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Diagnosis and Management of Acromegaly: A Consensus Statement of the Pituitary Study Group of the Portuguese Society of Endocrinology, Diabetes and Metabolism

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Keywords
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Abstract
Acromegaly is characterised by hypersecretion of growth hormone and presents diagnostic and therapeutic challenges that require consensus and guidelines for effective management. The Pituitary Study Group of the Portuguese Society of Endocrinology, Diabetes and Metabolism used a modified

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Delphi methodology to develop consensus recommendations for the diagnosis and management of acromegaly. A multidisciplinary panel of experts in acromegaly collaborated through this process to establish consensus-based statements. The authors did not receive any corporate funding or remuneration. The methodology employed to achieve these consensus recommendations included a literature review of specific topics, development of consensus statements, survey and interactive discussions, and a subsequent comprehensive analysis of the results to converge on key consensus statements for diagnosis, treatment, and monitoring strategies. By synthesising the available evidence and integrating expert opinion, this consensus document offers valuable insights for healthcare professionals, facilitating timely diagnosis, personalised treatment strategies developed by multidisciplinary teams, and enhanced patient care.

Introduction

Acromegaly is a rare, chronic, slowly progressive disorder caused by hypersecretion of growth hormone (GH, somatotropin) [1]. The term "acromegaly," historically known as "Marie's malady," was first coined in 1886 by the French neurologist Pierre Marie. He linked the term to a clinical disease with a characteristic phenotype: "a condition characterised by hypertrophy of the hands, feet, and the face exists which we propose to be called acromegaly which means hypertrophy of the extremities" [2].

In most cases, GH is persistently secreted by a monoclonal tumour of the anterior pituitary gland arising from somatotroph cells – a somatotroph tumour [1, 3]. The pathogenetic mechanisms underlying tumourigenesis are not fully established and may involve genetic and/or epigenetic alterations, resulting in cell cycle dysregulation, signalling defects, or loss of tumour suppressor factors [3].

GH is synthesised, stored, and secreted by somatotroph cells in response to a complex regulatory system, including hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin [4]. The secretion of GH is suppressed by somatostatin signalling, primarily through the somatostatin receptors subtype-2 (SST2) and subtype-5 (SST5). GH stimulates the production of insulin-like growth factor 1 (IGF-1), mainly from the liver but also from extra-hepatic tissues. IGF-1 is the main mediator of the somatic and metabolic effects of GH. In acromegaly, the excessive production of GH and IGF-1 leads to a multisystemic disease characterised by somatic overgrowth, physical disfigurement, metabolic disturbances, and multiple comorbidities [4]. If uncontrolled, this disorder is associated with significant morbidity and increased mortality [1, 5].

Due to the rarity of acromegaly, large population studies are needed to generate reliable epidemiological data. A recent systematic review and meta-analysis provided an update on the epidemiology of the disease [6]. The pooled prevalence of acromegaly from 22 studies was 5.9 cases per 100,000 people, and the incidence rate was 0.38 cases per 100,000 person-years; however, the authors considered that the quality of the studies was medium/low with marked heterogeneity [6]. Acromegaly is typically diagnosed between the fourth and the fifth decade of life, affecting both sexes, but its incidence appears to be slightly higher in females [1, 7].

The aims of treatment are to normalise hormonal hypersecretion, control tumour growth, manage comorbidities, improve the signs and symptoms of the disease, decrease morbidity and mortality, as well as improve the patient's quality of life. To achieve these goals, the treatment requires a multidisciplinary team using different therapeutic tools, including neurosurgery, medical therapy, e.g., somatostatin receptor ligands (SRLs), dopamine agonists (DAs), GH receptor antagonist (GHRA), and radiotherapy [8, 9].

A multidisciplinary group of experts from the Pituitary Study Group of the Portuguese Society of Endocrinology, Diabetes and Metabolism convened to develop a consensus statement on the diagnosis and management of acromegaly. The experts reviewed the current literature, focusing on key topics of diagnosis, disease control and remission, therapy with SRLs, DAs, GHRA, alone or in combination therapy, and radiotherapy. Herein, the authors present an up-to-date consensus document on the diagnosis and management of acromegaly.

Methods

The topics of interest for this consensus statement were identified through a literature search in PubMed for papers in English published up until December 2023, and the authors' personal archives were also screened for additional references. Search terms included "acromegaly" and terms associated with each topic: "biochemical outcomes," "tumour volume," "clinical symptoms," "somatostatin receptor ligand," "dopamine agonist," "GH receptor antagonist," "oestrogens," "selective oestrogen receptor modulators," "mortality," "complications," "surgical outcomes," "remission," "cure," and "guidelines." The panel was composed of experts in pituitary diseases with different backgrounds from the Pituitary Study Group of Portuguese Society of Endocrinology, Diabetes and Metabolism. Panellists were selected based on their demonstrated experience, knowledge, and contributions to the field,

ensuring a representation from different professional backgrounds. A modified Delphi methodology was employed to achieve consensus among the panellists [10]. This interactive process involved a first round to define the topics of interest and then the panel members were assigned to those specific topics. Panellists were asked to generate the statements and provide the supporting scientific evidence related to each topic of interest, based on the revision of the current scientific literature and on their expert opinions, when insufficient clinical evidence was available. In a second round, panellists were presented with the compiled list of statements and were then asked to vote each statement based on predefined criteria, such as "agree as is," "agree with modifications," "disagree," or "not my area of expertise." Panellists were also encouraged to provide comments or suggestions for refinement. This step was followed by the analysis of the responses and comments. The revised version of the statements were subjected to a final round for approval, and then the manuscript was prepared and approved by all authors. Each round aimed to converge towards a group consensus. Consensus was defined as ≥80% agreement among the panellists, and the resulting statements are presented and discussed in the following sections.

Diagnosis, Disease Control, and Remission of Acromegaly

Which Clinical Features and Conditions Should Raise Suspicion for the Diagnosis of Acromegaly?

In acromegaly, elevated levels of GH and IGF-1 lead to somatic overgrowth, physical disfigurement, multiple comorbidities, poor quality of life, and premature mortality [4]. Acromegaly affects both women and men, although men present at a younger age, and women appear to have a higher incidence and mortality risk [11]. The presentation of acromegaly can be insidious, and despite the latest advancements in management, that have reduced the overall mortality, the diagnosis is still often delayed, and this negatively impacts patients' quality of life and their morbi-mortality in the long term [4, 11]. Current guidelines suggest the screening of acromegaly in patients with typical clinical manifestations, especially those with facial and acral acromegaloid features, but also in patients who have several acromegaly-related conditions, even if typical manifestations are absent, and in individuals with a pituitary mass [4].

Key typical clinical features of acromegaly include enlargement of hands and feet, as well as craniofacial changes, such as coarse facies, frontal bossing, large nose and lips, prognathism, diastema, and macroglossia [4, 12, 13]. Accelerated linear growth or tall stature, particularly if the height is ≥2 standard deviations above the mid-parental height, are key manifestations of pituitary gigantism, resulting from exposure to excessive levels of GH/IGF-1 before the epiphyseal closure [14]. Other common features of acromegaly include thickened soft tissue, hyperhidrosis, oily skin, skin tags, hirsutism, hoarse voice, headache, visceromegaly, fatigue, and weight gain [4, 12, 13]. Some skin manifestations are uncommon in acromegaly, including acanthosis nigricans, pachydermia, and cutis verticis gyrata (i.e., a rare benign skin lesion characterised by thickened and folded scalp resembling brain gyri and sulci, of which acromegaly is among the main causes) [15, 16]. The following conditions and comorbidities are common in acromegaly: sleep apnoea syndrome (60–80%), arthralgia and debilitating arthritis (30–70%), carpal tunnel syndrome (40–60%), backache and vertebral disease (40–50%), glucose intolerance (16–46%), diabetes (20–56%), hypertension (20–50%), menstrual irregularities, erectile dysfunction, colonic polyps (≤45%), and malignant neoplasms (10–23%) [4, 12, 17].

Many individuals with acromegaloid appearance, tall stature or overgrowth, or acromegaly-related conditions will have normal variants of physical traits or growth. Some will have elevated GH/IGF-1 levels, leading to a diagnosis of acromegaly or pituitary gigantism. However, a few cases may display similar clinical features of acromegaly but without GH/IGF-1 abnormalities, falling into the pseudoacromegaly category. The term pseudoacromegaly describes patients with clinical features of acromegaly or pituitary gigantism but with no GH/IGF-1 abnormalities, encompassing a wide range of conditions (e.g., pachydermoperiostosis, Sotos syndrome, Weaver syndrome, Cantú syndrome, etc.) that are difficult to diagnose due to their rarity and heterogeneity, as well as due to the overlapping clinical characteristics among them [18, 19].

Consensus Statements

- This consensus panel recommends considering the diagnosis of acromegaly in patients presenting with typical clinical manifestations, particularly those with acral and facial features of acromegaly.
- This consensus panel recommends considering the diagnosis of acromegaly in patients with several acromegaly-related conditions, such as sleep apnoea syndrome, debilitating arthritis, carpal tunnel syndrome, diabetes, hypertension, colonic polyps, or cancer.
- This consensus panel recommends considering the diagnosis of acromegaly in patients with a pituitary mass, even if typical acromegaly manifestations are absent.

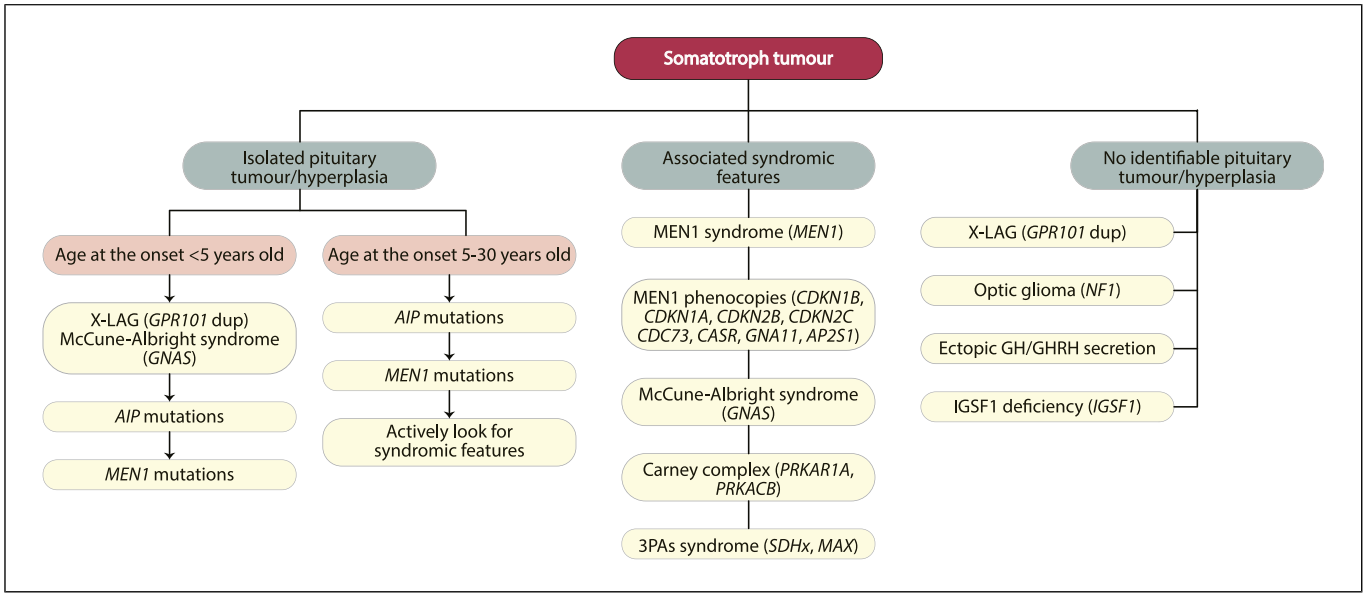

Fig. 1. Genetic approach to early-onset or syndromic-related somatotroph tumours (modified from [22]). *AIP*, aryl hydrocarbon receptor interacting protein; *APS2S1*, adaptor-related protein complex 2 subunit sigma 1; *CASR*, calcium-sensing receptor; *CDC73*, cell division cycle 73; *CDKN1A*, cyclin-dependent kinase inhibitor 1A; *CDKN1B*, cyclin-dependent kinase inhibitor 1B; *CDKN2B*, cyclin-dependent kinase inhibitor 2B; *CDKN2C*, cyclin-dependent kinase inhibitor 2C; GH, growth hormone; GHRH, growth hormone-releasing hormone; *GNA11*, G protein subunit alpha 11; *GNAS*, guanine nucleotide-binding protein alpha stimulating activity polypeptide; *GPR101*, G protein-coupled receptor 101; *IGSF1*, immunoglobulin superfamily member 1; *MAX*, MYC-associated factor X; *MEN1*, menin 1; *NF1*, neurofibromatosis type 1; *PRKAR1A*, protein kinase cAMP-dependent type I regulatory subunit alpha; *PRKACB*, protein kinase cAMP-activated catalytic subunit beta; *SHDx*, succinate dehydrogenase complex subunit; X-LAG, X-linked acrogigantism.

- This consensus panel recommends considering the diagnosis of pituitary gigantism in patients with accelerated linear growth or tall stature, particularly if the height is ≥2 standard deviations above the mid-parental height, and even more so if typical clinical features of acromegaly and/or acromegaly-related conditions or comorbidities coexist.
- This consensus panel recommends that the diagnosis of acromegaly may be considered in patients presenting with atypical features, specifically hyperhidrosis, pachydermia, and cutis verticis gyrata.

When Should Genetic Testing Be Offered, and Which Genes Should Be Tested?

Acromegaly and pituitary gigantism are most often caused by a somatotroph tumour. GH excess due to pituitary hyperplasia is less common and mainly occurs as part of genetic disorders, such as the Carney complex, X-linked acrogigantism (X-LAG), or McCune-Albright syndrome [20]. Rarely, GHRH-secreting neuroendocrine tumours or ectopic GH-secreting tumours may also lead to acromegaly [21]. Most somatotroph tumours occur sporadically, with ~40% of cases associated with somatic mutations in the *GNAS* gene. However, a subset of these cases may be familial [20]. To date, the percentage of familial forms of acromegaly remains unestablished, although it is known that nearly 50% of childhood-onset somatotroph tumours, leading to gigantism, have an identifiable genetic abnormality [14]. More broadly, about 5% of all pituitary tumours occur in the background of a predisposing germline mutation, more often in aryl hydrocarbon receptor-interacting protein (*AIP*) or menin 1 (*MEN1)* genes [22, 23]. Hereditary acromegaly may be accompanied by other conditions, as part of a syndromic disease, such as in multiple endocrine neoplasia type 1 or 4 (MEN1, MEN4), Carney complex, or the so-called "3 PAs syndrome" (i.e., paragangliomas, phaeochromocytomas, and pituitary tumours). It may also present as part of familial isolated pituitary adenoma (FIPA), a heterogeneous condition characterised by the occurrence of two or more pituitary tumour cases in the same family, in the absence of other syndromic manifestations (shown in Fig. 1) [22, 23].

FIPA is the most common cause of familial acromegaly or pituitary gigantism and can be categorised into three groups, depending on the genetic background: (i) *AIP* mutation-positive cases; (ii) X-LAG cases (rare); and (iii) FIPA with unknown genetic cause (most common scenario) [22, 23]. FIPA due to *AIP* mutations comprises about 10–20% of all FIPA families, predisposing individuals to young-onset pituitary tumours, that are typically aggressive, invasive, large, and refractory to conventional treatments, including SRLs [22–25]. About 50% of *AIP* mutation-positive kindreds present as sporadic cases due to the incomplete and relatively low penetrance of the disease, with only 20–23% of *AIP* mutation carriers developing a pituitary tumour [22, 23]. The prevalence of *AIP* mutations in apparently sporadic young-onset cases ranges from 4 to 14%, while ≤20% of apparently sporadic paediatric pituitary tumours may be due to an *AIP* mutation [25–30]. The risk of an *AIP* mutation is particularly high for patients ≤18 years old with a GH-secreting macroadenoma and a family history of pituitary tumours [31]. A lower frequency of *AIP* germline mutations (i.e., 1.8%) was reported in a Portuguese cohort of patients with sporadic pituitary macroadenomas diagnosed before the age of 40; however, the frequency of *AIP* mutations almost doubled (i.e., 3.4%) if only patients <30 years were considered and reached 5% in patients <18 years [32]. These data, combined with the observation that ~90% of all patients with clinically presenting *AIP* mutated pituitary tumours have disease onset at ≤30 years, support the use of this cut-off as probably the best for identifying young-onset sporadic cases [22, 23, 25, 33, 34]. X-LAG, caused by *GPR101* gene microduplications, is rare and is the main cause of gigantism in very young patients (i.e., below the age of 5), resulting from GH excess due to a somatotroph tumour or pituitary hyperplasia [33, 35].

MEN1 syndrome occurs due to germline mutations in the *MEN1* gene and typically involves the parathyroids (i.e., primary hyperparathyroidism), duodeno-pancreatic neuroendocrine tumours, and the pituitary, with pituitary tumours occurring in about 30–50% of subjects carrying a germline *MEN1* mutation [20]. Pituitary tumours may be the first manifestation of MEN1 syndrome in ≤15% of patients, with prolactinomas representing the majority of *MEN1*-related pituitary disease; however, 7–13% may be somatotroph tumours [36–39]. Acromegaly may also occur in other rare syndromes, such as MEN4, Carney complex, "3 PAs syndrome", neurofibromatosis type 1, and Lynch syndrome [20, 22].

Multifocal pituitary tumours are rare in sporadic settings but have been described more often in familial settings, such as Carney complex, MEN1, or *AIP* mutation-positive disease [40–42]. The presence of two or more pituitary tumours in the same patient may raise suspicion for an inherited condition; thus, genetic testing may be considered. Resistance to SRLs is a typical feature of *AIP* mutation-positive acromegaly [24, 25]. However, it was shown that *AIP* (or *MEN1*) testing in patients with acromegaly resistant to octreotide or lanreotide does not improve the detection rates of *AIP* (or *MEN1*) germline mutations [43]. Thus, genetic testing for patients with GH-secreting pituitary tumours resistant to SRLs and/or DAs cannot be generally recommended.

The identification of germline mutations in patients with acromegaly will enable genetic and clinical screening of at-risk family members, allowing for earlier identification and treatment of the disease, which can lead to better outcomes. For syndromic forms, such as MEN1 or "3 PAs syndrome," it facilitates the early screening, diagnosis, and treatment of other syndromic manifestations in the patient and their affected family members [20, 25, 44, 45].

Consensus Statements

- This consensus panel recommends considering sequential genetic testing for *AIP* and *MEN1* mutations, in this order (except if MEN1 syndromic features exist in the patient or any family member), and in the following situations: (i) family history of pituitary tumours (of any type); (ii) patients with GH-secreting pituitary tumours (micro or macroadenomas) with disease onset at age ≤18 years, including all cases of pituitary gigantism; and (iii) patients with GH-secreting pituitary macroadenomas with disease onset at age ≤30 years. Patients with double or multiple GH-secreting pituitary tumours may be considered for genetic testing, commencing with testing for *AIP,* if syndromic features are absent, followed by *MEN1*.
- This consensus panel recommends considering genetic testing for all patients with GH excess-related pituitary gigantism, starting with testing for *AIP,* if syndromic features are absent, followed by *MEN1*. In cases of accelerated growth/gigantism with onset at age ≤5 years, *GPR101* microduplications should be first assessed, followed by sequential genetic testing for *AIP* and then *MEN1,* if X-LAG is ruled out.
- This consensus panel recommends taking a detailed personal and familial history for patients with acromegaly or pituitary gigantism, and the presence of any syndromic features should guide the genetic testing: (i) kidney stones, primary hyperparathyroidism, duodeno-pancreatic neuroendocrine tumours, adrenal tumours,

angiofibromas, lipomas, and meningiomas – for MEN1 and MEN4 (genes *MEN1* and *CDKN1B*, respectively); (ii) cardiac myxomas, nevi, thyroid or adrenal tumours, lentiginosis, schwannomas, osteochondromyxomas, and primary pigmented nodular adrenocortical disease – for Carney complex (genes *PRKAR1A* and *PRKACB*); (iii) phaeochromocytomas or paragangliomas – for "3 PAs syndrome" (genes *SDHx* or *MAX*); (iv) café-au-lait macules, precocious puberty, fibrous dysplasia – for McCune-Albright syndrome (gene *GNAS*); (v) colon, brain, uterine, pancreatic, ovarian, and/or stomach cancer – for Lynch syndrome (genes *MSH2*, *MSH6*, *MLH1*, and *PMS2*); (vi) neurofibromas, optic gliomas, and phaeochromocytomas – for neurofibromatosis type 1 (gene *NF1*).

What Is the Most Appropriate Laboratory Workup in Acromegaly?

Patients with clinical symptoms of acromegaly, especially those with acral and facial features, should undergo biochemical screening, starting with the measurement of serum IGF-1 levels. The Endocrine Society also suggests measuring IGF-1 in patients without typical acromegaly clinical features but with several associated conditions, e.g., sleep apnoea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpel tunnel syndrome, hyperhidrosis, or hypertension [4]. It is also recommended to assess IGF-1 in patients with a pituitary mass [4, 46].

Serum IGF-1 is a reliable biochemical marker for assessing integrated GH secretion over the previous 24 h and is a crucial tool for the diagnosis of acromegaly [46]. In contrast to the pulsatile secretion of GH, serum IGF-1 levels remain stable throughout the day and do not have significant circadian variation. However, the reliability of serum IGF-1 may be affected by technical aspects, including issues with the validation and standardisation of IGF-1 laboratory methods and the establishment of normal reference ranges, as well as biological factors and medical conditions that influence IGF-1 concentrations (shown in Fig. 2) [47]. Some intrinsic characteristics of IGF-1 can introduce sources of error in its laboratory assessment. These include the strong binding of IGF-1 to high-affinity IGF-binding proteins (IGFBPs), glycosylation at the recognition site, IGFBP3 proteolysis, and the influence of other factors, such as age, sex, ethnicity, body mass index (BMI), thyroid hormone levels, among others [47, 48].

Serum IGF-1 levels are physiologically higher during adolescence and pregnancy, thereby posing difficulties in the interpretation of IGF-1 levels in these groups [49]. Thus, age-specific normal range intervals must be considered when interpretating serum IGF-1. On the other hand, serum IGF-1 levels can be blunted in patients with acromegaly who exhibit resistance to GH action related to advanced liver or kidney disease, severe hypothyroidism, malnutrition, anorexia, and poorly controlled diabetes mellitus, or in women receiving oral oestrogens [12, 49, 50]. Additionally, variability in IGF-1 assays across different laboratories may pose further challenges, as demonstrated in a multicentric UK-based study that found more than a twofold difference in the serum IGF-1 levels in the same sample among different laboratories, leading to diagnostic failure of acromegaly in 30% of the centres [51]. To overcome such variability and obtain accurate results, it is recommended that all pre-analytical variables be controlled, and serum IGF-1 should be assayed in the same laboratory for serial follow-up [50, 52]. Currently, there is no evidence that IGF-1 measurement by mass spectrometry is superior to immunoassays [53].

According to a recent consensus, in patients with typical signs and symptoms of acromegaly, IGF-1 levels >1.3 times the upper limit of normal for age confirm the diagnosis without the need for further testing [53]. In patients with equivocal results, it is advisable to repeat the IGF-1 measurement. Additionally, an oral glucose tolerance test (OGTT), assessing the GH nadir after administration of 75 g of oral glucose, may also be useful [53].

Random serum GH levels are inadequate for diagnosing acromegaly due to the pulsatile secretion of GH and the marked changes of GH concentrations throughout the day. In contrast, dynamic testing with a 75 g oral glucose load followed by serial measurements of GH levels may be useful to the diagnosis of acromegaly [53]. Normal subjects will exhibit suppression of GH to undetectable levels following a 75 g oral glucose load. However, the GH response during an OGTT may vary significantly in acromegalic and non-acromegalic individuals and should be interpreted cautiously, according to the individual physiological, pharmacological, pathological, and clinical factors [46, 52]. Random and during an OGTT GH levels may vary depending on several factors, such as sex, BMI, physical exercise, circadian rhythm, medications (e.g., oestrogen-containing oral contraceptives), glycaemic status, liver, and kidney function [52]. GH may fail to suppress in healthy adults, such as adolescents or young females (particularly those on oestrogen-containing oral contraceptives), or in individuals with liver or kidney disease, poorly controlled diabetes, anorexia, or other conditions (shown in Fig. 2) [4, 47, 50].

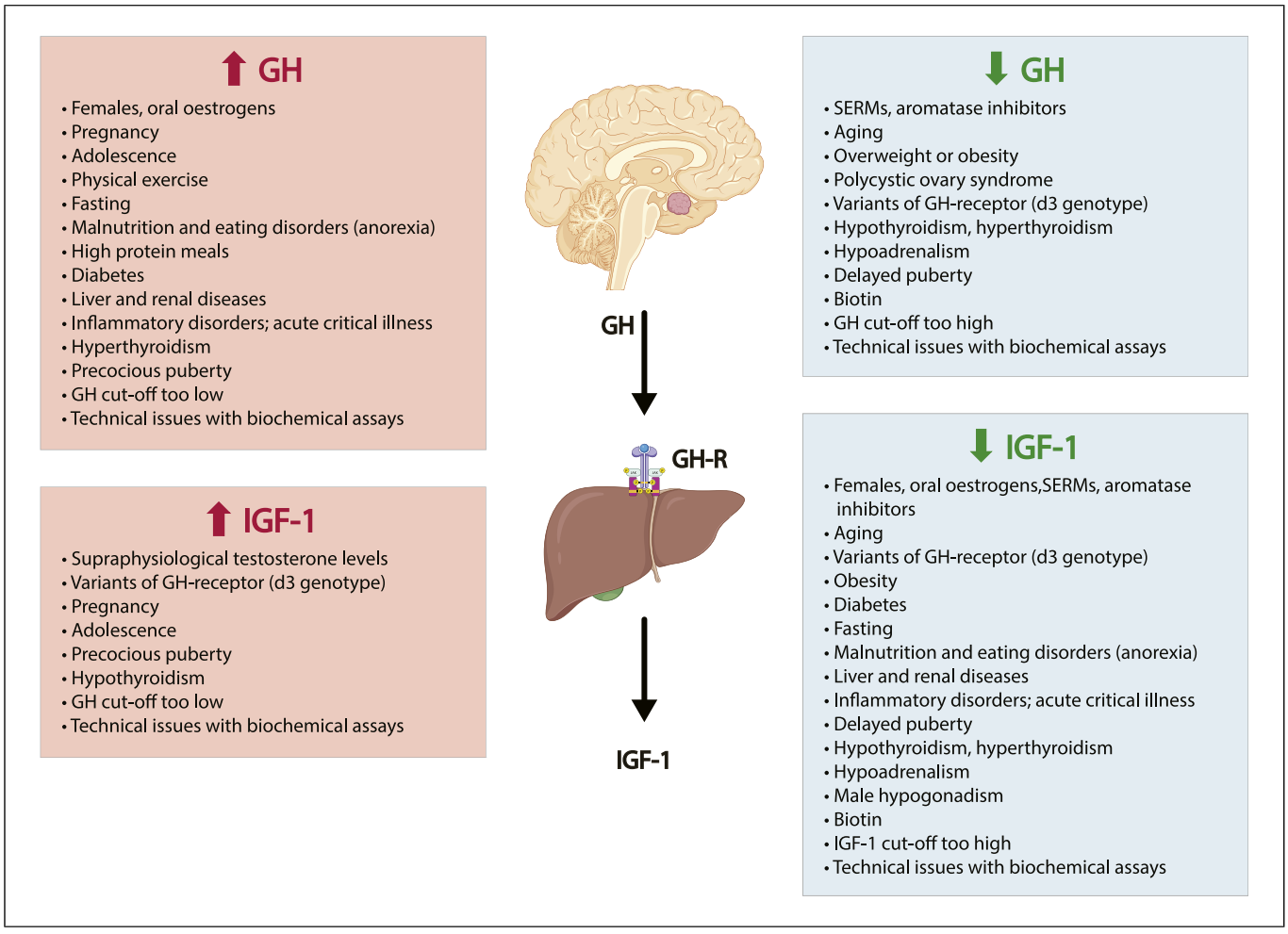

Fig. 2. Overview of the main technical, pharmacological, physiological, and pathological factors affecting the biochemical evaluation of the GH/IGF-1 axis, leading to high or low levels of serum IGF-1 or GH. GH, growth hormone; GH-R, growth hormone receptor; IGF-1, insulin-like growth factor 1; SERMs, selective oestrogen receptor modulators.

The appropriate GH nadir cut-off during an OGTT has been extensively debated over the years. The Endocrine Society guidelines, published in 2014, adopted a suppressibility cut-off of GH <1.0 μg/L, arguing that a GH nadir <1.0 μg/L within 2 h after oral glucose load usually excludes the diagnosis of acromegaly [4]. It was noted that a GH nadir <0.4 μg/L may be more reliable in establishing or ruling out acromegaly. However, this lower cut-off was not adopted at that time due to the insufficient accuracy of many assays at GH levels <1.0 μg/L [4]. Reference levels for GH nadir using the IDS-iSYS GH assay during an OGTT, that consider BMI, sex, and oestradiol-containing oral contraceptives have been established [11, 54].

According to the latest acromegaly consensus, if an OGTT is performed, 75 g of oral glucose should be administered in a fasting state, with GH levels assessed after 30, 60, 90, and 120 min [53]. The lack of suppression of BMI-based GH nadir level to <0.4 μg/L for BMI <25 kg/m^2 and <0.2 μg/L for BMI ≥25 kg/m^2 can be considered for diagnosis [53]. These proposed cut-offs derive from a large multicentre study investigating nadir levels of GH during an OGTT with the IDS-iSYS GH immunoassay, which concluded that BMI, sex, and oestrogen-containing oral contraceptives are major determinants of the OGTT GH nadir levels [54]. Healthy premenopausal women on oestrogen-containing oral contraceptives typically have higher GH levels; hence, it is recommended to discontinue these drugs 4 weeks prior to

Table 1. Evaluation of a patient with acromegaly (modified from references [4, 53, 62])

Assessment	Frequency and comments
Diagnosis	
IGF-1	• IGF-1 levels >1.3 times the upper limit of normal for age and characteristic clinical signs and symptoms of acromegaly confirm the diagnosis • For equivocal results, IGF-1 measurement can be repeated
OGTT	• For equivocal results, an OGTT may also be useful. The lack of suppression of BMI-based GH nadir level to <0.4 μg/L for BMI <25 kg/m^2 and <0.2 μg/L for BMI ≥25 kg/m^2 can be considered for diagnosis Comment: oral oestrogen therapy should be stopped 4 weeks before the OGTT
Evaluation of tumour effects	
Sellar area MRI	• Gadolinium-enhanced pituitary MRI should be performed at diagnosis using a high-quality, high-resolution equipment (1.5-3 Tesla). If MRI is unavailable or contraindicated, a CT scan may be considered as a second option
Visual field testing	• Visual field testing should be performed when the tumour abuts the optic chiasm on an imaging study; during pregnancy, serial visual field testing is suggested for patients with macroadenomas
Hypopituitarism and/or hyperprolactinaemia	• Total testosterone, SHBG, and PRL levels (in males) should be measured annually; consider testing free testosterone if there are doubts regarding the interpretation of total testosterone results • LH, FSH, 17β-oestradiol, and PRL levels (in females) should be measured annually, specifically in premenopausal females with menstrual dysfunction and when pregnancy is desired • Serum free T4 should be measured annually • Serum cortisol 8–9 am should be measured annually or whenever central adrenal insufficiency is suspected; a cosyntropin stimulation test should be performed if serum cortisol levels are low Comments: hypopituitarism is multifactorial, e.g., secondary to tumour compression, surgery, and radiotherapy. Hyperprolactinaemia may result from co-secretion, which occurs in ~30% of cases, or from the stalk compression effect; in either case, hypogonadism may be aggravated by hyperprolactinaemia. Central adrenal, gonadal, and thyroid insufficiencies should be monitored
Evaluation of comorbidities	
Clinical assessment of hypertension, osteoarthritis, and sleep apnoea syndrome	• Blood pressure should be measured at baseline and every 6 months or whenever there is a change in antihypertensive treatment • DXA scan should be performed every 2 years, particularly if osteopenia or osteoporosis is present • Vertebral morphometry on thoracic X-ray, as well as thoracic and lumbar spine X-ray should be done annually, particularly in patients with history of vertebral fracture, decrease in bone mineral density, kyphosis, symptoms of vertebral fracture, untreated hypogonadism, or lack of biochemical control of acromegaly • The Epworth scale or a sleep study should be conducted at baseline or before surgery if obstructive sleep apnoea is suspected Comments: hypertension, osteoarthritis, and obstructive sleep apnoea syndrome are frequent complications of acromegaly, affecting ~50%, ~70%, and ~70%, respectively. Acromegaly may also be associated with an increased risk of vertebral fractures, even in the presence of normal bone density; therefore, the fracture risk should be periodically assessed. In the presence of clinical lung disease or suspicion of thereof, or before surgery, lung function tests are advised

Table 1 (continued)

Assessment	Frequency and comments
Diabetes	• Fasting blood glucose should be measured every 6 months, particularly in patients with uncontrolled disease or those undergoing SRL therapy • HbA1c should be measured at least every 6 months, but the periodicity should be adjusted based on the clinical context, especially if diabetes or prediabetes is present Comments: impaired glucose tolerance and diabetes mellitus are a common finding, affecting <40% of patients
Dyslipidaemia	• We suggest that the diagnosis and management of dyslipidaemia should follow the guidelines for the general population Comments: patients with acromegaly exhibit a pro-atherogenic profile characterised by elevated small, dense low-density lipoproteins, lipoprotein (a), and triglyceride; however, the prevalence of dyslipidaemia in acromegaly is similar to the general population
Calcium metabolism	• Measurements of calcium, phosphorus, PTH, and 25(OH)vitamin D could be considered, particularly when there is history of urolithiasis Comments: hypercalciuria is frequent in patients with acromegaly, and hypercalcaemia may occur in ≤10% of patients
Cardiac disease	• Echocardiography and electrocardiogram should be performed annually, if abnormal Comments: valvular heart disease, particularly aortic or mitral regurgitation, and arrhythmias are common findings; however, the role of echocardiography and electrocardiogram at the time of acromegaly diagnosis is not yet established. Nevertheless, in the presence of clinical disease or suspicion of thereof, or before surgery, a detailed cardiac evaluation is advised
Colon neoplasia	• Screening for colon neoplasia with colonoscopy should be performed at the time of acromegaly diagnosis and repeated thereafter according to the guidelines for the general population if the patient does not have active acromegaly Comments: the risk for colon polyps is increased in patients with acromegaly
Thyroid neoplasia	• Screening for thyroid nodules should be performed clinically and a thyroid ultrasound is indicated when a nodule is clinically suspected Comments: thyroid cancer incidence appears to be increased in patients with acromegaly
Clinical assessment of psychological, social impairment, and quality of life	• AcroQoL should be measured annually Comments: patients with acromegaly experience significant psychological impacts, including impaired self-esteem, body image distortion, anxiety, and depression. They may also face social withdrawal, leading to decreased social participation and quality of life, even after biochemical remission

AcroQoL, Acromegaly Quality of Life Questionnaire; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FSH, follicle-stimulating hormone; GH, growth hormone; HbA1c, glycated haemoglobin; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PRL, prolactin; PTH, parathyroid hormone; SHBG, sex hormone-binding globulin.

the OGTT [53, 55]. It is also worth noting that around one-third of patients with acromegaly may show a paradoxical increase in GH after OGTT [56].

In patients with impaired oral glucose tolerance or type 2 diabetes mellitus, the OGTT appears to be safe and effective for the diagnosis of acromegaly using the BMI

cut-offs mentioned above. However, due to the suppressive effect of hyperglycaemia on GH, the results should be interpreted with caution, particularly in patients with uncontrolled diabetes [53].

Biochemical discrepancies between GH and IGF-1 levels are not uncommon in acromegaly [47, 57, 58]. A large meta-analysis encompassing 39 studies (7,071 patients with acromegaly) reported a pooled discordance rate between GH and IGF-1 of ~26%. The most frequent discrepancy (i.e., ~15%) was elevated IGF-1 with normal GH levels (GH status was based on mean value of a multiple-sample day curve, nadir value during an OGTT, or random basal sample of GH) [58]. In situations of discrepant values between GH and IGF-1, the use of other markers related to the GH action, such as IGFBP3 and the acid-labile subunit, may be helpful [11]. Soluble klotho levels correlate with GH and IGF-1 levels and correlate with clinical symptoms and quality of life in treated patients with acromegaly [11, 59, 60]. However, more studies are needed to establish whether soluble klotho is a valid marker in clinical practice. Metabolomics may also serve as a future auxiliary tool in the diagnosis and prognosis of pituitary tumours, including somatotroph tumours [61].

Metabolic, endocrine, cardiovascular, and other systemic complications that are common in acromegaly should be actively screened (shown in Table 1) [4, 62]. Routine biochemical tests, such as glucose, glycated haemoglobin (HbA1c), lipid profile, calcium, and phosphorus, help in the screening of diabetes, dyslipidaemia, and primary hyperparathyroidism, which may occur in MEN1 or MEN4. In acromegaly patients with parathyroid hormone-independent hypercalcaemia, measuring the serum levels of 1,25(OH) vitamin D can be useful [62, 63]. A comprehensive assessment of pituitary function should be also carried out, particularly in cases of pituitary macroadenoma. This should include free T4 (FT4), thyroid-stimulating hormone (TSH), morning serum cortisol (and, if necessary, the cosyntropin stimulation test), follicle-stimulating hormone (FSH), luteinising hormone (LH), total testosterone (in males), or oestradiol (in females). Prolactin (PRL) co-secretion occurs in 30% of patients with acromegaly, and its elevation may be functional, secondary to compression of the pituitary stalk by the tumour, or due to a mixed GH-PRL tumour [12].

Given the increased risk for colonic polyps in acromegaly, a screening colonoscopy at the time of diagnosis is recommended (shown in Table 1) [11]. After treatment of acromegaly, a colonoscopy can be repeated according to the guidelines for the general population, provided the patient no longer has active acromegaly [11]. Other exams may be needed to evaluate other acromegaly-related complications on an individual basis and according to the clinical scenario, including thyroid ultrasound (e.g., for clinically suspected thyroid nodules), echocardiography (e.g., for cardiomyopathy and heart valve disease), polysomnography (e.g., for sleep apnoea syndrome), among others (shown in Table 1).

Consensus Statements

- This consensus panel recommends measuring serum IGF-1 levels in patients with typical clinical features of acromegaly, as well as in other clinical situations where acromegaly is being considered (Statements 1.2 to 1.5). In a patient with typical clinical signs and symptoms of acromegaly, IGF-1 levels >1.3 times the upper limit of normal for age confirm the diagnosis.
- This consensus panel recommends that in patients with equivocal results, IGF-1 measurement can be repeated using the same assay, and an OGTT after administration of 75 g of glucose can additionally be considered. If OGTT is performed, the lack of suppression of BMI-based GH nadir to <0.4 μg/L for BMI <25 kg/m^2 and <0.2 μg/L for BMI ≥25 kg/m^2 can be considered for diagnosis. Assay/technical-, pharmacological-, physiological-, and pathological-related factors must be considered during the interpretation of the biochemical results.
- This consensus panel recommends that a patient with a recent diagnosis of acromegaly should be requested to undergo, as a minimum, the following biochemical tests: glucose, HbA1c, lipid profile, calcium, phosphorus, as well as FT4, TSH, serum morning cortisol, PRL, FSH, LH, total testosterone, or oestradiol (to assess the pituitary function status).
- This consensus panel recommends that a colonoscopy should be performed at the diagnosis of acromegaly and repeated thereafter according to the guidelines for the general population, if the patient does not have active acromegaly. Other exams may be needed to assess other acromegaly-related complications on an individual and clinically oriented basis.

What Is the Most Appropriate Imaging Modality?

After the biochemical diagnosis of acromegaly, an imaging study should be performed to identify the pituitary tumour [4, 64]. Magnetic resonance imaging (MRI) should be the first choice, with computed tomography (CT) scan as an alternative, if MRI is unavailable or contraindicated [4, 46, 65]. MRI should be performed using 1.5 Tesla or 3 Tesla scanners, with two-millimetre

slices, which is particularly important to identify small microadenomas, although most cases of pituitary acromegaly (~77%) are caused by macroadenomas [46]. MRI reports should be standardised and routinely include relevant information, such as the tumour size, intensity signal, and tumour relationship with neighbouring structures (e.g., optic chiasm, cavernous sinus, and sphenoid sinus). A detailed description of the supra- or infra-sellar extension, and the invasion of the cavernous sinus, using the modified Knosp classification, should also be reported. T2-weighted MRI signal intensity can predict the response to SRLs, with hypointense tumours showing better response to therapy with SRLs [53, 66].

Several groups have studied the role of functional imaging in detecting small microadenomas or sites of residual disease that may be amenable for repeat surgery or targeted radiotherapy, such as stereotactic radiosurgery [67]. Among the reported ligands, 11C-methionine has been shown to be particularly useful when MRI results are indeterminate or when the true extent of lateral tumour extension is unclear [67]. In a study involving 17 patients, functional imaging with 11C-methionine positron emission tomography (PET) showed higher sensitivity in detecting somatotroph tumours than 18F-fluorodeoxyglucose, with similar specificity [68]. Additionally, 18F-fluoroethyltyrosine has been successfully used to detect a somatotroph tumour in a paediatric patient who had undergone three previous transsphenoidal surgeries [69].

Very rarely, patients with biochemically confirmed acromegaly may not have a detectable tumour in the pituitary gland. In such cases, serum GHRH should be measured, and other imaging methods may be performed to investigate ectopic disease, such as thoracic and abdominal CT scan, and 68Ga-DOTA-somatostatin analogue PET/CT. 18F-fluorodeoxyglucose-PET should be reserved for the staging of ectopic tumours with aggressive behaviour [21, 70, 71].

Consensus Statements

- This consensus panel recommends that, after a biochemical diagnosis of acromegaly, a pituitary MRI scan, preferably with contrast, should be performed. If MRI is unavailable or contraindicated, a CT scan may be considered as a second choice.
- This consensus panel recommends that, when available, functional imaging studies may be considered, such as 11C-methionine PET and 18F-fluoroethyltyrosine, in the case of negative or equivocal MRI scan results.

When Is Acromegaly Controlled or in Remission?

Although biochemical remission is the primary treatment goal, it is not the only therapeutic objective in acromegaly [53]. Disease control is achieved when different goals are met: biochemical normalisation, control of tumour mass, preservation or replacement of pituitary function, prevention and control of symptoms and signs, management of comorbidities, improvement quality of life, and reduction of morbidity and mortality [5, 8, 50, 72].

For biochemical monitoring during or after treatment, both IGF-1 and GH levels may be measured, as they yield qualitatively different types of information. IGF-1 correlates more closely with improvement in symptoms and signs, while serum GH is more indicative of tumour secretory activity [73, 74]. Postoperative random GH levels and GH nadir during an OGTT are associated with long-term remission. An immediate postoperative GH level <1.0 μg/L is highly predictive of biochemical remission, and a GH nadir level <0.4 ng/mL 1 week postoperatively showed a positive predictive value >95% for surgical remission [13]. The postoperative decline of IGF-1 is slower than that of GH likely due to the longer half-life of IGFBPs. IGF-1 levels in the early postoperative are highly variable and stabilise approximately 12 weeks after surgery [75]. Therefore, serum IGF-1 should be measured at least 12 weeks postoperatively to determine the biochemical status of the disease [53]. If preoperative SRLs were used, serum IGF-1 should be repeated at 3–6 months to confirm remission, since the SRLs carryover effect may influence postoperative IGF-1 levels [53, 76, 77]. Moreover, some patients with acromegaly undergoing successful surgery have a delayed normalisation of serum IGF-1. In a series including 46 patients with acromegaly who underwent surgery and showed no residual tumour on MRI postoperatively, along with a nadir GH level <0.4 μg/L during an OGTT, it was found that 41% experienced a delayed (i.e., >3 months) IGF-1 normalisation, and 24% of them achieved a normal serum IGF-1 levels only 12–57 months after surgery [78].

The biochemical definition of remission is difficult and not consensual. Several biochemical tests have been used across different studies to define remission, including serum IGF-1, GH nadir during an OGTT, random GH, and mean GH on a GH day curve, with different laboratory assays, reference ranges, and cut-offs, complicating the establishment of robust conclusions. Therefore, there is no definitive evidence or universal consensus on the optimal evaluation to define postoperative remission, nor on the

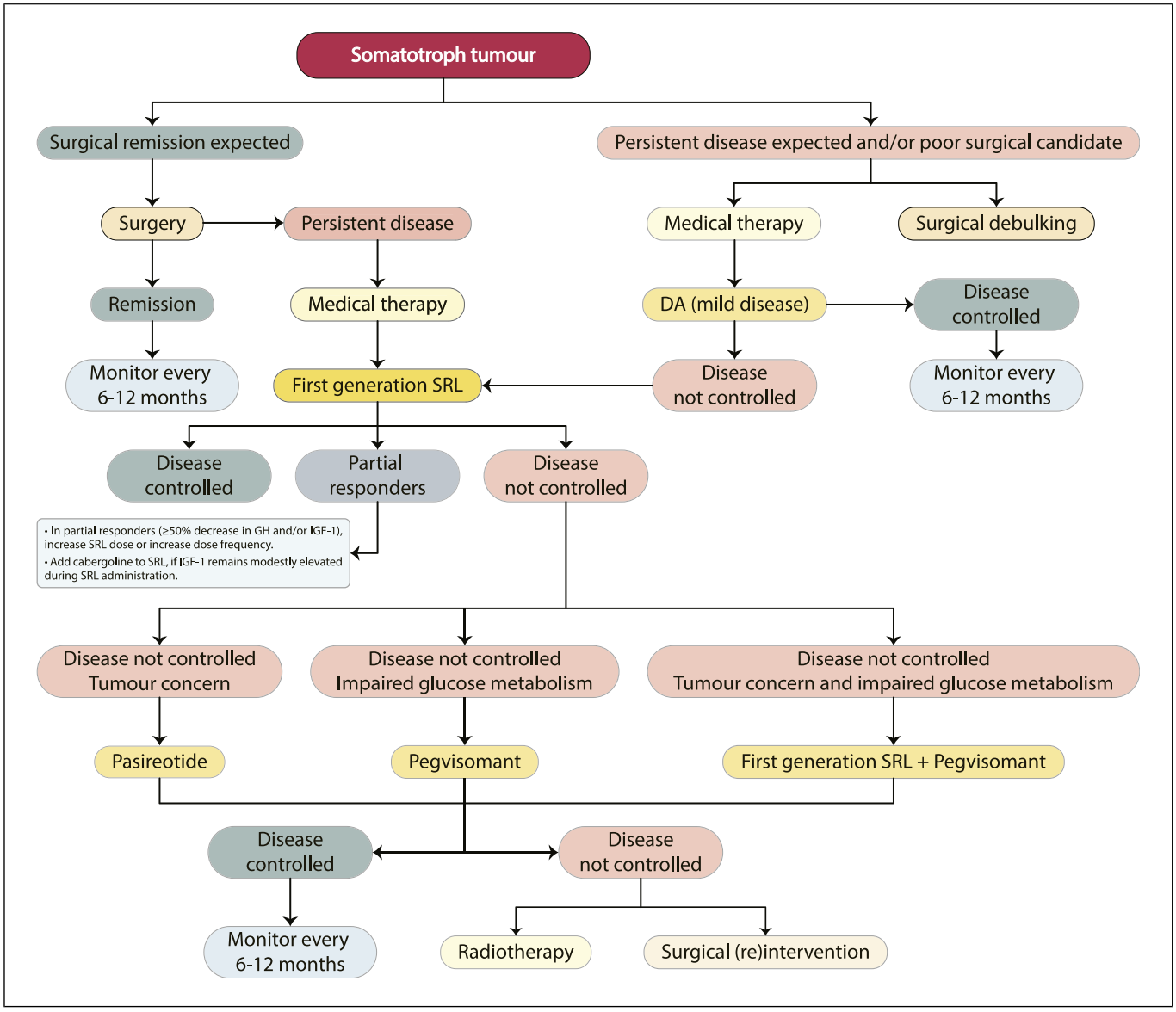

Fig. 3. A proposed management approach to the patient with acromegaly due to a somatotroph tumour (modified from [12, 79]). DA, dopamine receptor agonist; GH, growth hormone; IGF-1, insulin-like growth factor 1; SRL, somatostatin receptor ligand.

timing for such evaluations. In general, studies favour using serum IGF-1 to monitor the disease activity in the medium/long term, with normal age-adjusted IGF-1 levels as the goal. Given the variability of results between different immunoassays and between distinct laboratories, it is advisable to measure IGF-1 using the same assay and in the same laboratory during the follow-up of a patient with acromegaly [1, 4, 51]. Previous recommendations defined a random GH level <1.0 μg/L or a GH nadir level <0.4 μg/L during an OGTT as therapeutic targets. However, shortcomings of GH assessments at baseline or after glucose load limit their use as criteria to define remission or disease control in acromegaly [4, 53, 79]. A recent consensus established the efficacy goal as a normal age-adjusted serum IGF-1, while recognising the utility of GH nadir during an OGTT in the evaluation of patients with borderline IGF-1 levels and clinical signs of active acromegaly [53]. In cases where GH and IGF-1 are discrepant or unreliable indicators of changes in co-morbidities, monitoring of the disease may implicate a

direct assessment of acromegaly-related comorbidities (e.g., formal sleep studies, pulmonary function testing, or echocardiography) [80].

Consensus Statements

- This consensus panel recommends that normal serum IGF-1 levels adjusted for age should be achieved for controlled disease.
- This consensus panel recommends that serum IGF-1 should be measured in the same laboratory and using the same assay during the follow-up, to minimise the technical errors and to account for the inter-assay variability.
- This consensus panel recommends that the term "remission" should be used preferentially instead of "cure". Normal serum IGF-1 levels adjusted for age should be the main criteria to define remission. However, a random GH <1.0 μg/L or a GH nadir <0.4 μg/L measured during an OGTT with an ultrasensitive GH assay may be useful in defining remission in the cases of borderline IGF-1 levels.

Management of Acromegaly

What Is the First Treatment Option for Acromegaly?

The optimal management of patients with acromegaly requires a multidisciplinary team, including endocrinologists, pituitary neurosurgeons, neuroradiologists, neuropathologists, and radiotherapists with extensive expertise in pituitary and parasellar tumours. The therapeutic options in acromegaly are surgery, medical therapy, and radiotherapy. A proposed management algorithm is shown in Figure 3 [81, 82].

As the most effective option to achieve complete biochemical remission and provide tumour tissue for pathological characterisation, transsphenoidal tumourectomy is the cornerstone treatment for somatotroph tumours and the optimal primary treatment for eligible patients [4]. Surgical debulking should be considered when there is visual impairment and when a substantial amount of the tumour can be successfully removed to enhance the response to medical therapy and/or radiotherapy [4, 8]. Repeated pituitary surgery may also be considered in patients with acromegaly and residual intrasellar disease following the initial operation, particularly if the initial intervention was not performed at a pituitary tumour centre of excellence [4].

Currently, the choice of the surgical technique (i.e., endoscopic or microscopic approaches) depends on the neurosurgeon's expertise, as there are no definitive data recommending one approach over the other [83]. When performed by an experienced neurosurgeon, transsphenoidal surgery (TSS) is effective in 75–100% of acromegaly patients with microadenomas, but remission rates for macroadenomas drop down to 48–75% [4, 8, 84–86]. Perioperative complications include bleeding, cerebrospinal fluid rhinorrhoea, meningitis, arginine vasopressin deficiency, and hypopituitarism [4]. Perioperative mortality rates are <1% in expert hands [87].

Consensus Statements

- This consensus panel recommends transsphenoidal surgery as the initial treatment for patients with a somatotroph tumour entirely or mostly confined to the sella or for tumours causing visual impairment. Surgical debulking, including for cases of repeated pituitary surgery, should also be considered to improve the response to medical therapy and radiotherapy.

What Are the Indications for Preoperative Medical Treatment?

Published data are contradictory regarding the potential benefits of preoperative treatment with SRLs administered 3–6 months before surgery. While patients with severe acromegaly comorbidities and high surgical risk (e.g., severe pharyngeal thickening and sleep apnoea syndrome, or high-output heart failure) may have some improvement, routine preoperative SRL treatment is not recommended for other patients with acromegaly [4, 88]. Data on postsurgical remission rates are controversial. While short-term remission rates appear to improve after preoperative medical treatment, the long-term outcomes remain unchanged [88].

Preoperative medical treatment with SRLs should also be considered when an expert neurosurgeon is not available or when surgery is expected to be significantly delayed. However, effective SRL treatment should not postpone surgery, as it remains the first-line treatment for acromegaly [88].

Consensus Statements

- This consensus panel recommends that preoperative medical treatment should be considered in patients with severe pharyngeal thickening and sleep apnoea, or those with high-output heart failure.

When Is Surgery Not Advisable?

Although TSS is the first-choice treatment for most microadenomas and macroadenomas, around 40–60% of macroadenomas cannot be controlled by surgery alone. Some patients may refuse surgery or have contraindications due to high anaesthetic risk (e.g., severe cardiomyopathy or respiratory disease). Additionally, the lack of an experienced pituitary neurosurgeon, conducting at least 50 pituitary operations per year, has been associated with lower control rates and should prompt referral of the patient to a specialised centre [89]. The Endocrine Society guidelines, published in 2014, recommend the use of SRLs as the primary medical treatment in patients with acromegaly who cannot be cured surgically, those with tumours invading the cavernous sinus without compressing the optic chiasm, or for patients deemed poor surgical candidates [4]. The 2011 guidelines of the American Association of Clinical Endocrinology also suggest primary medical therapy in patients who have a macroadenoma without compressive effects, who have a tumour that cannot be completely removed surgically (because of extrasellar extension of the tumour, especially into the cavernous sinus), who are poor surgical candidates, or who prefer medical treatment [46, 49].

Different studies showed that primary therapy with long-acting SRLs reduces the hypersecretion of GH and IGF-1 in about one-third of patients naïve to therapy and decreases the tumour volume by 20% in two-thirds [90, 91]. When comparing head-to-head the efficacy of octreotide long-acting release (LAR) with surgery, a prospective randomised controlled trial showed that treatment outcomes were not significantly different [92].

In a series of patients with acromegaly who refused surgery or had severe comorbidities, 5 years of primary medical treatment with SRLs resulted in biochemical control and improvement of hypertension, dyslipidaemia, and respiratory complications [93]. Other studies revealed variable results but with a significant proportion of patients reducing at least 50% of tumour volume with SRLs, which was correlated with biochemical control (i.e., percent of IGF-1 and GH decrease) [94, 95].

When medical therapy fails or when it is the patient's preference (e.g., patient does not want to receive long-term injections), radiation therapy may be an alternative treatment option (shown in Fig. 3). However, medical therapy may be needed until the effectiveness of radiotherapy is established, which can take several years [4, 96].

Consensus Statements

- This consensus panel recommends that patients who refuse pituitary surgery or who are at high anaesthetic risk should be managed with primary medical treatment, preferably with SRLs.
- This consensus panel recommends considering primary medical therapy with SRLs in cases of tumours with cavernous sinus invasion without chiasmal compression, when significant debulking is not feasible.

How to Treat a Patient Who Is Not in Remission after Surgery?

Biochemical control of GH and IGF-1 remains the strongest predictor of patient outcomes and is one of the main treatment goals in acromegaly [11, 97]. TSS is the first-line treatment and the most effective option to rapidly achieve normal GH and IGF-1 levels and remission of the disease.

Large tumours, with extrasellar extension or cavernous sinus invasion, high preoperative serum GH levels, and female sex are associated with poor remission rates after pituitary surgery [85, 86, 98–101]. In cases of persistent or recurrent disease following TSS, medical therapy (i.e., SRLs, DAs, and GHRA, alone or in combination therapy) and radiotherapy are generally recommended as second-line and third-line options, respectively (shown in Fig. 3) [8, 49, 85, 86, 98–101].

The limited data on second surgical attempts, the variable success rates, and the increased risk for surgical complications, have maintained the debate open as to whether reoperations should be performed [102–104]. A recent meta-analysis evaluated 161 reoperations and 2,180 first-time surgeries reported a disease control rate for reoperation of ~47% and ~56% for first-time surgery. In microadenomas, the control rate was also similar (comparing first-time surgery to reoperation), however in macroadenomas reoperation was associated with a lower control rate in comparison to first-time surgery (i.e., ~28% vs. ~54%) [104]. Reoperation may be considered in patients with a potentially resectable residual tumour after an unsuccessful first surgery and in cases with significant residual tumours and poor response to postoperative medical therapy [8].

Consensus Statements

- This consensus panel recommends medical therapy and radiotherapy as second-line and third-line options,

Table 2. Medical therapy for acromegaly (modified from references [105–108])

Drug	Mechanism of action	Dosage	Biochemical efficacy (% of patients)	Patients with >20% tumour volume reduction, %	Side effects
Cabergoline	Dopamine receptor agonist	1.5–3.5 mg/week, per os	18%	33%	Gastrointestinal, nasal congestion, fatigue, orthostasis, headache, cardiac valve abnormalities
Octreotide long-acting release	Somatostatin receptor ligand (higher SST2 affinity)	10–40 mg/month, intramuscular	30–40%	73–80%	Gastrointestinal, injection site reactions
Oral octreotide capsules	Somatostatin receptor ligand (higher SST2 affinity)	20–40 mg twice daily, per os	38–58%; 91%[a]	–	Gastrointestinal
Lanreotide Autogel	Somatostatin receptor ligand (higher SST2 affinity)	60–120 mg/ month, deep subcutaneous	30–40%	63–79%	Gastrointestinal, injection site reactions
Pasireotide long-acting release	Somatostatin receptor ligand (higher SST5 affinity)	40–60 mg/month, subcutaneous	54%	80%	Hyperglycaemia, gastrointestinal, injection site reactions
Pegvisomant	Growth hormone receptor antagonist	10–40 mg/day, subcutaneous	70%	No effect	Injection site reactions, elevated liver function tests

SST, somatostatin receptor subtype. [a]Data from the head-to-head MPOWERED study, which compared octreotide LAR and lanreotide Autogel and defined biochemical response as IGF-1 <1.3 times the upper limit of normal [107]. In the third year of the open-label extension the biochemical response was 94% [108].

respectively, in the case of persistent or recurrent disease following TSS. Reoperation may be considered in patients with a tumour remnant that is susceptible to being totally or significantly removed.

What Is the Best Approach to Follow when Medical Therapy Is Needed?

When remission is not achieved with TSS, medical therapy should be initiated. There are three classes of drugs available: SRLs, DAs, and GHRA (shown in Table 2) [8, 11, 49, 84].

First-generation SRLs (e.g., octreotide LAR and lanreotide Autogel) are considered the first-line of medical treatment in most cases [8]. These drugs are usually administered monthly, either intramuscularly (octreotide) or subcutaneously (lanreotide), and they target the SST2 expressed by pituitary tumours and have concomitantly anti-secretory and anti-proliferative effects [49, 109]. Normal GH and IGF-1 levels may be achieved in 30% and 55% of cases, respectively, while significant tumour shrinkage (i.e., tumour volume reduction >20%) can be observed in ≤66% of patients [91, 109–115]. Among individuals previously controlled with long-acting first-generation SRLs, recent studies showed that extended-dosing intervals of 120 mg lanreotide Autogel (i.e., beyond 4 weeks) may still be effective [79, 116].

There is a new formulation of octreotide, i.e., oral octreotide capsules, approved by the US Food and Drug Administration (FDA), in 2020, and the European Medicines Agency (EMA), in 2022, respectively. This formulation has been demonstrated to be effective for patients who have achieved a biochemical response with stable doses of injectable octreotide LAR or lanreotide Autogel. So far, there is currently no data supporting the use of oral octreotide capsules as primary medical therapy in

SRL-naïve patients or in patients previously treated with pasireotide LAR [11, 117].

Pasireotide LAR is a second-generation SRL with higher affinity for SST4 and SST5 receptor subtypes, and also some affinity for SST2, approved by the FDA and EMA for acromegaly, in 2014 [118, 119]. Several prospective randomised trials showed that pasireotide LAR is effective in patients with acromegaly not controlled with maximal doses of octreotide LAR or lanreotide Autogel, achieving rates of biochemical remission ≤54% and higher response in tumour shrinkage [120–124]. However, the risk of drug-induced hyperglycaemia and/or diabetes mellitus is greater with pasireotide LAR (i.e., ≤70% and 40%, respectively), likely due to impaired insulin and incretin secretion combined with a minimal impact on glucagon production [62, 120, 125]. Considering its safety profile and efficacy, this drug should be used in patients with resistance to first-generation SRLs, especially those with normal glucose metabolism and when there is a concern with tumour mass [62, 79].

Cabergoline is a DA with a high affinity for dopamine D2 receptors and low affinity for dopamine D1, α1-and α2-adrenergic, and 5-HT1- and 5-HT2-serotonin receptors. It is more potent, long-lasting, and better tolerated than bromocriptine [126]. Although cabergoline has a modest effect on acromegaly control, low baseline serum IGF-1 levels have been considered predictors of higher likelihood of biochemical response to this drug [127–129]. For this reason, cabergoline is recommended as first-line medical therapy in patients in whom surgery has failed to achieve biochemical control and IGF-1 levels are only mildly elevated (i.e., <1.5 times the upper limit of normal) and may be considered as an add-on in cases of partial response to SRLs or pegvisomant [79, 127, 128]. IGF-1 normalisation is achieved in 35% of patients with high-dose cabergoline as monotherapy and in 50% when combined with SRLs [127].

Pegvisomant is a pegylated GH analogue with enhanced affinity for the GH receptor, preventing the signalling cascade activated by GH receptor-binding [130, 131]. This GHRA is usually recommended as a second-line medical therapy for patients with intolerance or incomplete biochemical response to maximal doses of SRLs; in addition, it can also be considered a treatment option in certain cases of persistent disease after surgery or when a surgical procedure is not performed [132]. Since pegvisomant does not target the pituitary tumour, GH hypersecretion persists during treatment, although tumour growth is rare (i.e., <5%) [133]. For this reason, in patients with large tumours abutting the optic chiasm and other vital structures, or in those with residual tumour, other tumour-targeted treatments should be preferred [8, 133]. Compared to other medical therapy, pegvisomant is of particular interest for individuals with diabetes or glucose intolerance, as it improves glycaemic control independently of IGF-1 control [134, 135]. Pegvisomant is highly effective in blocking the GH action, normalising the IGF-1 levels in 90% of patients in clinical trials and ≤73% in real-life studies [136–139]. The therapeutic control rate is dose-dependent and in particular situations, such as patients with higher baseline IGF-1 levels, diabetes, or higher BMI increased doses may be required to achieve IGF-1 normalisation [139].

The systematic evaluation of clinical and biochemical parameters is crucial for monitoring therapeutic response and optimising treatment decision in acromegaly. In addition, tools like SAGIT or ACRODAT can be used to assess the disease status and evolution and to guide treatment in patients with acromegaly [140, 141].

Response to either surgical or medical treatment is variable and inconsistent. Understanding which factors contribute to variability in the therapeutic response to SRLs will help clinicians to better manage patients with acromegaly. Age, sex, tumour size, genetic background, baseline GH and IGF-1, along with histological, and imaging characteristics of the tumour are possible predictors of biochemical response to SRLs [114]. Older age, female sex, lower serum IGF-1, and GH levels at baseline are associated with a higher likelihood of achieving biochemical control [49, 142]. Patients with germline mutations in the *AIP* gene typically have a reduced response to first-generation SRLs, but a better response to pasireotide LAR [24, 25, 143]. Patients with X-LAG due to *GPR101* microduplications also have a poor response to SRLs [33].

Several histopathological and molecular markers may also help predicting the response to SRLs. A lower Ki-67 index (i.e., <3%) and a higher SST2 expression have been associated with better treatment responses [49]. Densely granulated tumours are more likely to achieve remission compared to sparsely granulated tumours [144]. Moreover, patients with sparsely granulated tumours that are not controlled with SRLs appear to respond to a switch or addition of GHRA [144].

Imaging characteristics on MRI may also predict the response to SRLs. Tumours that secrete GH can be hypo-, iso- or hyperintense on T2-weighted MRI sequences [65]. The relationship between T2-weighted signal intensity on MRI and tumour response to SRLs as primary monotherapy was evaluated in a multicentre study. The

response to SRLs, evaluated through random GH levels, IGF-1 levels, and tumour volume was correlated with the calculated T2 intensity, and the lower the T2 signal intensity the greater the response to SRLs [65, 66].

Consensus Statements

- This consensus panel recommends medical therapy in cases of persistent disease after surgery. First-generation SRLs (octreotide LAR and lanreotide Autogel) are usually the first-line treatment to be offered. However, if there is only a mild elevation of IGF-1, cabergoline as monotherapy should be considered.
- This consensus panel recommends that pasireotide LAR or pegvisomant be considered as alternative options in patients with uncontrolled GH/IGF-1 levels despite treatment with first-generation SRLs. In patients with diabetes mellitus and small tumour remnants, pegvisomant should be preferred, while patients with larger tumour remnants may be considered for pasireotide LAR.

How to Adjust the Dosage of SRLs?

At the standard starting dose of SRLs, not all patients achieve biochemical remission and control of clinical disease. One approach is to start SRLs at a lower dose and titrate upwards at 3–6 months intervals, according to the serum levels of IGF-1. For octreotide LAR, the starting dose is typically 20 mg, administered by intramuscular injection every 4 weeks. If this dose fails to achieve normal IGF-1 levels after the first 3–6 months of treatment, the dose may be increased to 30 mg every 4 weeks, and then to the maximum dose of 40 mg every 4 weeks [145]. Lanreotide Autogel is started at doses of 60, 90, or 120 mg every 4 weeks. If serum IGF-1 levels do not normalise with lower doses of 60 or 90 mg every 4 weeks after 3–6 months, the dose may be gradually increased to 120 mg every 4 weeks [146, 147]. In selected cases with inadequately controlled disease by long-term conventional SRLs, the administration of lanreotide Autogel 120 mg more frequently (i.e., every 3 weeks) may control the disease in some of those patients [148].

Biochemical monitoring of patients on SRLs includes measuring serum IGF-1 levels every 3 months. Once normal serum IGF-1 levels are achieved, the doses of octreotide LAR or lanreotide Autogel should be maintained or eventually down-titrated. For lanreotide Autogel, the dose can be reduced or the dose intervals can be extended up to 6 or 8 weeks [11, 149]. The initial dose of pasireotide LAR is 40 mg every 4 weeks, but if serum IGF-1 levels do not normalise after 3–6 months, the dose can be increased to 60 mg every 4 weeks [150].

Switching between first-generation SRLs can improve the biochemical control and reduce adverse effects. When switching from octreotide LAR to lanreotide Autogel, doses of 60, 90, or 120 mg can be administered, regardless of the previous dose of octreotide LAR. However, when switching from lanreotide Autogel to octreotide LAR, the starting dose should be 20 mg every 4 weeks. In either case, serum IGF-1 levels should be measured regularly, and if the levels are not within the normal range the dose can be increased. When normal IGF-1 levels are not achieved after at least 6 months of treatment, with maximum doses of first-generation SRLs, therapy may be switched to pasireotide LAR [150].

SRLs are safe and effective for long-term use. In patients who achieve long-term control of acromegaly, reducing the dose or decreasing the frequency of administration of SRLs should be considered [151].

Consensus Statements

- This consensus panel recommends that patients treated with SRLs should have serum IGF-1 levels measured every 3–6 months, and the doses should be titrated based on the IGF-1 levels measured before drug administration until normal levels for age are achieved.

What Are the Adverse Effects of SRLs?

SRLs are generally well tolerated and safe, but patients should be informed about possible adverse events when starting treatment (shown in Table 2). The main adverse events of SRLs stem from their inhibitory effect on the secretion of pancreatic and gastrointestinal peptides, as well as their modulation of gastrointestinal functions (e.g., intestinal motility and gallbladder contractility) [152].

Octreotide LAR and lanreotide Autogel have similar side effects, which are generally transient, modest in severity, and may onset shortly after the first administration [153]. The frequency of adverse effects decreases progressively with continued treatment [46, 153]. These adverse effects include gastrointestinal disturbances (e.g., abdominal cramps, flatulence, diarrhoea, nausea, and vomiting), malabsorption (e.g., steatorrhoea), gallbladder disease (e.g., biliary sludge and gallstones), hair loss (rarely alopecia), and sinus bradycardia [46, 153]. Occasionally, SRLs may cause local skin irritation, erythema, and pain at the injection site [4]. Discontinuation of SRLs due to side effects is rare, primarily occuring in relation to

gastrointestinal complaints [46, 153]. Cholelithiasis is one of the most serious complications associated witn SRLs; it is usually asymptomatic and may occur even after SRLs withdrawal [153]. Incident gallstones, without major complications, were observed in 10–22% of cases in the studies leading to market authorisation of SRLs for treating neuroendocrine tumours [154–157]. In studies involving patients with acromegaly treated with SRLs, the reported incidence of cholelithiasis has been higher (42%–62%), although symptomatic disease requiring cholecystectomy is not common [158, 159]. Biliary stone disease is a frequent side effect of SRLs; however, given the infrequent occurrence of symptoms and/or related complications, only patients who have signs and symptoms of cholelithiasis should be evaluated by ultrasound [4].

The effects of SRLs on glucose tolerance and inducing hyperglycaemia-related events have yielded discordant findings in the literature (reviewed in [153]). However, the overall impact of SRLs on glucose metabolism appears to be beneficial, albeit modest and transient, except for pasireotide LAR, which is associated with significant hyperglycaemia and diabetes. This can be explained by the inhibitory effects of SRLs on insulin and glucagon, as well as GH secretion [4]. The greater risk of hyperglycaemia and diabetes with pasireotide LAR (e.g., occurring in 57% of patients) likely stems from impaired insulin and incretin secretion, with a minor effect on glucagon production, as previously mentioned, and the degree of hyperglycaemia is largely dependent on glycaemic control at baseline [62, 120, 123]. Patients being considered for treatment with pasireotide LAR should be carefully monitored for glycaemic adverse effects, and this drug should preferably be used in patients with normal glucose tolerance. Glucose levels should be monitored weekly for the first 3 months of treatment, as well as in the first 4–6 weeks after any dose increase. Ongoing monitoring of glucose status (e.g., glucose, HbA1C) should continue throughout treatment, as clinically indicated [79].

Other uncommon side effects of SRLs include asthenia, headache, dizziness, loss of appetite, constipation, pruritus, increased serum bilirubin, and decreased libido [160]. Additionally, SRLs can decrease TSH secretion leading to secondary hypothyroidism; thus, thyroid function tests should be carefully interpreted.

Consensus Statements

- This consensus panel recommends that in patients with acromegaly who are treated with SRLs, only those who exhibit clinical signs and symptoms of gallbladder disease should be monitored with ultrasound.
- This consensus panel recommends close monitoring of glucose status (e.g., glucose, HbA1C) for all patients receiving SRLs, especially in those under treatment with pasireotide LAR.

How to Adjust the Dosage of GHRA?

Pegvisomant is administered subcutaneously in daily doses of 10, 15, or 20 mg (daily dosing ranging from 10 to 40 mg) and has proven to be effective in clinical and biochemical control of acromegaly [161]. Given its long half-life (i.e., up to 100 h after subcutaneous administration), alternative dosing regimens, such as less frequent administration than daily, have also been shown to be equally effective and should be considered on an individual basis [162, 163]. So, alternate-day administration, once or twice weekly, or even monthly dosing, especially when pegvisomant is combined with SRLs, may be viable alternative therapeutic regimens, depending on several factors, such as the magnitude of IGF-1 elevation, planned monotherapy or combined therapy, prior irradiation, and patient's specific conditions. It should be emphasised that a heterogenous response in terms of efficacy (i.e., normalisation of IGF-1) has been reported in a subset of patients treated with pegvisomant [131]. This apparent lower-than-expected efficacy, observed especially in retrospective studies compared to clinical trials, may be explained by various factors, such as patient poor compliance to daily injections, inadequate dose titration, selection bias in clinical trials, technical issues with IGF-1 assay, and finally a true "biochemical resistance" to pegvisomant cannot be ruled out yet [131].

As a GHRA, pegvisomant has a shorter half-life than injectable SRLs, and IGF-1 should be monitored every 1–3 months after treatment initiation or dose adjustments to determine the optimal dosing regimen. After achieving stability, monitoring can be spaced out to every 6–12 months [53]. Most commercial GH assays (except IDS-iSYS hGH immunoassay) cannot differentiate between endogneous human GH and pegvisomant, resulting in the measurement of pegvisomant levels as well. In addition, to this mimicking effect of pegvisomant in laboratory tests, the rapid normalisation of IGF-1 levels induces an increase in endogenous GH concentrations due to the feedback loop between IGF-1 and GH secretion via the hypothalamus and pituitary, making the evaluation of GH during pegvisomant treatment uninformative, and it should not be performed. [164]. Thereby, serum IGF-1 is the sole reliable biomarker for evaluating pegvisomant efficacy.

The dose requirements of pegvisomant to achieve disease control appear to vary among specific groups of patients, and the response to pegvisomant was shown to be influenced by patient's age, BMI, and baseline IGF-1 levels [165, 166]. The starting dose of pegvisomant should be higher, with more rapid dose titration, in younger patients, in obese subjects, and in those with a more severe endocrine profile [165, 166]. Similarly, patients with diabetes appear to require higher doses and faster up-titration of pegvisomant to reduce and normalise IGF-1 levels compared to patients without diabetes [134, 167, 168]. Despite this, patients treated with pegvisomant may show improvement in glucose tolerance; therefore, glucose levels should be monitored more frequently during the first months of treatment, and antidiabetic drugs adjusted as needed [137, 169]. Additionally, it has also been showed that IGF-1 normalisation requires lower doses in male than in female patients, and in those who have undergone irradiation compared to non-irradiated patients [170].

When combined with SRLs, the required dose of pegvisomant may be lower than when used in monotherapy [171, 172]. During combined treatment, pegvisomant levels were shown to be increased because, while acting as competitive blocker, it has fewer endogenous GH molecules to compete with and a lower number of GH receptors to block [173]. When used as a monotherapy, a weekly mean dose of pegvisomant of 130 mg was needed to control IGF-1 in >90% of patients [137]. However, when combined with SRLs, the weekly necessary mean dose of pegvisomant to normalise IGF-1 dropped to 77–80 mg [137, 174]. A low-dose SRL regimen plus weekly pegvisomant (40–160 mg, provided as once or twice weekly injections) is a cost-effective option for patients requiring combination therapy [175, 176].

Consensus Statements

- This consensus panel recommends an individualised therapeutic approach for the pegvisomant regimen (e.g., daily or for longer periods), depending on the patient's response to previous treatments, as well as clinical and biochemical parameters.
- This consensus panel recommends against measuring GH during treatment with pegvisomant.
- This consensus panel recommends that higher doses of pegvisomant should be considered in specific groups, such as younger patients, and those with diabetes and obesity.

What Are the Adverse Effects of GHRA?

The long-term safety of pegvisomant was evaluated in several studies, demonstrating a good safety profile with few serious adverse events reported [136, 137, 161, 177]. The most frequent adverse events include injection site reactions, liver dysfunction, and changes in tumour size (shown in Table 2) [161].

Injection site reactions are typically mild and transient, presenting as localised erythema and soreness, and do not require treatment or drug discontinuation [136, 137]. Although rare (i.e., ~2%), lipohypertrophy at the injection site may occur, but it usually resolves with a rotation of the injection site and does not require discontinuation of pegvisomant [161].

A small proportion of patients (i.e., 5–8%) treated with pegvisomant develop liver dysfunction; however, it is generally mild and transient, with drug-induced hepatitis being rarely reported [131, 178]. Transaminase elevations do not appear to be dose-related and generally occur during the first year of treatment [179]. The incidence of liver dysfunction is higher in certain groups (i.e., ~14%), such as patients with prior liver impairment, diabetes, concomitant use of hepatotoxic drugs, or combined treatment with SRLs [174]. Therefore, ongoing monitoring of liver function is advised (e.g., liver function tests should be performed every 1–2 months for the first 6 months and thereafter every 6 months), and discontinuation of pegvisomant should be considered if transaminases exceed >2-fold the upper limit of normal [4, 180].

Pegvisomant does not have anti-proliferative effects on pituitary tumours and interrupts the negative feedback loop on GH secretion, raising theoretical concerns that somatotroph tumours may enlarge in patients receiving this drug [181]. Some studies have reported an increase in tumour size in patients treated with GHRA; however, there is no clear evidence supporting this association [4, 131]. A meta-analysis of observational longitudinal studies, involving 14 studies, reported tumour growth in ~7% of cases [182]. Both the German Pegvisomant Observational Study (~3–6%) and the ACROSTUDY (~7%) found similar growth rates based on local MRI scans; however, these rates decreased to ~3% in both studies after centralised image re-evaluation [161, 183]. Therefore, careful serial evaluation of MRI imaging by expert neuroradiologists is advised to establish tumour progression. Tumour growth appears to be more frequent during the first year of treatment with pegvisomant, which may reflect the natural history of the disease and/or the effect of withdrawal of prior SRL treatment [137, 183–185]. Patients with higher tumour expression of GH

and insulin receptors appear to be associated with a greater risk of tumour progression [183, 186]. Overall, pegvisomant is a safe second-line option for patients with active acromegaly, provided that no large tumour remnants are in contact with the optic chiasm or vital structures [4].

Consensus Statements

- This consensus panel recommends that patients receiving treatment with pegvisomant should undergo regular assessment of the liver enzymes, e.g., every 1–2 months for the first 6 months and thereafter every 6 months.
- This consensus panel recommends that pituitary MRI should be performed at 6 and 12 months after starting pegvisomant, and if tumour size is stable, MRI surveillance can be done on an annual basis, preferably by the same neuroradiologist with expertise in pituitary tumours.

When Should Combination Therapy Be Considered?

Combination therapy for acromegaly is increasingly being used and should be considered for patients who do not respond adequately to monotherapy [151]. Both cabergoline or pegvisomant can be added to SRLs, and the association of cabergoline with pegvisomant is also possible [4, 151]. The goal of combined medical therapy is to increase the treatment efficacy, reduce the adverse effects associated with monotherapy in high doses, and decrease the frequency of administrations and the dosage of a single drug [187].

The combination of first-generation SRLs with a GHRA is the most frequently used treatment regimen. The combination of pegvisomant 40–160 mg/week with SRLs resulted in normalisation of IGF-1 levels in 95–100% of patients [174, 188–192]. The combination of cabergoline with SRLs may be useful in patients with mild uncontrolled disease, achieving IGF-1 normalisation in 42–56% of patients with this association [190]. However, better outcomes were reported in patients with lower basal IGF-1 levels [4, 46]. For patients intolerant to SRLs, the combination of cabergoline and pegvisomant can be useful, particularly in patients with mild elevations of IGF-1 [193]. In a randomised trial including 52 patients treated with low-dose monthly octreotide LAR (10 mg) or lanreotide Autogel (60 mg) combined with weekly pegvisomant (40–160 mg/week) showed that the biochemical control rate was achieved in 96% of previously controlled and uncontrolled patients, with only 30% of cases requiring up-titration of pegvisomant [176]. This combination (i.e., low-dose monthly SRLs combined with weekly pegvisomant) had lower cost compared to high-dose monthly SRLs combined with weekly pegvisomant or low-dose monthly SRLs combined with daily pegvisomant [176]. A combination of octreotide LAR or lanreotide Autogel with pegvisomant may be considered for patients requiring control of the residual tumour with impaired glucose tolerance or diabetes [79].

The combination of pasireotide LAR with pegvisomant was also investigated in the PAPE study [194]. This study included 61 patients well controlled on octreotide/lanreotide plus pegvisomant. Patients were switched to pasireotide LAR with or without pegvisomant, depending if IGF-1 levels were or not >1.2 times the upper limit of normal, respectively. The primary outcome was treatment efficacy, and the secondary outcome was pegvisomant dose reduction compared to baseline. IGF-1 levels remained normal in ~93% of patients who transitioned to pasireotide LAR monotherapy. In patients with IGF-1 levels >1.2 upper limit of normal, ~67% normalised IGF-1 levels (i.e., IGF-1 ≤1.2 upper limit of normal) when treated with combination therapy of pasireotide LAR and pegvisomant. Furthermore, the pegvisomant dose was reduced by ~66% in these patients. However, the prevalence of diabetes increased from ~33%, at baseline to ~69% after 24 weeks in patients treated with pasireotide LAR [194]. Only 25% of patients were receiving antidiabetic medications at baseline, though after 24 weeks of pasireotide LAR 69% of patients required at least one antidiabetic medication [194]. No significant difference was observed in HbA1c levels between patients treated with pasireotide LAR monotherapy versus combination therapy with pegvisomant, suggesting that pegvisomant did not mitigate the pasireotide-induced hyperglycaemia [195]. The combination of pasireotide LAR and pegvisomant may be an option for patients with acromegaly and tumour growth when radiotherapy is contraindicated, not available, or while awaiting irradiation-induced tumour shrinkage [8].

Consensus Statements

- This consensus panel recommends that combination therapy should be used when monotherapy is insufficient to control acromegaly.
- This consensus panel suggests that low-dose octreotide LAR or lanreotide Autogel plus weekly pegvisomant may be a first option for patients with acromegaly requiring combination therapy. However, the regimen of the combination therapy should be individualised.

When Should Radiotherapy Be Considered?

The use of radiotherapy has decreased over the years due to advances in surgical techniques and medical treatments. However, it may still be considered a third-line therapy, following surgery and medical therapy, particularly when surgery is unsuccessful and there is resistance or intolerance to medical therapy [8, 196]. The benefits of radiotherapy include tumour volume control and decreased hormonal secretion; however, these advantages are hindered by the long latency of therapeutic effects and the high risk of long-term adverse events, such as hypopituitarism, radiation-induced optic neuropathy, cranial nerve deficit, brain necrosis, and secondary brain tumours [197, 198].

Conventional radiotherapy is administered by a linear accelerator (4–8 MeV) with a total dose of 40–45 Gy. It should be fractionated in at least 20 sessions [198]. This approach results in long-term tumour growth control in 80–100% of cases, with 60–80% achieving normalisation of GH/IGF-1 levels [8, 196].

The development of stereotactic methods has improved the precision of tumour targeting, while minimising damage to adjacent tissues. These methods include stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) [198, 199]. SRS, which includes Gamma Knife, CyberKnife, and linear accelerator, is potentially more effective than conventional radiotherapy in inducing biochemical remission [198, 200–203]. SRS is suggested for tumours of small to moderate size (<2.5–3 cm) [4]. If the tumour is located close to the optic apparatus, SRS can still be applied but the maximum dose delivered to the optic apparatus should be maintained below 8–10 Gy [199]. In clinical practice, SRS at doses of 16–25 Gy are a convenient approach for patients with relatively small tumours that are not in proximity (i.e., at least 2–4 mm) to the optic chiasm. For tumours with >2.5–3 cm and/or involving the optic chiasm, FSRT should be preferred [204, 205]. Long-term follow-up data show that around half of the patients with acromegaly treated with SRS or FSRT achieve and maintain biochemical control [96, 206]. However, up to one-third of patients with normal pituitary function before irradiation will develop hypopituitarism, underscoring the need for monitoring the pituitary function after radiotherapy. More studies are needed to evaluate the extent of long-term hypopituitarism and brain-sparing effects of these treatments [197, 207].

Consensus Statements

- This consensus panel recommends that, following surgery, if medical therapy fails or cannot be used, radiation therapy should be considered as a therapeutic option. SRS should be the preferred method, except in cases of large tumours and/or tumours affecting the visual pathways. In these cases, FSRT may be the preferred option. If FSRT is not available, conventional radiotherapy can be used.
- This consensus panel recommends that GH and IGF-1 levels should be measured at least annually to evaluate radiation efficacy. For the evaluation of hypopituitarism and other delayed radiation effects, clinical surveillance and annual hormonal testing are recommended.

How to Manage Women with Acromegaly during Preconception, Pregnancy, and Postpartum?

Acromegaly has been associated with decreased fertility through different mechanisms, such as hypopituitarism, hyperprolactinaemia due to stalk compression or related to a mixed GH and PRL-secreting tumour, and the direct effects of excessive levels of GH and IGF-1 in the hypothalamic-pituitary-gonadal axis [208]. However, some affected women can conceive, particularly those with a preserved hypothalamic-pituitary-gonadal axis and whose disease is controlled prior to pregnancy, as well as those who underwent assisted reproductive techniques [208].

Pregnancy appears to have a transient "therapeutic effect" on the clinical and biochemical activity of acromegaly, in part due to the increased oestrogen levels acting as GH antagonists in the liver, leading to a state of relative hepatic GH resistance [209]. This results in decreased maternal levels of serum IGF-1, particularly during the first trimester, although some individual variability is seen on IGF-1 levels [210]. During pregnancy, the placenta secretes a variant of GH which cross-reacts with pituitary-derived GH in most immunoassays [211]. Therefore, measuring serum GH and IGF-1 during pregnancy does not provide useful or reliable information, and it is not recommended [4, 212].

In fact, pregnancy in women with acromegaly is frequently associated with disease control and is generally safe in terms of foetal and maternal outcomes [213]. Most pregnant patients with acromegaly do not have an increase in tumour size during gestation (i.e., the overall frequency of tumour growth is estimated at 9%); nonetheless, clinical follow-up during pregnancy is recommended, and visual field testing should be performed in patients with macroadenomas, particularly those that extend superiorly to the optic chiasm [4, 213, 214]. In addition, non-contrast MRI should be considered in patients exhibiting visual changes [211].

The metabolic complications associated with the effects of GH on the mother, such as gestational diabetes or worsening of previous diabetes and hypertensive gestational disorders, appear to be only modestly increased in pregnant women with acromegaly (i.e., overall frequency described of 9% and 6%, respectively). Therefore, these conditions do not commonly adversely affect foetal growth or maternal outcomes in women with acromegaly [213–215]. Furthemore, the overall frequency of premature labour, spontaneous miscarriage, small for gestational age, and congenital malformations is also very low [213].

Usually, there is no need to use medications to control GH hypersecretion or tumour size in patients with acromegaly during pregnancy, and pharmacological treatment can safely be interrupted for most patients [214, 216]. Drug therapy is generally recommended only for tumour growth control and moderate to severe resistant headaches. An exception is made for women with aggressive somatotroph tumours who manage to conceive, as they require close monitoring and individualised treatment approach [211].

There are limited data documenting safety of medical therapy during pregnancy, particularly regarding potential adverse effects on foetal development. Therefore, their liberal use is not recommended, and prompt discontinuation upon confirmation of pregnancy is advised [211]. Nevertheless, cumulative data suggest that there are no major adverse consequences/teratogenicity of first-generation SRLs administered during gestation for either the mother and the foetus, even during the first trimester, when embryogenesis occurs [209]. No foetal malformations have been reported in children born to women who were treated with long-acting SRLs at the time of conception [217, 218]. Octreotide is known to bind to somatostatin receptors in the placenta and cross the placenta, potentially affecting foetal tissues, particularly the brain [219]. The experience with pegvisomant is significantly more limited, and its safety profile remains unestablished. Nonetheless, data from several women exposed to pegvisomant at some point during pregnancy appear to suggest no adverse consequences on pregnancy outcomes [212, 218, 220]. Long-acting formulations of SRLs and pegvisomant should be avoided approximately 2 months before attempting to conceive and during pregnancy [4, 216]. During the conception period, if necessary, subcutaneous injections of short-acting octreotide may be preferable until pregnancy is confirmed [4]. However, some patients may choose to continue long-acting SRLs until the confirmation of pregnancy, which may also be acceptable given the safety data thus far available [212]. If the tumour increases in size, DAs, particularly cabergoline, can be used with demonstrated safety for the developing foetus. In cases where there is no response to medical therapy, TSS may be performed during the second trimester if necessary [221].

Although the paucity of data limits evidence-based recommendations for preconception counselling and pregnancy surveillance, it is highly recommended to control tumour size and hormonal activity before pregnancy to ensure better outcomes, and surgical intervention should be attempted before pregnancy, when indicated, particularly in women with a recent diagnosis of acromegaly seeking fertility [212]. This underscores the need for prenatal counselling and a comprehensive care with frequent visits during pregnancy for all women with acromegaly who become pregnant [213].

After the delivery, a rebound in acromegaly activity is often observed; thus, restarting the medical treatment precociously may be necessary. However, this decision needs to be balanced between the activity of the disease after delivery and the desire of the women to breastfeed [214, 222]. In principle, breastfeeding is possible and not contraindicated, but medical therapy (particularly SRLs and pegvisomant) should be avoided in nursing mothers [212].

Consensus Statements

- This consensus panel recommends against measuring serum GH and IGF-1 levels during pregnancy.
- This consensus panel recommends that women with a recent diagnosis of acromegaly seeking pregnancy should have surgery as a first-line therapy.
- This consensus panel recommends that SRLs and pegvisomant should be discontinued 2 months before attempting to conceive or as soon as pregnancy is confirmed.
- This consensus panel suggests that in exceptional circumstances, e.g., an expanding mass and severe headaches, the maintenance or reintroduction of medical therapy may be considered.
- This consensus panel suggests that breastfeeding is feasible and should be carried out without exposure to SRLs or pegvisomant, while taking into account the different clinical circumstances, including disease activity.

Conclusions

Acromegaly is a rare, chronic, slowly progressive debilitating disorder caused by the hypersecretion of GH. If left untreated, it is associated with increased morbidity and mortality. The diagnosis is established by demonstrating elevated IGF-1 levels and/or autonomous GH

hypersecretion and detection of a pituitary tumour. Patients should be managed by an experienced multidisciplinary team, including endocrinologists, neurosurgeons, neuroradiologists, radiotherapists, and pathologists. Pituitary surgery is the first-line therapy for most patients, although primary medical therapy may be considered in selected cases. In patients where remission is not achieved after first surgery, reintervention or medical therapy should be considered. SRLs, DAs, and GHRA are pharmacological options that should be tailored to the individual patient and clinical scenario. Radiotherapy is, generally, the third-line of therapy and should be considered in the more challenging cases with active disease. New pharmacological agents are needed to improve disease control and patient's quality of life.

Conflict of Interest Statement

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Author Contributions

L.M.C., P.M., C.A., and D.C. conceptualised and coordinated the development of the consensus. D.C., C.A., D.D., I.M., J.P., L.C., L.M.C., P.M., S.A., T.M., T.P., and V.B.S. summarised recent available literature leading to the consensus statements. A.G., C.A., D.C., F.F., I.M., J.S.D., J.P., L.G., L.M.C., M.J.B., M.O., O.M., P.M., S.A., T.M., T.P., and V.B.S. participated in the Delphi process. L.M.C., P.M., C.A., and D.C. wrote the full draft manuscript from the author's contributions. L.M.C., P.M., M.T.P., A.A., R.A., S.A., M.J.B., M.B.C., L.C., D.B.D., J.S.D., F.F., L.G., I.M., O.M., T.M., M.J.O., I.P., J.P., A.P.S., V.B.S., I.T., C.A., and D.C. critically revised the initial draft, edited, and approved the final manuscript.

References

1 Capatina C, Wass JA. 60 years of neuroendocrinology: acromegaly. J Endocrinol. 2015;226(2):T141–60. https://doi.org/10.1530/JOE-15-0109
2 de Herder WW. The history of acromegaly. Neuroendocrinology. 2016;103(1):7–17. https://doi.org/10.1159/000371808
3 Melmed S. Pathogenesis of pituitary tumors. Nat Rev Endocrinol. 2011;7(5):257–66. https://doi.org/10.1038/nrendo.2011.40
4 Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51. https://doi.org/10.1210/jc.2014-2700
5 Lavrentaki A, Paluzzi A, Wass JA, Karavitaki N. Epidemiology of acromegaly: review of population studies. Pituitary. 2017;20(1):4–9. https://doi.org/10.1007/s11102-016-0754-x
6 Crisafulli S, Luxi N, Sultana J, Fontana A, Spagnolo F, Giuffrida G, et al. Global epidemiology of acromegaly: a systematic review and meta-analysis. Eur J Endocrinol. 2021;185(2):251–63. https://doi.org/10.1530/EJE-21-0216
7 Park KH, Lee EJ, Seo GH, Ku CR. Risk for acromegaly-related comorbidities by sex in Korean acromegaly. J Clin Endocrinol Metab. 2020;105(4):dgz317. https://doi.org/10.1210/clinem/dgz317
8 Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al. Multidisciplinary management of acromegaly: a consensus. Rev Endocr Metab Disord. 2020;21(4):667–78. https://doi.org/10.1007/s11154-020-09588-z
9 Bianchi A, Chiloiro S, Giampietro A, Gaudino S, Calandrelli R, Mazzarella C, et al. Multidisciplinary management of difficult/aggressive growth-hormone pituitary neuro-endocrine tumors. Front Endocrinol. 2023;14:1123267. https://doi.org/10.3389/fendo.2023.1123267
10 Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: how to decide its appropriateness. World J Methodol. 2021;11(4):116–29. https://doi.org/10.5662/wjm.v11.i4.116
11 Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021;24(1):1–13. https://doi.org/10.1007/s11102-020-01091-7
12 Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, et al. Acromegaly. Nat Rev Dis Primers. 2019;5(1):20. https://doi.org/10.1038/s41572-019-0071-6
13 Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol. 2022;10(11):804–26. https://doi.org/10.1016/S2213-8587(22)00244-3
14 Rostomyan L, Daly AF, Petrossians P, Nachev E, Lila AR, Lecoq AL, et al. Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. Endocr Relat Cancer. 2015;22(5):745–57. https://doi.org/10.1530/ERC-15-0320
15 Ben-Shlomo A, Melmed S. Skin manifestations in acromegaly. Clin Dermatol. 2006;24(4):256–9. https://doi.org/10.1016/j.clindermatol.2006.04.011
16 Roque J, Marques P. Acromegaly-related cutis verticis gyrata. Growth Horm IGF Res. 2022;66:101497. https://doi.org/10.1016/j.ghir.2022.101497
17 Fleseriu M, Barkan A, Del Pilar Schneider M, Darhi Y, de Pierrefeu A, Ribeiro-Oliveira A Jr, et al. Prevalence of comorbidities and concomitant medication use in acromegaly: analysis of real-world data from the United States. Pituitary. 2022;25(2):296–307. https://doi.org/10.1007/s11102-021-01198-5
18 Marques P, Korbonits M. Pseudoacromegaly. Front Neuroendocrinol. 2019;52:113–43. https://doi.org/10.1016/j.yfrne.2018.11.001
19 Marques P, Korbonits M. Approach to the patient with pseudoacromegaly. J Clin Endocrinol Metab. 2022;107(6):1767–88. https://doi.org/10.1210/clinem/dgab789

20 Marques P, Korbonits M. Genetic aspects of pituitary adenomas. Endocrinol Metab Clin North Am. 2017;46(2):335–74. https://doi.org/10.1016/j.ecl.2017.01.004
21 Garby L, Caron P, Claustrat F, Chanson P, Tabarin A, Rohmer V, et al. Clinical characteristics and outcome of acromegaly induced by ectopic secretion of growth hormone-releasing hormone (GHRH): a French nationwide series of 21 cases. J Clin Endocrinol Metab. 2012;97(6):2093–104. https://doi.org/10.1210/jc.2011-2930
22 Boguslawska A, Korbonits M. Genetics of acromegaly and gigantism. J Clin Med. 2021;10(7):1377. https://doi.org/10.3390/jcm10071377
23 Gadelha MR, Kasuki L, Korbonits M. The genetic background of acromegaly. Pituitary. 2017;20(1):10–21. https://doi.org/10.1007/s11102-017-0789-7
24 Daly AF, Tichomirowa MA, Petrossians P, Heliovaara E, Jaffrain-Rea ML, Barlier A, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. J Clin Endocrinol Metab. 2010;95(11):E373–83. https://doi.org/10.1210/jc.2009-2556
25 Marques P, Caimari F, Hernandez-Ramirez LC, Collier D, Iacovazzo D, Ronaldson A, et al. Significant benefits of AIP testing and clinical screening in familial isolated and young-onset pituitary tumors. J Clin Endocrinol Metab. 2020;105(6):e2247–60. https://doi.org/10.1210/clinem/dgaa040
26 Tichomirowa MA, Barlier A, Daly AF, Jaffrain-Rea ML, Ronchi C, Yaneva M, et al. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. Eur J Endocrinol. 2011;165(4):509–15. https://doi.org/10.1530/EJE-11-0304
27 Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocr Rev. 2013;34(2):239–77. https://doi.org/10.1210/er.2012-1013
28 Cazabat L, Bouligand J, Salenave S, Bernier M, Gaillard S, Parker F, et al. Germline AIP mutations in apparently sporadic pituitary adenomas: prevalence in a prospective single-center cohort of 443 patients. J Clin Endocrinol Metab. 2012;97(4):E663–70. https://doi.org/10.1210/jc.2011-2291
29 Ramirez-Renteria C, Hernandez-Ramirez LC, Portocarrero-Ortiz L, Vargas G, Melgar V, Espinosa E, et al. AIP mutations in young patients with acromegaly and the Tampico Giant: the Mexican experience. Endocrine. 2016;53(2):402–11. https://doi.org/10.1007/s12020-016-0930-9
30 De Sousa SMC, McCabe MJ, Wu K, Roscioli T, Gayevskiy V, Brook K, et al. Germline variants in familial pituitary tumour syndrome genes are common in young patients and families with additional endocrine tumours. Eur J Endocrinol. 2017;176(5):635–44. https://doi.org/10.1530/EJE-16-0944
31 Caimari F, Hernandez-Ramirez LC, Dang MN, Gabrovska P, Iacovazzo D, Stals K, et al. Risk category system to identify pituitary adenoma patients with AIP mutations. J Med Genet. 2018;55(4):254–60. https://doi.org/10.1136/jmedgenet-2017-104957
32 Gaspar LM, Goncalves CI, Saraiva C, Cortez L, Amaral C, Nobre E, et al. Low frequency of AIP mutations in patients with young-onset sporadic pituitary macroadenomas. J Endocrinol Invest. 2023;46(11):2299–307. https://doi.org/10.1007/s40618-023-02083-7
33 Beckers A, Lodish MB, Trivellin G, Rostomyan L, Lee M, Faucz FR, et al. X-linked acrogigantism syndrome: clinical profile and therapeutic responses. Endocr Relat Cancer. 2015;22(3):353–67. https://doi.org/10.1530/ERC-15-0038
34 Armeni E, Grossman A. The spectrum of familial pituitary neuroendocrine tumors. Endocr Pathol. 2023;34(1):57–78. https://doi.org/10.1007/s12022-022-09742-0
35 Iacovazzo D, Korbonits M. Gigantism: X-linked acrogigantism and GPR101 mutations. Growth Horm IGF Res. 2016;30-31:64–9. https://doi.org/10.1016/j.ghir.2016.09.007
36 Giusti F, Cianferotti L, Boaretto F, Cetani F, Cioppi F, Colao A, et al. Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. Endocrine. 2017;58(2):349–59. https://doi.org/10.1007/s12020-017-1234-4
37 Sakurai A, Suzuki S, Kosugi S, Okamoto T, Uchino S, Miya A, et al. Multiple endocrine neoplasia type 1 in Japan: establishment and analysis of a multicentre database. Clin Endocrinol. 2012;76(4):533–9. https://doi.org/10.1111/j.1365-2265.2011.04227.x
38 Verges B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, et al. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. J Clin Endocrinol Metab. 2002;87(2):457–65. https://doi.org/10.1210/jcem.87.2.8145
39 Wu Y, Gao L, Guo X, Wang Z, Lian W, Deng K, et al. Pituitary adenomas in patients with multiple endocrine neoplasia type 1: a single-center experience in China. Pituitary. 2019;22(2):113–23. https://doi.org/10.1007/s11102-019-00939-x
40 Magri F, Villa C, Locatelli D, Scagnelli P, Lagonigro MS, Morbini P, et al. Prevalence of double pituitary adenomas in a surgical series: clinical, histological and genetic features. J Endocrinol Invest. 2010;33(5):325–31. https://doi.org/10.1007/BF03346594
41 Marques P, Barry S, Ronaldson A, Ogilvie A, Storr HL, Goadsby PJ, et al. Emergence of pituitary adenoma in a child during surveillance: clinical challenges and the family members' view in an AIP mutation-positive family. Int J Endocrinol. 2018;2018:8581626. https://doi.org/10.1155/2018/8581626
42 Trouillas J, Labat-Moleur F, Sturm N, Kujas M, Heymann MF, Figarella-Branger D, et al. Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (MEN1): a case-control study in a series of 77 patients versus 2509 non-MEN1 patients. Am J Surg Pathol. 2008;32(4):534–43. https://doi.org/10.1097/pas.0b013e31815ade45
43 Daly AF, Cano DA, Venegas-Moreno E, Petrossians P, Dios E, Castermans E, et al. AIP and MEN1 mutations and AIP immunohistochemistry in pituitary adenomas in a tertiary referral center. Endocr Connect. 2019;8(4):338–48. https://doi.org/10.1530/EC-19-0027
44 Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011. https://doi.org/10.1210/jc.2012-1230
45 Xekouki P, Brennand A, Whitelaw B, Pacak K, Stratakis CA. The 3PAs: an update on the association of pheochromocytomas, paragangliomas, and pituitary tumors. Horm Metab Res. 2019;51(7):419–36. https://doi.org/10.1055/a-0661-0341
46 Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK. American association of clinical endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update: executive summary. Endocr Pract. 2011;17(4):636–46. https://doi.org/10.4158/ep.17.4.636
47 Peixe C, Sanchez-Garcia M, Grossman AB, Korbonits M, Marques P. Biochemical discrepancies in the evaluation of the somatotroph axis: elevated GH or IGF-1 levels do not always diagnose acromegaly. Growth Horm IGF Res. 2022;64:101467. https://doi.org/10.1016/j.ghir.2022.101467
48 Frystyk J, Freda P, Clemmons DR. The current status of IGF-I assays: a 2009 update. Growth Horm IGF Res. 2010;20(1):8–18. https://doi.org/10.1016/j.ghir.2009.09.004
49 Ershadinia N, Tritos NA. Diagnosis and treatment of acromegaly: an update. Mayo Clin Proc. 2022;97(2):333–46. https://doi.org/10.1016/j.mayocp.2021.11.007
50 Schilbach K, Strasburger CJ, Bidlingmaier M. Biochemical investigations in diagnosis and follow up of acromegaly. Pituitary. 2017;20(1):33–45. https://doi.org/10.1007/s11102-017-0792-z
51 Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ. Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. Clin Endocrinol. 2007;67(1):65–70. https://doi.org/10.1111/j.1365-2265.2007.02836.x

52 Kannan S, Kennedy L. Diagnosis of acromegaly: state of the art. Expert Opin Med Diagn. 2013;7(5):443–53. https://doi.org/10.1517/17530059.2013.820181
53 Giustina A, Biermasz N, Casanueva FF, Fleseriu M, Mortini P, Strasburger C, et al. Consensus on criteria for acromegaly diagnosis and remission. Pituitary. 2024;27(1):7–22. https://doi.org/10.1007/s11102-023-01360-1
54 Schilbach K, Gar C, Lechner A, Nicolay SS, Schwerdt L, Haenelt M, et al. Determinants of the growth hormone nadir during oral glucose tolerance test in adults. Eur J Endocrinol. 2019;181(1):55–67. https://doi.org/10.1530/EJE-19-0139
55 Chanson P, Arnoux A, Mavromati M, Brailly-Tabard S, Massart C, Young J, et al. Reference values for IGF-I serum concentrations: comparison of six immunoassays. J Clin Endocrinol Metab. 2016;101(9):3450–8. https://doi.org/10.1210/jc.2016-1257
56 Hage M, Janot C, Salenave S, Chanson P, Kamenicky P. Management of endocrine disease: etiology and outcome of acromegaly in patients with a paradoxical GH response to glucose. Eur J Endocrinol. 2021;184(6):R261–8. https://doi.org/10.1530/EJE-20-1448
57 Freda PU. Monitoring of acromegaly: what should be performed when GH and IGF-1 levels are discrepant? Clin Endocrinol. 2009;71(2):166–70. https://doi.org/10.1111/j.1365-2265.2009.03556.x
58 Kanakis GA, Chrisoulidou A, Bargiota A, Efstathiadou ZA, Papanastasiou L, Theodoropoulou A, et al. The ongoing challenge of discrepant growth hormone and insulin-like growth factor I results in the evaluation of treated acromegalic patients: a systematic review and meta-analysis. Clin Endocrinol. 2016;85(5):681–8. https://doi.org/10.1111/cen.13129
59 Coopmans EC, El-Sayed N, Frystyk J, Magnusson NE, Jorgensen JOL, van der Lely AJ, et al. Soluble Klotho: a possible predictor of quality of life in acromegaly patients. Endocrine. 2020;69(1):165–74. https://doi.org/10.1007/s12020-020-02306-4
60 Schweizer J, Schilbach K, Haenelt M, Giannetti AV, Bizzi MF, Soares BS, et al. Soluble alpha klotho in acromegaly: comparison with traditional markers of disease activity. J Clin Endocrinol Metab. 2021;106(8):e2887–99. https://doi.org/10.1210/clinem/dgab257
61 Pinzariu O, Georgescu B, Georgescu CE. Metabolomics-A promising approach to pituitary adenomas. Front Endocrinol. 2018;9:814. https://doi.org/10.3389/fendo.2018.00814
62 Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. J Clin Endocrinol Metab. 2020;105(4):dgz096. https://doi.org/10.1210/clinem/dgz096
63 Shah R, Licata A, Oyesiku NM, Ioachimescu AG. Acromegaly as a cause of 1,25-dihydroxyvitamin D-dependent hypercalcemia: case reports and review of the literature. Pituitary. 2012;15(Suppl 1):S17–22. https://doi.org/10.1007/s11102-010-0286-8
64 Famini P, Maya MM, Melmed S. Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2598 patients. J Clin Endocrinol Metab. 2011;96(6):1633–41. https://doi.org/10.1210/jc.2011-0168
65 Potorac I, Petrossians P, Daly AF, Alexopoulou O, Borot S, Sahnoun-Fathallah M, et al. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. Endocr Relat Cancer. 2016;23(11):871–81. https://doi.org/10.1530/ERC-16-0356
66 Puig-Domingo M, Resmini E, Gomez-Anson B, Nicolau J, Mora M, Palomera E, et al. Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. J Clin Endocrinol Metab. 2010;95(11):4973–8. https://doi.org/10.1210/jc.2010-0573
67 Gillett D, MacFarlane J, Bashari W, Crawford R, Harper I, Mendichovszky IA, et al. Molecular imaging of pituitary tumors. Semin Nucl Med. 2023;53(4):530–8. https://doi.org/10.1053/j.semnuclmed.2023.02.005
68 Rodriguez-Barcelo S, Gutierrez-Cardo A, Dominguez-Paez M, Medina-Imbroda J, Romero-Moreno L, Arraez-Sanchez M. Clinical usefulness of coregistered 11C-methionine positron emission tomography/3-T magnetic resonance imaging at the follow-up of acromegaly. World Neurosurg. 2014;82(3–4):468–73. https://doi.org/10.1016/j.wneu.2013.11.011
69 Veldhuijzen van Zanten SEM, Neggers S, Valkema R, Verburg FA. Positive [(18)F] fluoroethyltyrosine PET/MRI in suspected recurrence of growth hormone-producing pituitary adenoma in a paediatric patient. Eur J Nucl Med Mol Imaging. 2021;49(1):410–1. https://doi.org/10.1007/s00259-021-05458-1
70 Borson-Chazot F, Garby L, Raverot G, Claustrat F, Raverot V, Sassolas G, et al. Acromegaly induced by ectopic secretion of GHRH: a review 30 years after GHRH discovery. Ann Endocrinol. 2012;73(6):497–502. https://doi.org/10.1016/j.ando.2012.09.004
71 Potorac I, Bonneville JF, Daly AF, de Herder W, Fainstein-Day P, Chanson P, et al. Pituitary MRI features in acromegaly resulting from ectopic GHRH secretion from a neuroendocrine tumor: analysis of 30 cases. J Clin Endocrinol Metab. 2022;107(8):e3313–20. https://doi.org/10.1210/clinem/dgac274
72 Abreu A, Tovar AP, Castellanos R, Valenzuela A, Giraldo CM, Pinedo AC, et al. Challenges in the diagnosis and management of acromegaly: a focus on comorbidities. Pituitary. 2016;19(4):448–57. https://doi.org/10.1007/s11102-016-0725-2
73 Puder JJ, Nilavar S, Post KD, Freda PU. Relationship between disease-related morbidity and biochemical markers of activity in patients with acromegaly. J Clin Endocrinol Metab. 2005;90(4):1972–8. https://doi.org/10.1210/jc.2004-2009
74 Barkan AL. Biochemical markers of acromegaly: GH vs. IGF-I. Growth Horm IGF Res. 2004;14(Suppl A):S97–100. https://doi.org/10.1016/j.ghir.2004.03.022
75 Feelders RA, Bidlingmaier M, Strasburger CJ, Janssen JA, Uitterlinden P, Hofland LJ, et al. Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) insulin-like growth factor I, acid-labile subunit, and growth hormone-binding protein levels. J Clin Endocrinol Metab. 2005;90(12):6480–9. https://doi.org/10.1210/jc.2005-0901
76 Apaydin T, Ozkaya HM, Keskin FE, Haliloglu OA, Karababa K, Erdem S, et al. Daily life reflections of acromegaly guidelines. J Endocrinol Invest. 2017;40(3):323–30. https://doi.org/10.1007/s40618-016-0567-9
77 Yang C, Li G, Jiang S, Bao X, Wang R. Preoperative somatostatin analogues in patients with newly-diagnosed acromegaly: a systematic review and meta-analysis of comparative studies. Sci Rep. 2019;9(1):14070. https://doi.org/10.1038/s41598-019-50639-6
78 Shin MS, Yu JH, Choi JH, Jung CH, Hwang JY, Cho YH, et al. Long-term changes in serum IGF-1 levels after successful surgical treatment of growth hormone-secreting pituitary adenoma. Neurosurgery. 2013;73(3):473–9; quiz 79. https://doi.org/10.1227/01.neu.0000431480.87160.84
79 Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552–61. https://doi.org/10.1038/s41574-018-0058-5
80 Clemmons DR, Bidlingmaier M. Interpreting growth hormone and IGF-I results using modern assays and reference ranges for the monitoring of treatment effectiveness in acromegaly. Front Endocrinol. 2023;14:1266339. https://doi.org/10.3389/fendo.2023.1266339
81 Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, et al. Criteria for the definition of pituitary tumor centers of excellence (PTCOE): a pituitary society statement. Pituitary. 2017;20(5):489–98. https://doi.org/10.1007/s11102-017-0838-2

82 Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros AL, Sosa E, et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab. 2014;99(12):4438–46. https://doi.org/10.1210/jc.2014-2670
83 Buchfelder M, Schlaffer SM, Zhao Y. The optimal surgical techniques for pituitary tumors. Best Pract Res Clin Endocrinol Metab. 2019;33(2):101299. https://doi.org/10.1016/j.beem.2019.101299
84 Bray DP, Mannam S, Rindler RS, Quillin JW, Oyesiku NM. Surgery for acromegaly: indications and goals. Front Endocrinol. 2022;13:924589. https://doi.org/10.3389/fendo.2022.924589
85 Babu H, Ortega A, Nuno M, Dehghan A, Schweitzer A, Bonert HV, et al. Long-term endocrine outcomes following endoscopic endonasal transsphenoidal surgery for acromegaly and associated prognostic factors. Neurosurgery. 2017;81(2):357–66. https://doi.org/10.1093/neuros/nyx020
86 Buchfelder M, Schlaffer SM. The surgical treatment of acromegaly. Pituitary. 2017;20(1):76–83. https://doi.org/10.1007/s11102-016-0765-7
87 Swearingen B, Barker FG 2nd, Klibanski A, Katznelson L, Biller BM, Grinspoon S, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 1998;83(10):3419–26. https://doi.org/10.1210/jcem.83.10.5222
88 Albarel F, Cuny T, Graillon T, Dufour H, Brue T, Castinetti F. Preoperative medical treatment for patients with acromegaly: yes or No? J Endocr Soc. 2022;6(9):bvac114. https://doi.org/10.1210/jendso/bvac114
89 Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009;94(5):1509–17. https://doi.org/10.1210/jc.2008-2421
90 Bevan JS. Clinical review: the antitumoral effects of somatostatin analog therapy in acromegaly. J Clin Endocrinol Metab. 2005;90(3):1856–63. https://doi.org/10.1210/jc.2004-1093
91 Caron PJ, Bevan JS, Petersenn S, Flanagan D, Tabarin A, Prevost G, et al. Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282–90. https://doi.org/10.1210/jc.2013-3318
92 Colao A, Cappabianca P, Caron P, De Menis E, Farrall AJ, Gadelha MR, et al. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. Clin Endocrinol. 2009;70(5):757–68. https://doi.org/10.1111/j.1365-2265.2008.03441.x
93 Colao A, Auriemma RS, Galdiero M, Lombardi G, Pivonello R. Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, tumor shrinkage, and cardiovascular disease: a prospective study. J Clin Endocrinol Metab. 2009;94(10):3746–56. https://doi.org/10.1210/jc.2009-0941
94 Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, et al. Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. J Clin Endocrinol Metab. 2002;87(10):4554–63. https://doi.org/10.1210/jc.2001-012012
95 Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, et al. Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. J Clin Endocrinol Metab. 2006;91(6):2112–8. https://doi.org/10.1210/jc.2005-2110
96 Knappe UJ, Petroff D, Quinkler M, Schmid SM, Schofl C, Schopohl J, et al. Fractionated radiotherapy and radiosurgery in acromegaly: analysis of 352 patients from the German Acromegaly Registry. Eur J Endocrinol. 2020;182(3):275–84. https://doi.org/10.1530/EJE-19-0784
97 Colao A, Grasso LFS, Di Cera M, Thompson-Leduc P, Cheng WY, Cheung HC, et al. Association between biochemical control and comorbidities in patients with acromegaly: an Italian longitudinal retrospective chart review study. J Endocrinol Invest. 2020;43(4):529–38. https://doi.org/10.1007/s40618-019-01138-y
98 Coopmans EC, Postma MR, Wolters TLC, van Meyel SWF, Netea-Maier R, van Beek AP, et al. Predictors for remission after transsphenoidal surgery in acromegaly: a Dutch multicenter study. J Clin Endocrinol Metab. 2021;106(6):1783–92. https://doi.org/10.1210/clinem/dgab069
99 Anthony JR, Alwahab UA, Kanakiya NK, Pontell DM, Veledar E, Oyesiku NM, et al. Significant elevation of growth hormone level impacts surgical outcomes in acromegaly. J Am Coll Endocrinol Am Assoc Clin Endocrinologists. 2015;21(9):1001–9. https://doi.org/10.4158/ep14587.or
100 Park SH, Ku CR, Moon JH, Kim EH, Kim SH, Lee EJ. Age- and sex-specific differences as predictors of surgical remission among patients with acromegaly. J Clin Endocrinol Metab. 2018;103(3):909–16. https://doi.org/10.1210/jc.2017-01844
101 Ioachimescu AG, Handa T, Goswami N, Pappy AL 2nd, Veledar E, Oyesiku NM. Gender differences and temporal trends over two decades in acromegaly: a single center study in 112 patients. Endocrine. 2020;67(2):423–32. https://doi.org/10.1007/s12020-019-02123-4
102 Jahangiri A, Wagner J, Han SW, Zygourakis CC, Han SJ, Tran MT, et al. Morbidity of repeat transsphenoidal surgery assessed in more than 1000 operations. J Neurosurg. 2014;121(1):67–74. https://doi.org/10.3171/2014.3.JNS131532
103 Wilson TJ, McKean EL, Barkan AL, Chandler WF, Sullivan SE. Repeat endoscopic transsphenoidal surgery for acromegaly: remission and complications. Pituitary. 2013;16(4):459–64. https://doi.org/10.1007/s11102-012-0457-x
104 Almeida JP, Ruiz-Trevino AS, Liang B, Omay SB, Shetty SR, Chen YN, et al. Re-operation for growth hormone-secreting pituitary adenomas: report on an endonasal endoscopic series with a systematic review and meta-analysis of the literature. J Neurosurg. 2018;129(2):404–16. https://doi.org/10.3171/2017.2.JNS162673
105 Maia B, Kasuki L, Gadelha MR. Novel therapies for acromegaly. Endocr Connect. 2020;9(12):R274–85. https://doi.org/10.1530/EC-20-0433
106 Yuen KCJ, Samson SL. Oral octreotide: a review of recent clinical trials and practical recommendations for its use in the treatment of patients with acromegaly. Endocr Pract. 2022;28(6):637–45. https://doi.org/10.1016/j.eprac.2022.04.009
107 Fleseriu M, Dreval A, Bondar I, Vagapova G, Macut D, Pokramovich YG, et al. Maintenance of response to oral octreotide compared with injectable somatostatin receptor ligands in patients with acromegaly: a phase 3, multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2022;10(2):102–11. https://doi.org/10.1016/S2213-8587(21)00296-5
108 Fleseriu M, Molitch M, Dreval A, Pokramovich Y, Bondar I, Poteshkin Y, et al. MPOWERED trial open-label extension: long-term efficacy and safety data for oral octreotide capsules in acromegaly. J Clin Endocrinol Metab. 2023;108(12):3214–22. https://doi.org/10.1210/clinem/dgad365
109 Carmichael JD, Bonert VS, Nuno M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014;99(5):1825–33. https://doi.org/10.1210/jc.2013-3757
110 Giustina A, Bronstein MD, Casanueva FF, Chanson P, Ghigo E, Ho KK, et al. Current management practices for acromegaly: an international survey. Pituitary. 2011;14(2):125–33. https://doi.org/10.1007/s11102-010-0269-9
111 Frara S, Maffezzoni F, Mazziotti G, Giustina A. The modern criteria for medical management of acromegaly. Prog Mol Biol Transl Sci. 2016;138:63–83. https://doi.org/10.1016/bs.pmbts.2015.10.015

112 Alquraini H, Del Pilar Schneider M, Mirakhur B, Barkan A. Biochemical efficacy of long-acting lanreotide depot/Autogel in patients with acromegaly naive to somatostatin-receptor ligands: analysis of three multicenter clinical trials. Pituitary. 2018;21(3):283–9. https://doi.org/10.1007/s11102-018-0867-5

113 Lamberts SWJ, Hofland LJ. Anniversary review: octreotide, 40 years later. Eur J Endocrinol. 2019;181(5):R173–83. https://doi.org/10.1530/EJE-19-0074

114 Colao A, Auriemma RS, Pivonello R, Kasuki L, Gadelha MR. Interpreting biochemical control response rates with first-generation somatostatin analogues in acromegaly. Pituitary. 2016;19(3):235–47. https://doi.org/10.1007/s11102-015-0684-z

115 Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. PLoS One. 2012;7(5):e36411. https://doi.org/10.1371/journal.pone.0036411

116 Neggers SJ, Pronin V, Balcere I, Lee MK, Rozhinskaya L, Bronstein MD, et al. Lanreotide Autogel 120 mg at extended dosing intervals in patients with acromegaly biochemically controlled with octreotide LAR: the LEAD study. Eur J Endocrinol. 2015;173(3):313–23. https://doi.org/10.1530/EJE-15-0215

117 Samson SL, Nachtigall LB, Fleseriu M, Gordon MB, Bolanowski M, Labadzhyan A, et al. Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide. J Clin Endocrinol Metab. 2020;105(10):e3785–97. https://doi.org/10.1210/clinem/dgaa526

118 Hofland LJ, van der Hoek J, van Koetsveld PM, de Herder WW, Waaijers M, Sprij-Mooij D, et al. The novel somatostatin analog SOM230 is a potent inhibitor of hormone release by growth hormone- and prolactin-secreting pituitary adenomas in vitro. J Clin Endocrinol Metab. 2004;89(4):1577–85. https://doi.org/10.1210/jc.2003-031344

119 Fleseriu M, Cuevas-Ramos D. Pasireotide: a novel treatment for patients with acromegaly. Drug Des Devel Ther. 2016;10:227–39. https://doi.org/10.2147/dddt.s77999

120 Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014;99(3):791–9. https://doi.org/10.1210/jc.2013-2480

121 Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(11):875–84. https://doi.org/10.1016/S2213-8587(14)70169-X

122 Colao A, Bronstein MD, Brue T, De Marinis L, Fleseriu M, Guitelman M, et al. Pasireotide for acromegaly: long-term outcomes from an extension to the Phase III PAOLA study. Eur J Endocrinol. 2020;182(6):583. https://doi.org/10.1530/eje-19-0762

123 Gadelha M, Bex M, Colao A, Pedroza Garcia EM, Poiana C, Jimenez-Sanchez M, et al. Evaluation of the efficacy and safety of switching to pasireotide in patients with acromegaly inadequately controlled with first-generation somatostatin analogs. Front Endocrinol. 2019;10:931. https://doi.org/10.3389/fendo.2019.00931

124 Shimon I, Adnan Z, Gorshtein A, Baraf L, Saba Khazen N, Gershinsky M, et al. Efficacy and safety of long-acting pasireotide in patients with somatostatin-resistant acromegaly: a multicenter study. Endocrine. 2018;62(2):448–55. https://doi.org/10.1007/s12020-018-1690-5

125 Schmid HA, Brue T, Colao A, Gadelha MR, Shimon I, Kapur K, et al. Effect of pasireotide on glucose- and growth hormone-related biomarkers in patients with inadequately controlled acromegaly. Endocrine. 2016;53(1):210–9. https://doi.org/10.1007/s12020-016-0895-8

126 Marazuela M, Ramos-Levi A, Sampedro-Nunez M, Bernabeu I. Cabergoline treatment in acromegaly: pros. Endocrine. 2014;46(2):215–9. https://doi.org/10.1007/s12020-014-0206-1

127 Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35. https://doi.org/10.1210/jc.2010-2443

128 Kasuki L, Dalmolin MD, Wildemberg LE, Gadelha MR. Treatment escape reduces the effectiveness of cabergoline during long-term treatment of acromegaly in monotherapy or in association with first-generation somatostatin receptor ligands. Clin Endocrinol. 2018;88(6):889–95. https://doi.org/10.1111/cen.13595

129 Hacisahinogullari H, Yalin GY, Selcukbiricik OS, Gul N, Bilgic B, Uzum AK, et al. Effect of cabergoline treatment on disease control in acromegaly patients. Horm Metab Res. 2022;54(10):664–70. https://doi.org/10.1055/a-1930-6585

130 Melmed S. Medical progress: acromegaly. N Engl J Med. 2006;355(24):2558–73. https://doi.org/10.1056/NEJMra062453

131 Giustina A, Arnaldi G, Bogazzi F, Cannavo S, Colao A, De Marinis L, et al. Pegvisomant in acromegaly: an update. J Endocrinol Invest. 2017;40(6):577–89. https://doi.org/10.1007/s40618-017-0614-1

132 van der Lely AJ, Kuhn E, Muhammad A, Coopmans EC, Neggers SJ, Chanson P. Pegvisomant and not somatostatin receptor ligands (SRLs) is first-line medical therapy for acromegaly. Eur J Endocrinol. 2020;182(6):D17–29. https://doi.org/10.1530/eje-19-0998

133 Katznelson L. Pegvisomant for the treatment of acromegaly-translation of clinical trials into clinical practice. Nat Clin Pract Endocrinol Metab. 2007;3(7):514–5. https://doi.org/10.1038/ncpendmet0533

134 Brue T, Lindberg A, Jan van der Lely A, Akerblad AC, Koltowska-Haggstrom M, Gomez R, et al. Diabetes in patients with acromegaly treated with pegvisomant: observations from acrostudy. Endocrine. 2019;63(3):563–72. https://doi.org/10.1007/s12020-018-1792-0

135 Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, et al. Pegvisomant improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. J Clin Endocrinol Metab. 2019;104(7):2892–902. https://doi.org/10.1210/jc.2018-02281

136 Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7. https://doi.org/10.1056/NEJM200004203421604

137 van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;358(9295):1754–9. https://doi.org/10.1016/s0140-6736(01)06844-1

138 Fleseriu M, Fuhrer-Sakel D, van der Lely AJ, De Marinis L, Brue T, van der Lans-Bussemaker J, et al. More than a decade of real-world experience of pegvisomant for acromegaly: acrostudy. Eur J Endocrinol. 2021;185(4):525–38. https://doi.org/10.1530/EJE-21-0239

139 Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, et al. Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. Eur J Endocrinol. 2018;179(6):419–27. https://doi.org/10.1530/EJE-18-0616

140 Giustina A, Bevan JS, Bronstein MD, Casanueva FF, Chanson P, Petersenn S, et al. SAGIT®: clinician-reported outcome instrument for managing acromegaly in clinical practice-development and results from a pilot study. Pituitary. 2016;19(1):39–49. https://doi.org/10.1007/s11102-015-0681-2

141 van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, et al. Development of ACRODAT®, a new software medical device to assess disease activity in patients with acromegaly. Pituitary. 2017;20(6):692–701. https://doi.org/10.1007/s11102-017-0835-5

142 Petersenn S, Houchard A, Sert C, Caron PJ, PRIMARYS Study Group. Predictive factors for responses to primary medical treatment with lanreotide autogel 120 mg in acromegaly: post hoc analyses from the PRIMARYS study. Pituitary. 2020;23(2):171–81. https://doi.org/10.1007/s11102-019-01020-3

143 Puig-Domingo M, Bernabeu I, Pico A, Biagetti B, Gil J, Alvarez-Escola C, et al. Pasireotide in the personalized treatment of acromegaly. Front Endocrinol. 2021;12:648411. https://doi.org/10.3389/fendo.2021.648411
144 Kiseljak-Vassiliades K, Carlson NE, Borges MT, Kleinschmidt-DeMasters BK, Lillehei KO, Kerr JM, et al. Growth hormone tumor histological subtypes predict response to surgical and medical therapy. Endocrine. 2015;49(1):231–41. https://doi.org/10.1007/s12020-014-0383-y
145 Giustina A, Bonadonna S, Bugari G, Colao A, Cozzi R, Cannavo S, et al. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. Eur J Endocrinol. 2009;161(2):331–8. https://doi.org/10.1530/EJE-09-0372
146 Ludlam WH, Anthony L. Safety review: dose optimization of somatostatin analogs in patients with acromegaly and neuroendocrine tumors. Adv Ther. 2011;28(10):825–41. https://doi.org/10.1007/s12325-011-0062-9
147 Mazziotti G, Porcelli T, Bogazzi F, Bugari G, Cannavo S, Colao A, et al. Effects of high-dose octreotide LAR on glucose metabolism in patients with acromegaly inadequately controlled by conventional somatostatin analog therapy. Eur J Endocrinol. 2011;164(3):341–7. https://doi.org/10.1530/EJE-10-0811
148 Giustina A, Mazziotti G, Cannavo S, Castello R, Arnaldi G, Bugari G, et al. High-dose and high-frequency lanreotide autogel in acromegaly: a randomized, multicenter study. J Clin Endocrinol Metab. 2017;102(7):2454–64. https://doi.org/10.1210/jc.2017-00142
149 Colao A, Lombardi G. Dose optimization of somatostatin analogues for acromegaly patients. J Endocrinol Invest. 2010;33(2):125–7. https://doi.org/10.1007/BF03346566
150 Chin SO, Ku CR, Kim BJ, Kim SW, Park KH, Song KH, et al. Medical treatment with somatostatin analogues in acromegaly: position statement. Endocrinol Metab Seoul. 2019;34(1):53–62. https://doi.org/10.3803/EnM.2019.34.1.53
151 Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, et al. Expert consensus document: a consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. 2014;10(4):243–8. https://doi.org/10.1038/nrendo.2014.21
152 Maffezzoni F, Formenti AM, Mazziotti G, Frara S, Giustina A. Current and future medical treatments for patients with acromegaly. Expert Opin Pharmacother. 2016;17(12):1631–42. https://doi.org/10.1080/14656566.2016.1199687
153 Grasso LF, Auriemma RS, Pivonello R, Colao A. Adverse events associated with somatostatin analogs in acromegaly. Expert Opin Drug Saf. 2015;14(8):1213–26. https://doi.org/10.1517/14740338.2015.1059817
154 Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33. https://doi.org/10.1056/NEJMoa1316158
155 Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016;23(3):191–9. https://doi.org/10.1530/ERC-15-0490
156 Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27(28):4656–63. https://doi.org/10.1200/JCO.2009.22.8510
157 Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. Neuroendocrinology. 2017;104(1):26–32. https://doi.org/10.1159/000443612
158 Attanasio R, Mainolfi A, Grimaldi F, Cozzi R, Montini M, Carzaniga C, et al. Somatostatin analogs and gallstones: a retrospective survey on a large series of acromegalic patients. J Endocrinol Invest. 2008;31(8):704–10. https://doi.org/10.1007/BF03346419
159 Prencipe N, Bona C, Cuboni D, Parasiliti-Caprino M, Berton AM, Fenoglio LM, et al. Biliary adverse events in acromegaly during somatostatin receptor ligands: predictors of onset and response to ursodeoxycholic acid treatment. Pituitary. 2021;24(2):242–51. https://doi.org/10.1007/s11102-020-01102-7
160 Gomes-Porras M, Cardenas-Salas J, Alvarez-Escola C. Somatostatin analogs in clinical practice: a review. Int J Mol Sci. 2020;21(5):1682. https://doi.org/10.3390/ijms21051682
161 van der Lely AJ, Biller BM, Brue T, Buchfelder M, Ghigo E, Gomez R, et al. Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab. 2012;97(5):1589–97. https://doi.org/10.1210/jc.2011-2508
162 Higham CE, Thomas JD, Bidlingmaier M, Drake WM, Trainer PJ. Successful use of weekly pegvisomant administration in patients with acromegaly. Eur J Endocrinol. 2009;161(1):21–5. https://doi.org/10.1530/EJE-08-0990
163 Jehle S, Reyes CM, Sundeen RE, Freda PU. Alternate-day administration of pegvisomant maintains normal serum insulin-like growth factor-I levels in patients with acromegaly. J Clin Endocrinol Metab. 2005;90(3):1588–93. https://doi.org/10.1210/jc.2004-1967
164 Neggers SJ, Muhammad A, van der Lely AJ. Pegvisomant treatment in acromegaly. Neuroendocrinology. 2016;103(1):59–65. https://doi.org/10.1159/000381644
165 Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, et al. Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. Eur J Endocrinol. 2006;154(3):467–77. https://doi.org/10.1530/eje.1.02112
166 Parkinson C, Burman P, Messig M, Trainer PJ. Gender, body weight, disease activity, and previous radiotherapy influence the response to pegvisomant. J Clin Endocrinol Metab. 2007;92(1):190–5. https://doi.org/10.1210/jc.2006-1412
167 van der Lely AJ, Jonsson P, Wilton P, Akerblad AC, Cara J, Ghigo E. Treatment with high doses of pegvisomant in 56 patients with acromegaly: experience from ACROSTUDY. Eur J Endocrinol. 2016;175(4):239–45. https://doi.org/10.1530/EJE-16-0008
168 Droste M, Domberg J, Buchfelder M, Mann K, Schwanke A, Stalla G, et al. Therapy of acromegalic patients exacerbated by concomitant type 2 diabetes requires higher pegvisomant doses to normalise IGF1 levels. Eur J Endocrinol. 2014;171(1):59–68. https://doi.org/10.1530/EJE-13-0438
169 Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, et al. Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. Eur J Endocrinol. 2007;156(1):75–82. https://doi.org/10.1530/eje.1.02312
170 Marazuela M, Lucas T, Alvarez-Escola C, Puig-Domingo M, de la Torre NG, de Miguel-Novoa P, et al. Long-term treatment of acromegalic patients resistant to somatostatin analogues with the GH receptor antagonist pegvisomant: its efficacy in relation to gender and previous radiotherapy. Eur J Endocrinol. 2009;160(4):535–42. https://doi.org/10.1530/EJE-08-0705
171 van der Lely AJ, Bernabeu I, Cap J, Caron P, Colao A, Marek J, et al. Coadministration of lanreotide Autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone. Eur J Endocrinol. 2011;164(3):325–33. https://doi.org/10.1530/EJE-10-0867

172 Franck SE, Muhammad A, van der Lely AJ, Neggers SJ. Combined treatment of somatostatin analogues with pegvisomant in acromegaly. Endocrine. 2016;52(2):206–13. https://doi.org/10.1007/s12020-015-0810-8
173 Jorgensen JO, Feldt-Rasmussen U, Frystyk J, Chen JW, Kristensen LO, Hagen C, et al. Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. J Clin Endocrinol Metab. 2005;90(10):5627–31. https://doi.org/10.1210/jc.2005-0531
174 Neggers SJ, Franck SE, de Rooij FW, Dallenga AH, Poublon RM, Feelders RA, et al. Long-term efficacy and safety of pegvisomant in combination with long-acting somatostatin analogs in acromegaly. J Clin Endocrinol Metab. 2014;99(10):3644–52. https://doi.org/10.1210/jc.2014-2032
175 Strasburger CJ, Mattsson A, Wilton P, Aydin F, Hey-Hadavi J, Biller BMK. Increasing frequency of combination medical therapy in the treatment of acromegaly with the GH receptor antagonist pegvisomant. Eur J Endocrinol. 2018;178(4):321–9. https://doi.org/10.1530/EJE-17-0996
176 Bonert V, Mirocha J, Carmichael J, Yuen KCJ, Araki T, Melmed S. Cost-effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. J Clin Endocrinol Metab. 2020;105(9):dgaa444. https://doi.org/10.1210/clinem/dgaa444
177 Ramos-Levi AM, Bernabeu I, Alvarez-Escola C, Aller J, Lucas T, de Miguel P, et al. Long-term treatment with pegvisomant for acromegaly: a 10-year experience. Clin Endocrinol. 2016;84(4):540–50. https://doi.org/10.1111/cen.12993
178 Biering H, Saller B, Bauditz J, Pirlich M, Rudolph B, Johne A, et al. Elevated transaminases during medical treatment of acromegaly: a review of the German pegvisomant surveillance experience and a report of a patient with histologically proven chronic mild active hepatitis. Eur J Endocrinol. 2006;154(2):213–20. https://doi.org/10.1530/eje.1.02079
179 Giustina A, Ambrosio MR, Beck Peccoz P, Bogazzi F, Cannavo S, De Marinis L, et al. Use of pegvisomant in acromegaly. An Italian society of Endocrinology guideline. J Endocrinol Invest. 2014;37(10):1017–30. https://doi.org/10.1007/s40618-014-0146-x
180 Ragonese M, Grottoli S, Maffei P, Alibrandi A, Ambrosio MR, Arnaldi G, et al. How to improve effectiveness of pegvisomant treatment in acromegalic patients. J Endocrinol Invest. 2018;41(5):575–81. https://doi.org/10.1007/s40618-017-0773-0
181 Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev. 2002;23(5):623–46. https://doi.org/10.1210/er.2001-0022
182 Leonart LP, Tonin FS, Ferreira VL, Fernandez-Llimos F, Pontarolo R. Effectiveness and safety of pegvisomant: a systematic review and meta-analysis of observational longitudinal studies. Endocrine. 2019;63(1):18–26. https://doi.org/10.1007/s12020-018-1729-7
183 Buchfelder M, Weigel D, Droste M, Mann K, Saller B, Brubach K, et al. Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. Eur J Endocrinol. 2009;161(1):27–35. https://doi.org/10.1530/EJE-08-0910
184 Hodish I, Barkan A. Long-term effects of pegvisomant in patients with acromegaly. Nat Clin Pract Endocrinol Metab. 2008;4(6):324–32. https://doi.org/10.1038/ncpendmet0831
185 Jimenez C, Burman P, Abs R, Clemmons DR, Drake WM, Hutson KR, et al. Follow-up of pituitary tumor volume in patients with acromegaly treated with pegvisomant in clinical trials. Eur J Endocrinol. 2008;159(5):517–23. https://doi.org/10.1530/EJE-08-0205
186 Marazuela M, Paniagua AE, Gahete MD, Lucas T, Alvarez-Escola C, Manzanares R, et al. Somatotroph tumor progression during pegvisomant therapy: a clinical and molecular study. J Clin Endocrinol Metab. 2011;96(2):E251–9. https://doi.org/10.1210/jc.2010-1742
187 Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, et al. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. Eur J Endocrinol. 2017;176(5):645–55. https://doi.org/10.1530/EJE-16-1064
188 Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, et al. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. J Clin Endocrinol Metab. 2008;93(10):3853–9. https://doi.org/10.1210/jc.2008-0669
189 Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA, et al. Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. Lancet. 2005;365(9471):1644–6. https://doi.org/10.1016/S0140-6736(05)63011-5
190 Puig-Domingo M, Soto A, Venegas E, Vilchez R, Blanco C, Cordido F, et al. Use of lanreotide in combination with cabergoline or pegvisomant in patients with acromegaly in the clinical practice: the ACROCOMB study. Endocrinol Nutr. 2016;63(8):397–408. https://doi.org/10.1016/j.endonu.2016.05.010
191 Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P, Giustina A. Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. J Clin Endocrinol Metab. 2009;94(5):1500–8. https://doi.org/10.1210/jc.2008-2332
192 Auriemma RS, Grasso LF, Galdiero M, Galderisi M, Pivonello C, Simeoli C, et al. Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly. Endocrine. 2017;55(3):872–84. https://doi.org/10.1007/s12020-016-0995-5
193 Higham CE, Atkinson AB, Aylwin S, Bidlingmaier M, Drake WM, Lewis A, et al. Effective combination treatment with cabergoline and low-dose pegvisomant in active acromegaly: a prospective clinical trial. J Clin Endocrinol Metab. 2012;97(4):1187–93. https://doi.org/10.1210/jc.2011-2603
194 Muhammad A, van der Lely AJ, Delhanty PJD, Dallenga AHG, Haitsma IK, Janssen J, et al. Efficacy and safety of switching to pasireotide in patients with acromegaly controlled with pegvisomant and first-generation somatostatin analogues (PAPE study). J Clin Endocrinol Metab. 2018;103(2):586–95. https://doi.org/10.1210/jc.2017-02017
195 Muhammad A, Coopmans EC, Delhanty PJD, Dallenga AHG, Haitsma IK, Janssen J, et al. Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and somatostatin analogues: PAPE extension study. Eur J Endocrinol. 2018;179(5):269–77. https://doi.org/10.1530/EJE-18-0353
196 Cordido F, Garcia Arnes JA, Marazuela Aspiroz M, Torres Vela E, grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y N. [Practical guidelines for diagnosis and treatment of acromegaly. Grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y Nutricion]. 2013(8);60:457 e1–5. https://doi.org/10.1016/j.endoen.2013.10.012
197 Cohen-Inbar O, Ramesh A, Xu Z, Vance ML, Schlesinger D, Sheehan JP. Gamma knife radiosurgery in patients with persistent acromegaly or Cushing's disease: long-term risk of hypopituitarism. Clin Endocrinol. 2016;84(4):524–31. https://doi.org/10.1111/cen.12938
198 Gheorghiu ML. Updates in outcomes of stereotactic radiation therapy in acromegaly. Pituitary. 2017;20(1):154–68. https://doi.org/10.1007/s11102-016-0783-5
199 Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. Radiat Oncol. 2016;11(1):135. https://doi.org/10.1186/s13014-016-0710-y
200 Ramakrishna N, Rosca F, Friesen S, Tezcanli E, Zygmanszki P, Hacker F. A clinical comparison of patient setup and intra-fraction motion using frame-based radiosurgery versus a frameless image-guided radiosurgery system for intracranial lesions. Radiother Oncol. 2010;95(1):109–15. https://doi.org/10.1016/j.radonc.2009.12.030

201 Kuo JS, Yu C, Petrovich Z, Apuzzo ML. The CyberKnife stereotactic radiosurgery system: description, installation, and an initial evaluation of use and functionality. Neurosurgery. 2008;62(Suppl 2):785–9. https://doi.org/10.1227/01.neu.0000316282.07124.31
202 Wu A, Lindner G, Maitz AH, Kalend AM, Lunsford LD, Flickinger JC, et al. Physics of gamma knife approach on convergent beams in stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 1990;18(4):941–9. https://doi.org/10.1016/0360-3016(90)90421-f
203 Abu Dabrh A, Asi N, Farah W, Mohammed K, Wang Z, Farah M, et al. Radiotherapy vs. Radiosurgery in treating patients with acromegaly: systematic review and meta-analysis. Endocr Pract. 2015;18:1–33. https://doi.org/10.4158/EP14574.RA
204 Minniti G, Clarke E, Scaringi C, Enrici RM. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. Rep Pract Oncol Radiother. 2016;21(4):370–8. https://doi.org/10.1016/j.rpor.2014.09.004
205 Kuhn E, Chanson P. Fractionated stereotactic radiotherapy: an interesting alternative to stereotactic radiosurgery in acromegaly. Endocrine. 2015;50(3):529–30. https://doi.org/10.1007/s12020-015-0768-6
206 Graffeo CS, Donegan D, Erickson D, Brown PD, Perry A, Link MJ, et al. The impact of insulin-like growth factor index and biologically effective dose on outcomes after stereotactic radiosurgery for acromegaly: cohort study. Neurosurgery. 2020;87(3):538–46. https://doi.org/10.1093/neuros/nyaa054
207 Hannon MJ, Barkan AL, Drake WM. The role of radiotherapy in acromegaly. Neuroendocrinology. 2016;103(1):42–9. https://doi.org/10.1159/000435776
208 Grynberg M, Salenave S, Young J, Chanson P. Female gonadal function before and after treatment of acromegaly. J Clin Endocrinol Metab. 2010;95(10):4518–25. https://doi.org/10.1210/jc.2009-2815
209 Leung KC, Johannsson G, Leong GM, Ho KK. Estrogen regulation of growth hormone action. Endocr Rev. 2004;25(5):693–721. https://doi.org/10.1210/er.2003-0035
210 Persechini ML, Gennero I, Grunenwald S, Vezzosi D, Bennet A, Caron P. Decreased IGF-1 concentration during the first trimester of pregnancy in women with normal somatotroph function. Pituitary. 2015;18(4):461–4. https://doi.org/10.1007/s11102-014-0596-3
211 Abucham J, Bronstein MD, Dias ML. Management of endocrine disease: acromegaly and pregnancy: a contemporary review. Eur J Endocrinol. 2017;177(1):R1–2. https://doi.org/10.1530/EJE-16-1059
212 Luger A, Broersen LHA, Biermasz NR, Biller BMK, Buchfelder M, Chanson P, et al. ESE Clinical Practice Guideline on functioning and nonfunctioning pituitary adenomas in pregnancy. Eur J Endocrinol. 2021;185(3):G1–33. https://doi.org/10.1530/EJE-21-0462
213 Bandeira DB, Olivatti TOF, Bolfi F, Boguszewski CL, Dos Santos Nunes-Nogueira V. Acromegaly and pregnancy: a systematic review and meta-analysis. Pituitary. 2022;25(3):352–62. https://doi.org/10.1007/s11102-022-01208-0
214 Caron P, Broussaud S, Bertherat J, Borson-Chazot F, Brue T, Cortet-Rudelli C, et al. Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women. J Clin Endocrinol Metab. 2010;95(10):4680–7. https://doi.org/10.1210/jc.2009-2331
215 Chanson P, Vialon M, Caron P. An update on clinical care for pregnant women with acromegaly. Expert Rev Endocrinol Metab. 2019;14(2):85–96. https://doi.org/10.1080/17446651.2019.1571909
216 Muhammad A, Neggers SJ, van der Lely AJ. Pregnancy and acromegaly. Pituitary. 2017;20(1):179–84. https://doi.org/10.1007/s11102-016-0740-3
217 Laway BA. Pregnancy in acromegaly. Ther Adv Endocrinol Metab. 2015;6(6):267–72. https://doi.org/10.1177/2042018815603927
218 Cheng V, Faiman C, Kennedy L, Khoury F, Hatipoglu B, Weil R, et al. Pregnancy and acromegaly: a review. Pituitary. 2012;15(1):59–63. https://doi.org/10.1007/s11102-011-0330-3
219 Maffei P, Tamagno G, Nardelli GB, Videau C, Menegazzo C, Milan G, et al. Effects of octreotide exposure during pregnancy in acromegaly. Clin Endocrinol. 2010;72(5):668–77. https://doi.org/10.1111/j.1365-2265.2009.03706.x
220 van der Lely AJ, Gomez R, Heissler JF, Akerblad AC, Jonsson P, Camacho-Hubner C, et al. Pregnancy in acromegaly patients treated with pegvisomant. Endocrine. 2015;49(3):769–73. https://doi.org/10.1007/s12020-014-0508-3
221 Molitch ME. Prolactinoma in pregnancy. Best Pract Res Clin Endocrinol Metab. 2011;25(6):885–96. https://doi.org/10.1016/j.beem.2011.05.011
222 Cheng S, Grasso L, Martinez-Orozco JA, Al-Agha R, Pivonello R, Colao A, et al. Pregnancy in acromegaly: experience from two referral centers and systematic review of the literature. Clin Endocrinol. 2012;76(2):264–71. https://doi.org/10.1111/j.1365-2265.2011.04180.x