptor ligand, *GHRA* growth hormone receptor agonist, *IGF-1* insulin-like growth factor-1, *DA* dopamine agonist. [a] Off-label use

3 Biochemical control: Targets and treatment efficacy

3.1 Biochemical control targets

The hormone targets currently recommended by the Endocrine Society Clinical Practice Guidelines are: age-normalised serum levels for IGF-1 and random GH levels of <1.0 μg/L [2]. Indeed, mortality can be reduced to the level of the general population when GH levels are <1 μg/L or IGF-1 is normalised [4, 20, 21]. Notably, most clinical trials, including those investigating the efficacy of newly developed drugs (i.e, pasireotide), had used a GH cut-off of 2.5 μg/L until recently [13], while the updated threshold of <1 μg/L was only used in the latest studies [22]. Applying these international guideline criteria at a local level is undermined by many practical issues: there can be as much as a 2-fold variation in GH and IGF-1 values measured between different laboratories, different assay performance and differing interpretation of IGF-1 levels depending on the reference ranges used [23]. For this reason, expert consensus recommend that the same assay is used in the management of a given patient [9]; that clinicians familiarise themselves with appropriate hormone standards, assay specificity and sensitivity; and that GH cut-offs are assay- and method-specific [8].

Routine use of the post-glucose GH nadir levels, obtained during an oral glucose tolerance test (OGTT), is not recommended in patient follow-up during medical treatments [2, 9]. However, results of a recent study dispute the appropriateness of this approach: patients apparently controlled with SRL therapy failed to suppress GH levels in response to OGTT [24]. Due to the complexity of the assessment of the IGF-1 system, in the past some authors speculated about the possible use of the acid-labile subunit (ALS) as a relative GH-independent sign of disease activity [25].

3.2 Does pharmacological treatment reach biochemical targets?

According to meta-analyses, biochemical control of GH levels is achieved by 57–58% of patients treated with octreotide and 48–64% of patients treated with lanreotide [13, 26], while 55–

67% of patients who receive octreotide and 47–61% of patients treated with lanreotide reach the normalization (age-adjusted) of IGF-1 levels [13, 26]. Of note, some of the studies included in these meta-analyses preselected patients based on responsiveness to SRL treatment [27]. Therefore, more recent studies conducted in treatment-naïve patients show that the control of both GH and IGF-1 levels is achieved in about 20–30% of patients treated with octreotide and 30–50% of those treated with lanreotide [27].

Of note, patients' preselection in clinical studies on acromegaly includes variable designs, such as the evaluation of subjects previously treated with different formulations of the same drug (i.e. octreotide s.c. vs octreotide LAR and/or lanreotide SR vs lanreotide Autogel), post-operative SRL treatment in patients who underwent successful pre-surgical treatment, or the inclusion based on the response to an acute octreotide test. Particularly, the role of the acute octreotide test in predicting long-term responsiveness to SRL treatment remains controversial [28]. This is partially due to the heterogeneity of data presentation (GH nadir vs percent GH reduction; lack of standardized GH cut-offs), as well as to the different design of the procedure observed among centres [29–34]. To our opinion, taking into account the above mentioned limitations, data from literature suggest that the acute octreotide test can predict long-term responsiveness to SRL treatment with high sensitivity, although counterbalanced by a relatively lower specificity.

According to a meta-analysis of relevant studies including a limited and biased number of patients, cabergoline monotherapy seems associated with control of IGF-1 levels in 34% of patients [35]. Low baseline IGF-1 concentration, longer duration of treatment and high baseline prolactin concentration were identified as factors predictive of successful treatment [35]. In the study with the largest number of patient included in this meta-analysis, the majority of those normalizing IGF-1 had very mild disease activity [36]. The current recommendation is to consider a first-line treatment with cabergoline if IGF-1 levels are <2.5 x ULN [9].

According to the last Consensus Statement, medical therapy options to achieve biochemical control in patients partially responsive or resistant to first-generation SRLs therapy (octreotide and lanreotide) include: increasing the dose of SRL, combination therapy with pegvisomant or cabergoline, switching to pegvisomant monotherapy or to pasireotide depending on glucose metabolism, tumor volume and the response degree to first-line SRLs [9].

The first clinical trials evaluating the efficacy of pegvisomant in acromegaly [37, 38] showed a great efficacy of the drug in the achievement of normal age-adjusted IGF-1 levels (89% and 97% of patients, respectively), at least one time during the study period. Following data from real-world evidences report a significant lower rate of biochemical control (65–70% of treated patients) during long term treatment [22]. On the other hand, pasireotide has been shown to be superior to octreotide long-acting release (LAR) in terms of efficacy in a prospective, randomised, double-blind study conducted in 358 patients [39]. Furthermore, among patients inadequately controlled on first-generation SRL monotherapy, complete biochemical control (GH <2.5 μg/L and normal IGF-1) was achieved with add-on pasireotide (40–60 mg, 1 injection every 4 weeks) in 15% of patients in the 40 mg group and 20% in the 60 mg group, while none of the patients who remained on first-generation SRL monotherapy experienced biochemical control [40].

Combination medical therapy led to biochemical control in 54% of patients in a German registry study and 60–70% of patients included in the French Acromegaly Registry (the majority of recipients of combination therapy received a SRL plus a dopamine agonist) [16, 21]. In a narrative review of studies that evaluated combination therapies in the treatment of acromegaly, the authors concluded that the SRL plus pegvisomant combination allowed the majority of patients to achieve normal IGF-1 levels (58–100%), while SRL plus cabergoline combination was most effective in patients with mildly elevated IGF-1 levels [41].

3.3 Does biochemical control produce clinical disease control?

The insidious nature of acromegaly often means a significant lag time between disease presentation and diagnosis, resulting in long-term exposure to elevated levels of GH and IGF-1 [42]. Some, but not all, of the complications or comorbidities may be reversed or minimised after therapy-induced biochemical control [43, 44]. However, it is interesting to note that some complications of acromegaly are not directly related to circulating GH and IGF-1 levels (i.e., neurocognitive deficits [45]).

This section reviews the effectiveness of acromegaly treatment (focusing on medical therapy) on clinical disease control, and whether biochemical control is associated with clinical disease control.

3.4 Treatment impact on acromegaly signs, symptoms and comorbidities

As discussed, medical therapy achieves biochemical control in a significant proportion of patients. Previous reviews of clinical studies have concluded that the SRLs octreotide [46], lanreotide [47, 48], pasireotide [12, 39] and the GHRA pegvisomant [22, 49] generally improve selected signs and symptoms of acromegaly. It seems, therefore, that biochemical control is associated with an improvement in the clinical signs and symptoms of the disease in most cases.

The correlation between biochemical control and its impact on comorbidities is crucial, moving from the perspective of a

holistic approach to the disease. In the recent years a number of studies focused on the description and characterization of acromegaly related comorbidities, together with their impact on patients' health status and cost-of-illness, by use of national registers (i.e. German, French, Swedish registers) [16, 21, 50] or large international surveys (i.e. Liège Acromegaly Survey (LAS) Database) [51]. Particularly, the LAS database, evaluating the clinical features at diagnosis of >3100 acromegaly patients from 14 different Countries, highlighted a high prevalence of cardiovascular comorbidities (mainly cardiac hypertrophy and hypertension), metabolic disorders (i.e. diabetes mellitus) and respiratory diseases (sleep apnea) in the largest cohort of acromegaly patients published so far. In line with these findings, the analysis of data collected from the French and Swedish registers focused on the outcome of disease related comorbidities after long-term treatment [21] and their economic burden on the whole disease direct and indirect medical costs [50].

This huge amount of data strength the clinical need to consider the recognition, management and follow-up of acromegaly comorbidities as primary goals of disease management, besides to the biochemical control of GH and IGF-1 excess.

3.5 Cardiovascular comorbidities

Cardiovascular complications are the most common comorbidities of acromegaly and significant contributors to the increased mortality [52]. Older age at diagnosis is associated with an increased risk of major cardiovascular events [53].

Cardiac complications characteristically associated with acromegaly are represented by left ventricular hypertrophy (LVH), diastolic dysfunction (LVDD), reduced left ventricular ejection fraction (LVEF), systolic dysfunction (LVSD), arrhythmias, valvulopathy, and endothelial dysfunction (early atherosclerosis) [44, 54].

In this context, a number of studies, including a meta-analysis published in 2007, have shown improvement in cardiovascular complications, primarily LVH and LVDD, following biochemical control achieved by medical treatment [55–65].

However, other authors did not find a direct correlation between GH and/or IGF-1 normalization and improvement in LVH, LVDD as well as left ventricular mass (index) (LVMi), cardiomyopathy and maximum heart rate [53, 66–71] (Table 2). In detail, Akdeniz et al. [67] and dos Santos Silva and colleagues [70] showed that, after SRL treatment, LVH and LVEF did not significantly differ in patients achieving biochemical control, compared to those with uncontrolled disease. Likewise, Kuhn and colleagues reported no significant changes in LVEF or LVM in patients treated with pegvisomant alone or in combination with SRLs or cabergoline [69].

Of note, another study even showed a lower prevalence of LVH in uncontrolled patients compared to those achieving normal age-adjusted IGF-1 levels, while (as expected) the presence of cardiomyopathy was higher in patients with active disease. In this latest study, most patients received surgery followed by medical therapy during almost 6 years of follow-up. Interestingly, the authors had no explanation for their finding [71].

Valvulopathy is another common cardiovascular complication [52]. Aortic valve regurgitation occurs in 30% of patients, whereas mitral regurgitation in 5%, with disease duration being a significant risk factor [72]. In this context, a prospective study showed that increased GH and IGF-1 levels are associated with a progression of valvular disease, with a significant increase in valvular regurgitation observed after 24 months follow-up [73]. Of note, the detrimental effect of uncontrolled disease may remain even after long-term biochemical control [72, 74].

Furthermore, the presence of arrhythmias has been also correlated to acromegaly, possibly due to the high prevalence of cardiac fibrosis and to the effect of IGF-1 on calcium channels [44]. However, a real increase of cardiac rhythm disturbances in acromegaly patients is still debated. Indeed, a study conducted using a 24-h ECG Holter monitoring reported more frequent and severe ventricular arrhythmias in acromegaly patients compared to controls [75], while two other studies did not find any clinical significant arrhythmia in the acromegaly subjects evaluated [76, 77]. In this context, other groups focused on the QT interval duration corrected for heart rate (QTc) as a possible marker of increased arrhythmia risk. Some authors demonstrated that QTc was longer in active acromegaly patients compared to control subjects [78, 79], with one report even showing that SRL treatment was associated with shorten (and even normalized) QTc [79]. On the contrary, a study from Orosz and colleagues did not find any differences in QTc between acromegaly patients and controls [80].

In conclusion, an improvement with biochemical control occurs in some, but not all cardiovascular complications, and the risk of cardiovascular events remains high and warrants attention. Indeed, it has been shown that regardless of disease control, a high Framingham risk score is associated with reduced life expectancy [81]. Furthermore, another study showed that the risk of coronary heart disease over a 5-year period was independent of biochemical control and estimated disease duration [82].

3.6 Hypertension

Hypertension is a relatively common comorbidity. Recent data from registries estimate a 23–40% prevalence of hypertension in patients with acromegaly [21, 50, 83]. Disease control is associated with better control of blood pressure in patients with acromegaly and hypertension [62, 84, 85], as well as with

Table 2 Studies published after 2007 investigating the main cardiovascular outcomes in patients treated for acromegaly

Study	Patients (n)	Treatment	Duration	Outcome
Maison et al. 2007 [58]	Patients with acromegaly treated with SRLs ($n = 290$)	Octreotide 0.15–0.6 mg/day Octreotide LAR 20 mg/28 days Lanreotide PR 30 mg/10–15 days	1 day[a]–18 months	• Significant reductions in heart rate, LVMi, IVST, LVPWT, E/A and improved exercise tolerance • **Changes in blood pressure, left ventricular end-systolic dimension and fractional shortening were not significant**
Pivonello et al. 2007 [59]	Patients with active acromegaly ($n = 17$)	Pegvisomant 10 mg/day, increased by 5 mg/day until disease control or maximum dose of 40 mg/day is reached	6 months	• LVMi significantly reduced from baseline • **No significant changes in LVEF, E/A and IVRT**
	Patients with active acromegaly ($n = 12$)		18 months	• LVMi significantly reduced compared with 6 months • Significant increases in LVEF and E/A. IVRT significantly decreased compared with baseline • Proportion of patients with cardiac insufficiency declined from 76% to 8%
Colao et al. 2008 [60]	Patients with active acromegaly ($n = 89$)	First-line depot SRLs ($n = 56$) First-line transsphenoidal surgery ($n = 33$)	12 months	• LVMi and E/A significantly reduced both in patients treated with SRLs and surgery • LVEF was significantly reduced only in patients treated with SRLs • **No changes in SBP were observed in either group**, while DBP was significantly decreased both in patients treated with SRLs and surgery
De Marinis et al. 2008 [61]	Patients with active acromegaly following transsphenoidal surgery ($n = 36$)	Octreotide LAR 20 mg/28 days	12 months	• LVMi, prevalence of LVH, LVPWT and IVST were significantly reduced both in patients treated with octreotide LAR and in patients with controlled disease after surgery • E/A was significantly increased in both groups
	Patients with controlled acromegaly after transsphenoidal surgery (n = 12)	Transsphenoidal surgery		
Colao et al. 2009 [62]	Patients with newly diagnosed acromegaly ($n = 45$)	Octreotide LAR 20 mg/28 days ($n = 28$) Lanreotide SR 30 mg/14 days Lanreotide Autogel 60 mg/28 days (n = 17)	5 years	• LVMi and blood pressure significantly decreased in both groups • LVEF and E/A significantly increased in both groups • No significant differences between the two groups were observed
Bogazzi et al. 2010 [63]	Patients with active acromegaly ($n = 14$)	Lanreotide Autogel 120 mg/28 days	6 months	• Mean LVM and LVMi significantly decreased. LVH reverted in 6 out of 10 patients. • Patients with controlled disease had higher reduction of LVMi than those with uncontrolled acromegaly
Jayasena et al. 2011 [66]	Patients with acromegaly treated with multimodal strategies ($n = 116$)	Surgery Medical therapy (SRLs or DAs) Surgery + medical therapy	19.2 years	• **No significant differences in the prevalence of cardiomyopathy based on the last known GH and IGF-1 levels** • Higher IGF-1 (but not GH) burden correlated with higher prevalence of cardiomyopathy
Akdeniz et al. 2012 [67]	Patients with active acromegaly ($n = 16$) Patients with cured/well controlled acromegaly ($n = 26$) Healthy age- and sex-matched controls ($n = 30$)	Surgery Octreotide LAR Lanreotide Autogel	n.s.	• The prevalence of LVH and LVDD were increased in acromegaly • **No differences in LVH and LVDD between the active acromegaly and the cured/well controlled groups**
	Patients with newly diagnosed acromegaly	Lanreotide Autogel	6 months	• **SBP and DBP were unchanged**

Table 2 (continued)

Study	Patients (n)	Treatment	Duration	Outcome
Annamalai et al. 2013 [68]	(n = 30)			• **LVMi regressed in men but not in women** • Significant improvements in arterial stiffness (aortic pulse wave velocity) and endothelial function (flow mediated dilatation) were observed
Comunello et al. 2015 [64]	Patients with active acromegaly (n = 28)	Octreotide LAR Lanreotide Autogel	n.s.	• Significant reductions in minimum and average heart rate. **Maximum heart rate remained unchanged** • Significant increases in the time domain parameters of heart rate variability • Significant increases in several frequency domain parameters of heart rate variability • **LF%, HF% and LF/HF ratio remained unchanged**
Kuhn et al. 2015 [69]	Patients with active acromegaly treated with Pegvisomant (alone or in combination) ($n = 42$)	Pegvisomant ($n = 19$) Pegvisomant + SRLs or DAs ($n = 23$)	≥ 3 months	• **No significant change in LVEF or LVM in patients treated with pegvisomant alone or in combination with SRLs or cabergoline** • In patients with an EF ≤ 60%, a significant increase of the EF was observed
dos Santos Silva et al. 2015 [70]	Patients with active acromegaly (n = 30)	Octreotide LAR 20–30 mg/28 days	12 months	• There was **no difference in LVMi and LVEF among patients with ($n = 12$) and without ($n = 18$) disease control**
Sardella C et al. 2016 [53]	Patients followed-up at a tertiary referral center ($n = 200$)	Cured after surgery Controlled after SRLs Uncontrolled after SRLs	≥ 12 months	• Univariate analysis showed a six-fold higher risk of hypertension in patients with uncontrolled acromegaly compared to patients cured after surgery • At multivariate analysis **uncontrolled acromegaly was not a predictor of hypertension**
Carmichael et al. 2017 [71]	Patients with acromegaly treated with multimodal strategies ($n = 120$)	Surgery Medical therapy (SRLs or DAs) Surgery + medical therapy	8.8 years	• Cardiomyopathy and hypertension were more prevalent in uncontrolled versus controlled patients • **LVH more prevalent in controlled patients compared to uncontrolled ones (11.4% vs 9.8%)**
Auriemma et al. 2017 [65]	Patients with acromegaly resistant to SRLs ($n = 50$)	Octreotide LAR 30–40 mg/28 days + pegvisomant 30–280 mg/week Lanreotide 120–240 mg/28 days + pegvisomant 30–280 mg/week	78 months	• Significant reductions in LVEF, LVMi, E/A, IVRT and DT • **No change was found in SBP and DBP**

In bold type we highlight the studies showing a discrepancy between acromegaly treatment and/or biochemical control compared to cardiovascular outcomes

Legend: DA, dopamine agonist; DBP, diastolic blood pressure; DT, deceleration time; E/A, early-to-late mitral flow velocity; HF, high-frequency component; IVRT, isovolumetric relaxation time; IVST, intraventricular septum thickness; LAR, long-acting repeatable; LF, low-frequency component; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index, LVPWT, left ventricular poster wall thickness; n.s., not specified; SBP, systolic blood pressure; PR, prolonged release; SRL, somatostatin receptor ligand. [a] Single injection of octreotide subcutaneous included in the meta-analysis only for the evaluation of heart rate

a lower incidence of hypertension among acromegaly patients (41.8% vs 58.5%) [71]. Furthermore, biochemical control may also prevent progression to hypertension in normotensive acromegalic patients [86].

However, the increased prevalence of hypertension observed in acromegaly patients needs to be completely elucidated from a pathophysiological perspective, since it involves a balance between the antinatriuretic effect of GH and the potential role of IGF-1 in reducing vascular resistance [87–89]. As a consequence, biochemical control shows a positive correlation with the prevalence of hypertension in some studies, but not in others [44]. As an example, a retrospective study evaluated 105 patients with acromegaly receiving antihypertensive drugs. All patients were treated with SRLs in the context of a multimodal approach (monotherapy, neoadjuvant, adjuvant setting). After 24 months only patients reaching normal GH and IGF-1 showed significantly lower diastolic (DBP) and systolic blood pressure (SBP) as compared to baseline, while uncontrolled patients showed only a lowering in DBP levels [85]. In 2008, Colao and colleagues compared the efficacy of first-line SRL treatment vs first-line surgery in 89 patients with active acromegaly (12-month follow-up). The authors found that both treatment modalities resulted in a significant decrease of DBP levels, while SBP was unchanged [60].

On the other hand, a recent study showed that a 24 weeks treatment with lanreotide failed to significantly reduce SBP or DBP in treatment-naïve patients with acromegaly [68].

As far as treatment with the GH-receptor antagonist pegvisomant, an early study including 14 patients treated for 12 months, SBP and DBP were not affected at the end of follow-up. However, when only hypertensive patients were considered, pegvisomant therapy was found to significantly reduce DBP [84]. On the contrary, data from 62 acromegaly patients included in the German pegvisomant observational study demonstrated that after 12 months treatment, both SBP and DBP were significantly lower in controlled (normal IGF-1) than in partially-controlled patients (IGF-1 reduced without normalization) [90]. Moreover, SBP significantly decreased during treatment in controlled patients, while not in partially-controlled ones [90].

3.7 Metabolic complications

Glucose metabolism disorders found in patients with acromegaly mainly include impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and diabetes mellitus [52]. Recent registry studies indicate that diabetes is found in 17–30% of patients with acromegaly [21, 50, 83], and glucose intolerance in about 20% [83]. Since the direct action of GH is diabetogenic (through increasing lipolysis and inducing insulin resistance) [52], biochemical control would be expected to reduce insulin resistance, notwithstanding the small beneficial effect of excess IGF-1 on insulin sensitivity [52]. However, IGF-1 levels seem to show a better correlation than GH with the presence of glycometabolic comorbidities [91].

Biochemical control after transsphenoidal surgery improves glucose tolerance and reduces the prevalence of diabetes mellitus, whereas the effects of medical therapy vary between drug classes and treatment modalities [52] (Table 3). Several studies have shown that conventional SRLs reduce insulin resistance, while simultaneously reducing insulin and glucagon secretion [92, 93]. On the other hand, pegvisomant has been demonstrated to improve insulin sensitivity, increase glucose tolerance as well as decrease fasting glucose and glycosylated hemoglobin levels (HbA1c) [94]. Conflicting findings are often reported on the effect of SRL treatment on glucose tolerance in patients with acromegaly, likely due to the variations in study methodology [52].

A retrospective study conducted on 200 consecutive patients reported a three-fold higher risk of diabetes in patients with acromegaly uncontrolled after SRL treatment as compared with those in remission after surgery (hazard ratio [HR] 3.32, $p = 0.006$). However, only a 1.4-fold higher risk was recorded in those with biochemical control induced by SRLs compared with neurosurgery recipients (HR 1.43, $p = 0.38$) [53].

Data from prospective clinical trials suggest that the second-generation SRL pasireotide is associated with a significantly higher incidence and a greater degree of severity of hyperglycaemia-related adverse events than first-generation SRLs [12]. However, a number of recent studies have shown that the hyperglycaemic effect of pasireotide is often predictable, mainly based on baseline fasting plasma glucose and HbA1c, and changes in glucose metabolism are reversible [95]. Moreover, proactive monitoring and treatment results

Table 3 Effects of different medical therapies on glucose metabolism and body weight

	Drugs				
Parameters	OCT	LAN	PAS	DA	PEG
Fasting glucose	↑[a]	↑[a]	↑↑	↓[a,b]	↓
HbA1c	=/↑	=	↑	↓[a,b]	↓
Insulin	↓	↓	↓	↓	↓
Plasma glucose post OGTT	↑	=[b]	n.a.	↓[b]	n.a.
HOMA-β%	↓	↓[b]	↓	n.a.	↑[c]
HOMA-IR	↓	↓	n.a.	n.a.	↓
Body weight	=	=	n.a.	n.a.	n.a.

Legend: *OCT* octreotide, *LAN* lanreotide, *PAS* pasireotide, *DA* dopamine agonist, *PEG* pegvisomant, ↑ increase, ↓ decrease, = no significant changes, *HbA1c* glycated haemoglobin, *HOMA-β%* pancreatic β-cell funcition, *HOMA-IR* insulin resistance; [a] observed a clear trend towards increase/decrease, although not statistically significant; [b] evaluated in only one study; [c] compared to octreotide; n.a.: not available

in a rapid and successful control of hyperglycaemia in most patients [95].

A meta-analysis from Mazziotti and colleagues, published in 2009, showed that SRLs treatment does not affect fasting plasma glucose (FPG), HbA1c and glucose response to OGTT, while the authors found a significant reduction of fasting plasma insulin (FPI). However, on a metaregression analysis, the effects of SRLs treatment on these parameters was not significantly correlated with biochemical control (percent of patient achieving safe GH and normal IGF-1 levels) [96]. More recently, another meta-analysis confirmed that SRLs resulted in a significant lowering of FPI, although resulting in a significant improvement of insulin-resistance (HOMA-I) and β-cell function (HOMA-β). Furthermore, no major changes were observed for FPG levels after SRLs. However, differently from the previous report from Mazziotti et al., the authors reported a worsened glucose response to OGTT as well as a mild, but significant, increase in HbA1c. Interestingly, the reduction of both GH and IGF-1 levels was directly correlated with the drop in insulin levels, while IGF-1 levels affected HOMA-I values [97].

On the other hand, pegvisomant monotherapy mainly results in beneficial effect on glucose metabolism in acromegaly [22]. Of note, the majority of studies reporting the effects of pegvisomant treatment on glucose metabolism included patients completely or partially resistant to SRLs. Therefore, it could be speculated that this effect might be due to a better biochemical control of the disease. However, a direct beneficial activity of pegvisomant cannot be ruled out. In this context, a multicentre, open-label, 32-week study evaluated glucose homeostasis in patients converted from SRLs to pegvisomant [98]. The authors showed a significant improvement in glucose-related indices after the switch to pegvisomant, also in the subset of patients who had normal IGF-I concentrations during previous SRL treatment [98].

In summary, despite disease control, disorders of glucose metabolism may persist, particularly in acromegaly patients treated with SRLs compared to those cured after adenomectomy or treated with pegvisomant [99].

3.8 Osteoarticular and musculoskeletal complications

Arthropathy is common in acromegaly: the incidence of acral complications may be as high as 70% at diagnosis [100]. There is evidence that certain signs and symptoms may improve with medical therapy [101], however, arthropathy and established degenerative arthritis may persist despite biochemical control [6, 102]. On the other hand, normalization of GH and IGF-1 levels seems to be associated with improved joint thickness. Indeed, after 12 months of long-acting octreotide, 25–29% of patients with controlled disease experienced a maximum decrease in joint thickness (across all joint sites) as compared with 58% of patients without disease control [103]. However, a prospective follow-up study of patients with controlled acromegaly for a mean of 17.6 years reported joint function deterioration over the long term [104]. Progressive osteophytosis and joint space narrowing have been reported in over 70% of patients with long-term control of IGF-1 levels. In addition, the highest rates of joint disease progression has been reported in patients on medical therapy [105]. This has led some authors to conclude that elevated circulating GH levels despite SRL treatment, are responsible for the persistence of osteoarticular complications in acromegaly [106].

Furthermore, it is known that GH (and IGF-1) excess negatively affects bone status [107, 108].

A wide range in prevalence of vertebral fractures (VFs) has been reported (10–40% of patients) [6] and duration of active disease seems to be the most important determinant of VFs in acromegaly, while an adequate treatment can reduce this risk [100, 109]. In a recent meta-analysis, the risk of VFs was three times higher in uncontrolled patients when compared with controlled ones (odds ratio [OR] 3.35, 95% confidence interval [CI] 1.61–6.96) [107]. Anyway, some patients with controlled acromegaly still maintained high fracture risk, specifically in presence of preexisting VFs, thus reflecting a sort of domino-effect [108]. In this context, the presence of uncontrolled hypogonadism and/or diabetes mellitus has been associated with a higher risk of VFs in acromegaly patients, as well (Fig. 2). Notably, despite biochemical control, skeletal complications may progress in up to 20% of patients [105].

Patients with acromegaly have increased bone turnover, which results in a peculiar bone structure. Particularly, high GH and IGF-I levels mainly affect trabecular microarchitecture, while cortical bone density is often increased [110]. Dual X-ray absorptiometry (DXA) measurement of bone mineral density (BMD) does not distinguish between cortical and trabecular bone in acromegaly, and therefore most patients show normal or even increased BMD at various skeletal sites [107]. According to a study examining bone architecture and BMD at the lumbar spine, fracture risk may persist because of irreversible alterations in trabecular bone architecture [111]. Indeed, biochemical control of acromegaly is associated with a decrease of biochemical markers of bone turnover, accompanied by variable changes in BMD. However, this is generally associated with a persistently abnormal bone structure even after reversal of GH hypersecretion [108].

Finally, carpal tunnel syndrome is another common symptom of acromegaly and represents one of the hallmark of the disease, with much research focus on medial nerve neuropathy at the carpal tunnel level [112]. An ultrasound study in patients with acromegaly sought to examine the effects of biochemical control not only on the median but also the ulnar nerve cross-sectional area [112, 113]. Full or partial biochemical control was associated with smaller nerve cross-sectional area than in patients with uncontrolled hormone levels

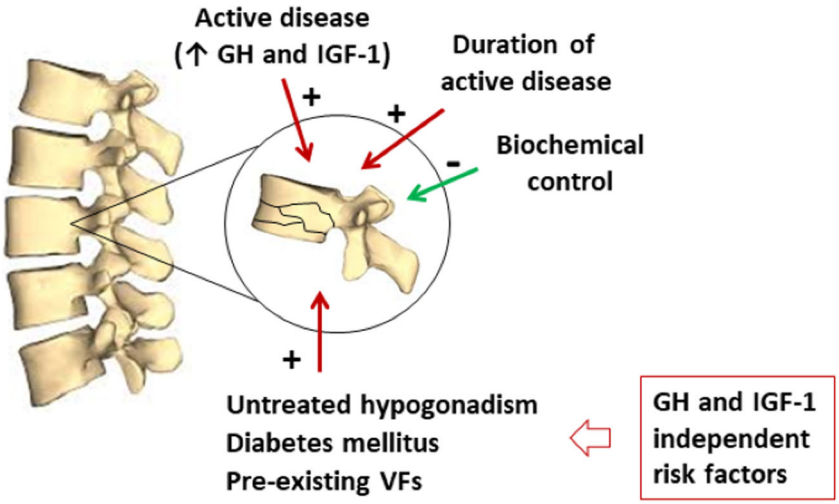

Fig. 2 A relevant percentage of acromegaly patients present vertebral fractures (VFs) during their clinical history. Active disease and disease duration correlate with a higher risk of VFs, while biochemical control seems to reduce their prevalence. However, other clinical conditions (i.e. untreated hypogonadism and diabetes mellitus) and the presence of pre-existing VFs have been highlighted as GH and IGF-1 independent risk factors in acromegaly patients

[112]. However, after 1-year follow-up, it appeared that biochemical control was associated with only partial reversal of nerve enlargement [113].

3.9 Respiratory disorders

Respiratory insufficiency and sleep breathing disorders, mainly sleep apnoea, are the main respiratory complications of acromegaly [52]. Disease activity, older age, and neck circumference have been reported to be independent predictors of sleep apnoea [114].

Biochemical control has been shown to improve sleep breathing disorders and respiratory insufficiency in patients with acromegaly by reducing the number of apnoeic and hypopneic episodes, improving central control of breathing and reducing soft tissue hypertrophy [52]. Interestingly, some authors showed that, following SRLs treatment, lung volume and distensibility decrease, while diffusion capacity remained stable [115].

A registry study reported a lower incidence of sleep apnoea in patients with controlled disease versus uncontrolled ones (20.3% vs 26.8%) [71]. However, sleep apnoea can persist after recovery of acromegaly, although in a multivariate analysis higher IGF-1 levels have been associated with the presence of this complication [116]. Furthermore, the observed improvements of sleep breathing disorders can result in a limited clinical benefit because the indication for positive airway pressure therapy may remain, even in those subjects with improved sleep apnoea due to biochemical control [117].

Because the soft tissue hypertrophy associated with acromegaly is the main factor driving the development of respiratory comorbidities, prompt treatment may allow for these changes to be reversed. Therefore, permanent anatomical changes due to delayed diagnosis or therapeutic inertia are the reason for the persistence of respiratory complications following biochemical remission [52].

3.10 Quality of life

The effect of biochemical control on QoL is unclear. QoL is generally assessed using the disease-specific AcroQoL questionnaire. While several studies have found no improvement in QoL in patients with controlled disease [118–121], others have reported improved QoL in patients reaching biochemical control [122–125]. A meta-analysis on the relationship between QoL and disease-activity, as reflected by biochemical control, confirmed the 'mixed-bag' of results [19]. The authors concluded that there are currently insufficient published data to confirm a beneficial effect of biochemical control on the QoL of patients with acromegaly [19].

In this context, the results from a recent 5-year prospective study show that QoL remains impaired in patients with acromegaly ($n = 58$) as compared with matched healthy controls ($n = 116$), despite long-term biochemically stable disease [121].

QoL is per se multifactorial, and there are several possibilities for the persistence of impaired QoL in patients with acromegaly in "remission", according to standard definitions. These include persistent physical and psychological limitations due to the irreversible effects of long-term exposure to GH and IGF-1 excess [126], such as irreversible craniofacial changes [127] and persistent joint complaints [128]. Furthermore, QoL may also be affected by depressive symptoms and anxiety [19, 129], negative illness perceptions [130, 131], body mass index and metabolic comorbidities [19], burden of ongoing treatment and follow-up [126], duration of remission [125],

impaired physical function and psychosocial wellbeing [121].

4 Clinical disease control with different medical therapy regimens

4.1 Second versus first-generation somatostatin receptor ligands

The first-generation SRLs octreotide and lanreotide preferentially bind somatostatin receptor type 2 (SST_2) [48] while the second-generation SRL pasireotide is a 'panligand', showing the highest affinity for SST_5 and SST_2 (namely, $SST_5 > SST_2 > SST_3 > SST_1$) [48]. Pasireotide was more effective than octreotide in improving QoL as first-line medical therapy [39] and improved QoL in patients with poorly-controlled disease after first-generation SRLs [40]. In detail, in a prospective, randomized, double-blind, multicentre, 12-month study of 358 patients with medically-naïve acromegaly [39], pasireotide LAR was associated with a larger increase in AcroQoL score than octreotide LAR (7.0 vs 4.9 points; baseline scores were similar in the two treatment groups). Improvements in symptom severity scores for all symptoms assessed were generally similar in the two treatment groups. Pasireotide LAR resulted in a greater inhibition of IGF-1 levels than octreotide LAR, while the two compounds had a similar impact on GH reduction [39]. However, hyperglycaemia-related adverse events were more frequent in the pasireotide LAR than the octreotide LAR group (57.3% vs 21.7%) [39].

The difference in efficacy and safety profile between pasireotide and a first generation SRLs may be partially explained by the pharmacodynamic differences between these agents, involving their extra-pituitary effects, as well as the differential receptor binding profile [132–134].

4.2 Growth hormone receptor antagonist versus first-generation somatostatin receptor ligands

Pegvisomant has been compared with octreotide in a phase III trial in patients with medically-naïve acromegaly ($n = 113$). The authors found no significant difference in disease signs and symptoms, ring size variation and AcroQoL total scores between the two treatment groups [135]. However, pegvisomant was more effective than octreotide in the achievement of normal IGF-1 in patients with more severe disease (IGF-1 ≥ 2 x ULN), in whom a trend towards greater improvement in AcroQoL scores was also observed [135]. On the other hand, in a cross-sectional study of 133 patients with acromegaly, patients were asked to complete questionnaires on QoL (AcroQoL), symptoms of depression (Beck's Depression Inventory [BDI]) and satisfaction with their medical therapy. Particularly, the Treatment Satisfaction Questionnaire for Medication (TSQM) evaluates patients' perceptions of effectiveness, side effects, convenience and global satisfaction. In this context, pegvisomant treatment (alone or in combination with SRLs) was associated with significantly lower convenience scores and a tendency towards a lower score for global satisfaction compared with octreotide and lanreotide monotherapy. Considering the peculiar treatment schedule of the patients included in the study, the authors suggested that this finding might be explained by the requirement for daily pegvisomant injections [136].

4.3 Combination of somatostatin receptor ligands plus growth hormone receptor antagonist

Therapies combining drugs with different mechanisms of action may be a rational choice to increase the likelihood of achieving clinical control and improving patients' signs, symptoms and QoL. Van der Lely and colleagues have shown that co-administration of lanreotide and pegvisomant decreased mean acromegaly symptom scores, with the greatest reductions observed in arthralgia and soft tissue swelling. Small improvements in global QoL score were also recorded, although considerable data variability was noted. Interestingly, there was no correlation between changes in IGF-1 z-score and change in the QoL score [137].

When low-dose pegvisomant was added to SRL in patients already adequately controlled on SRL monotherapy, QoL improved [122]. However, these results were not confirmed in a study using a different approach (progressive reduction of SRL dosage during pegvisomant treatment) [138]. In the placebo-controlled crossover study by Neggers and colleagues ($n = 20$), the addition of pegvisomant 40 mg weekly to SRL therapy (lanreotide or octreotide) was associated with significantly greater improvements in AcroQoL total scores ($p = 0.008$) and physical subscale scores ($p = 0.002$) compared to SRL monotherapy [122]. This improvement was observed without a significant decrease in IGF-1 levels [122]. Improvement in QoL was correlated with improvement in GH-dependent symptoms such as loss of body weight, perspiration, soft tissue swelling and AcroQoL physical subscale score [122].

The controversial study by Neggers and colleagues introduced the concept of 'extra-hepatic' acromegaly [134], which in turn prompted the discussion of whether the current approach to the treatment of patients with acromegaly may need to be re-evaluated. However, confirmation of this hypothesis is still warranted.

As for acromegaly-related metabolic complications, combination therapy with SRLs and pegvisomant has been reported to improve insulin response to OGTT in patients with either controlled [138] or inadequately controlled disease during SRL therapy [139, 140]. In a historical-prospective study of

50 patients, SRL monotherapy was associated with higher glucose compared with the combination treatment (SRL plus pegvisomant) during OGTT [141]. In addition, when SRL was withdrawn, and pegvisomant continued, glycaemic response further improved significantly. This effect was observed in both patients with biochemically controlled and uncontrolled disease [141]. However, SRL plus pegvisomant combination seemed not to improve other measures of glucose metabolism, such as fasting plasma glucose, HbA1c, insulin resistance and beta-cell function, compared to SRL treatment [138, 140].

Finally, no direct comparison of the effects of pasireotide and pegvisomant on disease and symptom control has been published to date.

5 Conclusions

Adequate biochemical control plays a role in reducing the impact of several comorbidities in acromegaly. Current guidelines already suggest longitudinal monitoring and rigorous management of hypertension, cardiovascular disease, diabetes mellitus, osteoarthritis and sleep apnoea [2, 9]. However, in the present review, we aimed to highlight clinical disease control as a primary focus of acromegaly patient management, besides biochemical control based on currently accepted criteria. In this light, it is widely recognised that early diagnosis and timely therapeutic intervention improve clinical outcomes [142]. Moreover, focusing exclusively on the biochemical control of the disease is affected by issues related to timely changing hormone targets, hormone assay [2], discrepancy between GH and IGF-1 levels in SRL-treated patients [16], and, as a consequence, lack of appropriate dose up-titration in the daily clinical practice [16]. Although some aspects of patients' QoL may be improved with biochemical control, there is some evidence that QoL should be considered a separate treatment target in addition to biochemical control, i.e., as a standalone entity [19]. Acromegaly comorbidities impact QoL [19], and some of them do not improve, even when biochemical control is achieved, suggesting that without an early diagnosis and intervention, long-term exposure to excess GH and IGF-1 levels lead to irreversible effects (i.e., degenerative arthritis, craniofacial abnormalities) [6]. Specific interventions, aimed at targeting factors associated with reduced QoL, such as depression and obesity [19], should be developed, as well as the importance of treating comorbidities to further reduce mortality risk is mandatory [143]. Finally, although data are currently limited, newer drugs with (also) a peripheral action, such as pegvisomant and, via different mechanisms, pasireotide, may lead to a better control of the disease, not only identified as the normalisation of biochemical parameters, but also at the clinical level.

Acknowledgments Financial support for medical editorial assistance was provided by Novartis Pharma AG. We thank Tracy Harrison and Georgii Filatov, Springer Healthcare Communications for the medical writing assistance.

Compliance with ethical standards

Conflicts of interest/financial disclosures FG has been a speaker for Novartis and has participated on advisory boards of Novartis, AMCo Ltd. and IONIS Pharmaceuticals. DF has been a speaker for and participated on advisory boards and received research grants from Novartis and Ipsen. The other Authors have no conflicts of interest to declare.

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