Acromegaly: pathogenesis, diagnosis, and management

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Growth hormone-secreting pituitary adenomas that cause acromegaly arise as monoclonal expansions of differentiated somatotroph cells and are usually sporadic. They are almost invariably benign, yet they can be locally invasive and show progressive growth despite treatment. Persistent excess of both growth hormone and its target hormone insulin-like growth factor 1 (IGF-1) results in a wide array of cardiovascular, respiratory, metabolic, musculoskeletal, neurological, and neoplastic comorbidities that might not be reversible with disease control. Normalisation of IGF-1 and growth hormone are the primary therapeutic aims; additional treatment goals include tumour shrinkage, relieving symptoms, managing complications, reducing excess morbidity, and improving quality of life. A multimodal approach with surgery, medical therapy, and (more rarely) radiation therapy is required to achieve these goals. In this Review, we examine the epidemiology, pathogenesis, diagnosis, complications, and treatment of acromegaly, with an emphasis on the importance of tailoring management strategies to each patient to optimise outcomes.

Introduction

Acromegaly is a rare disorder characterised by hypersecretion of growth hormone and its peripheral target hormone insulin-like growth factor 1 (IGF-1). Most patients have a growth hormone-secreting pituitary adenoma and exhibit multiple, often serious, comorbidities as well as impaired quality of life (QoL) at the time of diagnosis because of substantial delays in recognising the disorder. Despite newer, more precise growth hormone and IGF-1 assays and imaging advances, substantial gaps remain in elucidation of diagnosis and morbidity management.[1–4]

Treatment goals include achievement of normal (age-specific and sex-specific) IGF-1 concentrations and growth hormone concentrations measured by both random testing and after oral glucose tolerance test (OGTT) as needed,[5] tumour growth control, symptom relief, complication management, and improved QoL. Although surgical resection of the growth hormone-secreting pituitary adenoma is usually the first-line treatment, in some countries patients might be medically treated preoperatively to reduce the burden of disease if there are delays in surgery access or reduced availability of specialised neurosurgeons, or they might be treated with primary medical therapy if the adenoma is large and chances of surgical cure are thus low. Comorbidities are important to recognise and require rigorous screening, diagnosis, and targeted management. Nowadays, given the array of novel medical treatment options, clinicians should aim to tailor treatment to individual patients' unique characteristics and preferences. Personalised management approaches, such as those delivered by multidisciplinary teams in pituitary tumour centres of excellence,[6] should enhance outcomes and ultimately reduce disease-associated mortality.

Epidemiology of acromegaly: the past decades have brought change

Between 1955 and 2013, an annual incidence of 0·2–1·1 new cases per 100 000 people was reported in epidemiological studies mostly done in Europe, and data suggest an increase over the observed period of time.[7,8] The reported prevalence range between 2001 and 2013 is wide, between 2·8 cases per 100 000 people and 13·7 cases per 100 000 people.[7] A meta-analysis covering the period 1955–2016 showed an annual incidence of 0·38 (95% CI 0·32–0·44) per 100 000 people and a pooled global prevalence of 5·9 (4·4–7·9) per 100 000 people, with considerable between-study heterogeneity.[9] Data variability is due to differences in inclusion criteria, selection bias (eg, tertiary referral centre *vs* country-wide analysis), and heterogeneous retrospective data collection from different medical records, national registries, pituitary databases, surveys, and medical claims databases.[7,9] Increasing rates of acromegaly have been detected in areas of high industrial pollution, which might be due to increased concentrations of endocrine-disrupting chemicals.[9] Some populations might be at increased risk for acromegaly and gigantism because of a higher prevalence of aryl hydrocarbon receptor-interacting protein (*AIP*) germline mutations,[7,9] although, because of low penetrance, the overall rates of acromegaly in geographical areas of high *AIP* mutation carrier rates might not be different from other areas. Nevertheless, reports indicate that prevalence of acromegaly is increasing (from 5–6 per 100 000 people between 1971 and 1989 to 13–14 per 100 000 people between 2012 and 2014), probably due to improved diagnostic techniques, including development of more sensitive growth hormone assays and shifts in biochemical diagnostic criteria allowing for diagnosis of milder cases, improved disease awareness, and increased survival of patients receiving improved surgical and pharmacological treatments.[7,9] Most patients are diagnosed in the fifth decade of life,[7] although an increasing number of older patients (aged >65 years) are being diagnosed with acromegaly.[10] Rarely, acromegaly is also diagnosed in children with pituitary gigantism and in young adults, from infancy to age 22 years. In a large retrospective study of young adults with pituitary gigantism,

acromegaly was diagnosed at an earlier age in female patients (15·8 years) than in male patients (21·5 years). These patients are more likely to have more aggressive disease, with high growth hormone concentrations and large tumour size at diagnosis, resistance to medical therapy, and a high symptom burden.[11]

Delay in diagnosis can range from 5 years to 14 years after symptom onset,[12–14] although it is most commonly between 5 years and 6 years.[7,12,15,16] Few publications report a shorter time to diagnosis of approximately 2·5 years.[17,18] A large European registry suggested decreasing diagnostic delays over time, from more than 20 years in patients diagnosed before 1990, to approximately 10 years in the 1990s and approximately 5 years in the 2000s.[14]

Overall, there is a slight predominance of female individuals diagnosed with acromegaly (52–60%),[19] although not all studies substantiate this trend.[20,21] In a meta-analysis, weighted percentage of female individuals with acromegaly was 53·3% (95% CI 51·5–55·2), albeit with sizeable heterogeneity among the studies.[8]

Male individuals are diagnosed at a younger age than are female individuals, with a median difference of 4·5 years (IQR 1·8–6·6).[19] In turn, this difference affects diagnostic delay: delay in women is 2–4·6 years longer than in men (perimenopause might be a contributing factor[15,19]), despite women consulting physicians more frequently before diagnosis.[19]

Lower IGF-1 concentrations in female individuals possibly reflect an oestrogen effect on liver growth hormone receptors.[8,22] Premenopausal women also have a greater degree of cavernous sinus invasion than do men younger than 50 years.[23]

Overall, the high frequency of pituitary macroadenomas and later age at diagnosis appear to have remained unchanged over a 20-year period (1991–2011),[24] indicating that more efforts are needed to improve early diagnosis.

Pathogenesis of somatotroph adenomas

Hypothalamic growth hormone-releasing hormone (GHRH) stimulates somatotroph growth hormone production through its receptor (GHRHR) to activate adenylyl cyclase through $G_s\alpha$, whereas somatostatin mediated by somatostatin (SST) receptors 2 and 5 suppresses growth hormone secretion (appendix p 5). Growth hormone is also stimulated by ghrelin synthesised in the gastrointestinal tract. Many growth-promoting effects of growth hormone are mediated by its target hormone IGF-1.

The PIT1 transcription factor drives differentiation of mammosomatotroph, somatotroph, lactotroph, and thyrotroph cells.[25] Accordingly, PIT1-lineage tumours encompass somatotroph, lactotroph, and thyrotroph adenomas that hypersecrete growth hormone or prolactin, or both, and very rarely plurihormonal adenomas, which hypersecrete growth hormone, prolactin, and thyroid-stimulating hormone. Growth hormone-secreting pituitary adenomas arise as monoclonal expansions of differentiated somatotroph cells and most are sporadic.[25]

Activating *GNAS* (commonly known as *Gsp*) mutations present in up to 40% of somatotroph adenomas inhibits GTPase activity leading to cAMP accumulation and excess synthesis of growth hormone.[25] Substitution of Arg201, or Gln227, causes constitutive activation of the mutated $G_s\alpha$ subunit. Somatotroph adenomas also exhibit high levels of *PDE4D* expression, further sustaining cAMP accumulation.[26] People with acromegaly and *Gsp* mutations are older than people with wild-type *Gsp* acromegaly, and have smaller, less invasive tumours that are more densely granulated. Very rarely, a *GPR101* mutation also causes growth hormone excess and somatotroph proliferation, and *GPR101* duplication leads to X-linked acrogigantism (appendix p 2),[27] with adenoma overexpression of GPR101 receptor constitutively activating G_s and $G_{q/11}$. Duplication of the gene leads to abundant GPR101 expression.[28] Hypothalamic or tumour-derived ectopic GHRH induces cAMP, leading to DNA damage in addition to growth hormone induction, with abundant somatic copy number alterations.[26] Thus, constitutive cAMP activation mimics excess GHRH signalling to induce somatotroph proliferation with DNA damage and growth hormone overproduction.

PTTG, the index mammalian securin, maintains chromosomal stability. Overabundant PTTG is a marker of adenoma invasiveness and is associated with chromosomal instability and aneuploidy due to non-faithful centromere separation.[29] Other cell cycle markers including pRB, p21, and p16 are associated with adenoma recurrence or aggression, chromosomal instability, and more chromosomal copy number alterations in somatotrophs than in non-secreting adenomas. Thus, provoked aneuploidy, chromosomal insta bility, and DNA damage are associated with cellular senescence markers characterised by largely irreversible cell cycle arrest that promote antiproliferative responses.[30] Cellular senescence (ie, premature cell cycle arrest) explains the benign nature of these adenomas, as senescence is protective of malignant transformation.

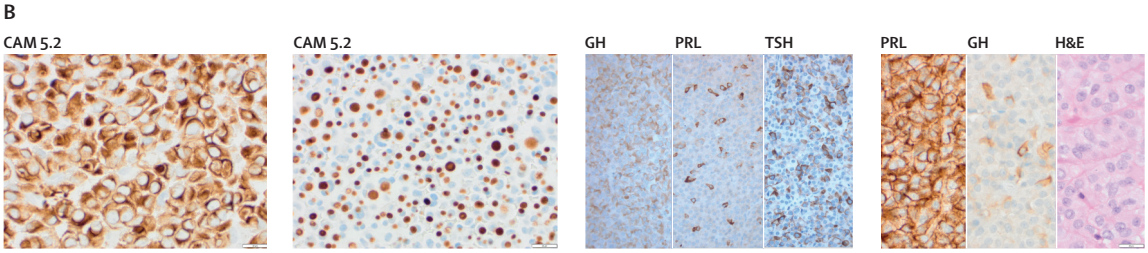
Pangenomic profiling of pituitary adenomas enables further subcellular acromegaly classification.[31] A genome-wide association study of 771 pituitary adenomas reported genetic susceptibility loci suggesting that formation of sporadic pituitary adenomas is also associated with as yet unknown inherited genetic variations.[32] Whole-exome sequencing of 42 pituitary adenomas identified chromosome copy number alterations in 29% of samples, more frequently in growth hormone-secreting adenomas.[33] In a prospective study of 159 resected pituitary adenomas, somatic copy number alterations

See Online for appendix

A

Pituitary adenoma type (transcription factor)	Pathology	MRI	Clinical features
Densely granulated somatotroph adenoma (PIT1)	• Growth hormone, α-subunit • Perinuclear cytokeratin	Usually hypointense or isointense on T2	• Increased growth hormone and IGF-1 concentrations • Favourable somatostatin receptor ligand response
Sparsely granulated somatotroph adenoma (PIT1)	• Growth hormone • Fibrous bodies	Often hyperintense on T2	• More aggressive than densely granulated somatotroph adenoma • Reduced growth hormone and IGF-1 concentrations • Younger age • Adverse somatostatin receptor ligand response
Mammosomatotroph adenoma (PIT1 and ERα)	• Growth hormone and prolactin staining in the same cell, α-subunit	Might be more frequently cystic	• Similar to densely granulated somatotroph adenoma • Often elevated prolactin concentrations
Mixed somatotroph and lactotroph adenoma (PIT1 and ERα)	• Growth hormone and prolactin staining in different cells, with or without α-subunit	Might be more frequently cystic	• Invasive • Often elevated prolactin concentrations
Mature plurihormonal PIT1–positive adenoma (PIT1, ERα, and GATA3)	• Growth hormone, prolactin, and thyroid-stimulating hormone, α-subunit in the same cell (variable expression)	Not defined	• Variable growth hormone and prolactin excess, and hyperthyroidism
Immature plurihormonal PIT1-positive adenoma (PIT1, ERα, and GATA3)	• Growth hormone, prolactin, and thyroid-stimulating hormone, α-subunit in the same cell (variable expression) • Immature cells	Not defined	• Variable growth hormone and prolactin excess, and hyperthyroidism • Can be hormonally silent
Acidophil stem-cell adenoma (PIT1 and ERα)	• Prolactin staining > growth hormone staining • Immature cells, cytoplasmic vacuoles	Not defined	• Aggressive • Usually elevated prolactin concentrations

B



Densely granulated somatotroph adenoma (cytoplasmic staining) | Sparsely granulated somatotroph adenoma (fibrous bodies) | Plurihormonal PIT1-positive adenoma (triple hormone expression) | Acidophil stem-cell adenoma (PRL > GH, cytoplasmic vacuoles on H&E)

Figure 1: **Pathology of acromegaly**
(A) Characteristics of different adenoma subtypes defined by transcription factor and hormone staining. (B) Representative staining patterns in adenoma subtypes. CAM 5.2=cytokeratin stain. GH=growth hormone stain. H&E=haematoxylin and eosin stain. IGF=insulin-like growth factor. PRL=prolactin stain. TSH=thyroid-stimulating hormone stain.

were more abundant in growth hormone and prolactin-secreting adenomas than in other hormone-secreting and non-hormone-secreting adenomas.[26]

Non-genomic factors contributing to adenoma pathogenesis include STAT3,[34] Klotho, and hypomethylated DNA sites. Bromodomain-containing protein 4 (BRD4), which regulates the epigenetic initiation and elongation of oncogene transcription, is overexpressed in growth hormone-secreting pituitary adenomas, likely enhancing adenoma growth.[35]

Somatotroph adenomas are almost invariably benign, yet they can be locally invasive and show progressive growth even after treating patients with one or more treatment methods including surgery, medication, and radiotherapy.[25] According to the 2022 WHO classification,[36] growth hormone-secreting pituitary adenomas are classified as PIT1-lineage pituitary adenomas together with lactotroph and thyrotroph adenomas because they arise from a common lineage and share the PIT1 transcription factor. Pure growth hormone-secreting adenomas secrete only growth hormone and can be densely or sparsely granulated. Mammosomatotroph adenomas, mixed growth hormone and prolactin-secreting adenomas, mature plurihormonal adenomas, immature plurihormonal adenomas, and acidophil stem-cell adenomas express more than one hormone (figure 1).[36]

Histological distinction between adenoma types has important clinical relevance. Adenomas secreting both growth hormone and prolactin were less likely to achieve surgical remission (20% *vs* 68%) and more likely to require adjuvant therapy (80% *vs* 32%) than pure growth hormone-secreting adenomas.[37] Adenomas secreting both hormones might appear more cystic on pituitary

MRI than pure growth hormone adenomas.[38] Both pure growth hormone-secreting adenomas and plurihormonal adenomas might present without hormonal hypersecretion and are clinically silent.[39]

Growth hormone-secreting pituitary adenomas are present in approximately 99% of people with acromegaly, whereas, in the remaining 1% of cases, acromegaly develops due to rare ectopic tumours secreting GHRH or growth hormone, or both.[5,40] More than 70% of somatotroph adenomas are macroadenomas at presentation.[24] Absence of an adenoma in people who have received a biochemical diagnosis of acromegaly should prompt suspicion for ectopic disease; however, in some people, the pituitary MRI does not show an adenoma, and, in others, an empty sella has been reported.[41]

Ectopic tumoral GHRH secretion[5,40] leads to secondary pituitary somatotroph hyperplasia, appearing as an enlarged pituitary gland on MRI and often mimicking a pituitary adenoma. Primary somatotroph hyperplasia can also be present in rare genetic syndromes. Ectopic growth hormone production by a neuroendocrine tumour or lymphoma is very rare and MRI might show a normal-sized or small pituitary gland.[40,42]

Diagnosis: recognising growth hormone excess

Acromegaly is usually suspected on the basis of several clinical signs and symptoms (figure 2; appendix p 6). Acral enlargement and coarsening of facial features are considered pathognomonic and are present in more than 80% of people with acromegaly.[13] Other common manifestations include arthropathy, hyperhidrosis, snoring, and carpal tunnel syndrome. Patients often present with hypertension, type 2 diabetes, and sleep apnoea. A large study reported visual field defects in 18% of patients.[24] However, some individuals might have only mild or subtle symptoms, particularly early in the disease course or when adenomas have low or intermittent growth hormone secretion.[39] Conversely, patients presenting with hyperprolactinaemia and an incidental pituitary adenoma should be assessed for a mixed growth hormone and prolactin-secreting adenoma.[43] If growth hormone hypersecretion occurs before epiphyseal closure, linear growth is accelerated, with resultant features of gigantism. An increasing number of genetic defects, including for *AIP* and *GPR101*, have been observed in individuals with pituitary gigantism, yet no mutation has been reported in more than 50% of these patients.[11] Pituitary gigantism is a male-predominant disorder and is characterised by the presence of aggressive macroadenomas, often with more primitive cell characteristics.[5,11]

Biochemical diagnosis: screening and confirmatory testing

Generally, biochemical diagnosis of acromegaly is established on the basis of elevated IGF-1 concentrations

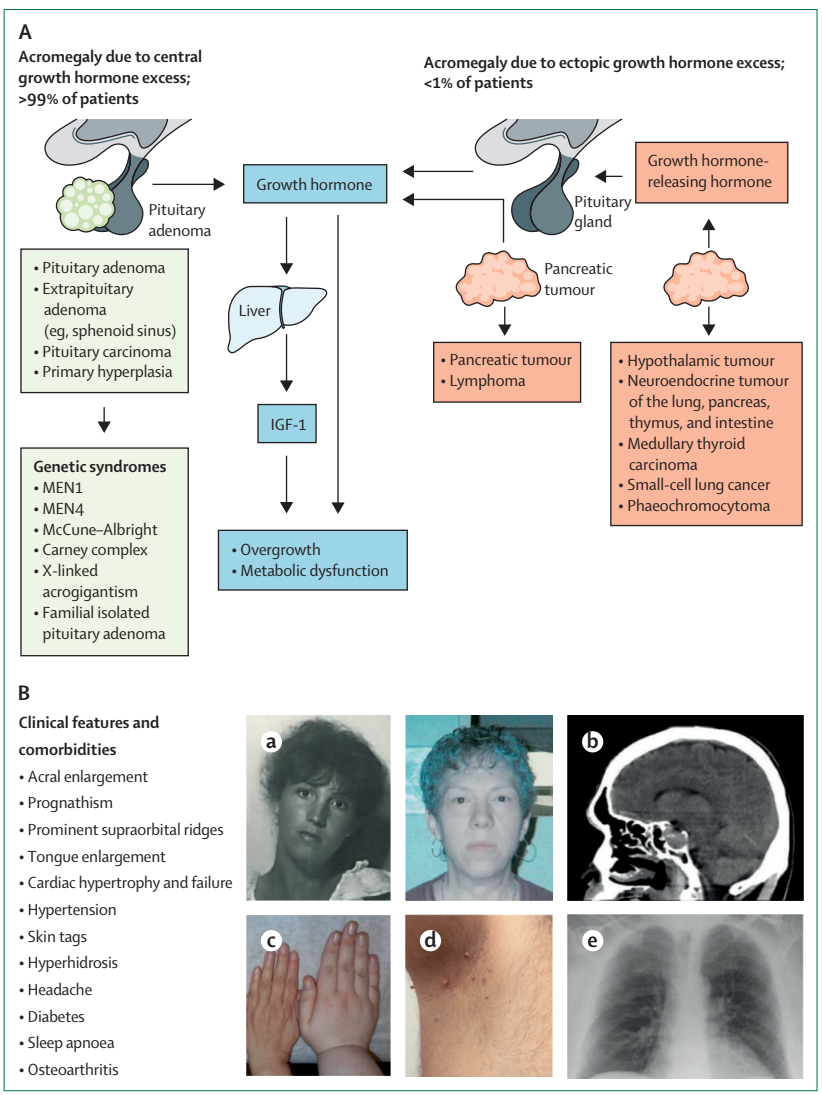


Figure 2: **Causes of acromegaly and clinical characteristics of acromegaly**
(A) Causes of acromegaly due to central (left) and ectopic (right) growth hormone excess. (B) Clinical features and comorbidities common in patients with acromegaly, with further examples in pictures: (a) changes in facial features due to uncontrolled growth hormone excess between early adulthood (left picture) and more than 20 years later, after delayed diagnosis (right picture); (b) CT scan showing prominent supraorbital ridges and pituitary macroadenoma; (c) hand of a patient with acromegaly compared with the hand of a physician; (d) skin tags; and (e) chest x-ray showing enlarged heart.

in serum and absence of growth hormone suppression after glucose load during an OGTT.[4,44] Random measurement of growth hormone concentrations in isolation is not helpful by itself, because of pulsatile growth hormone production and variations in response to physiological and non-physiological factors. The OGTT reflects a physiological mechanism of growth hormone suppression via the inhibition of GHRH or the induction of somatostatin release, or both, in response to 75 g glucose load and provides an accurate measure of non-physiological growth hormone secretion.

IGF-1 is produced mainly in the liver and has a half-life of 15 h, unlike growth hormone, which has

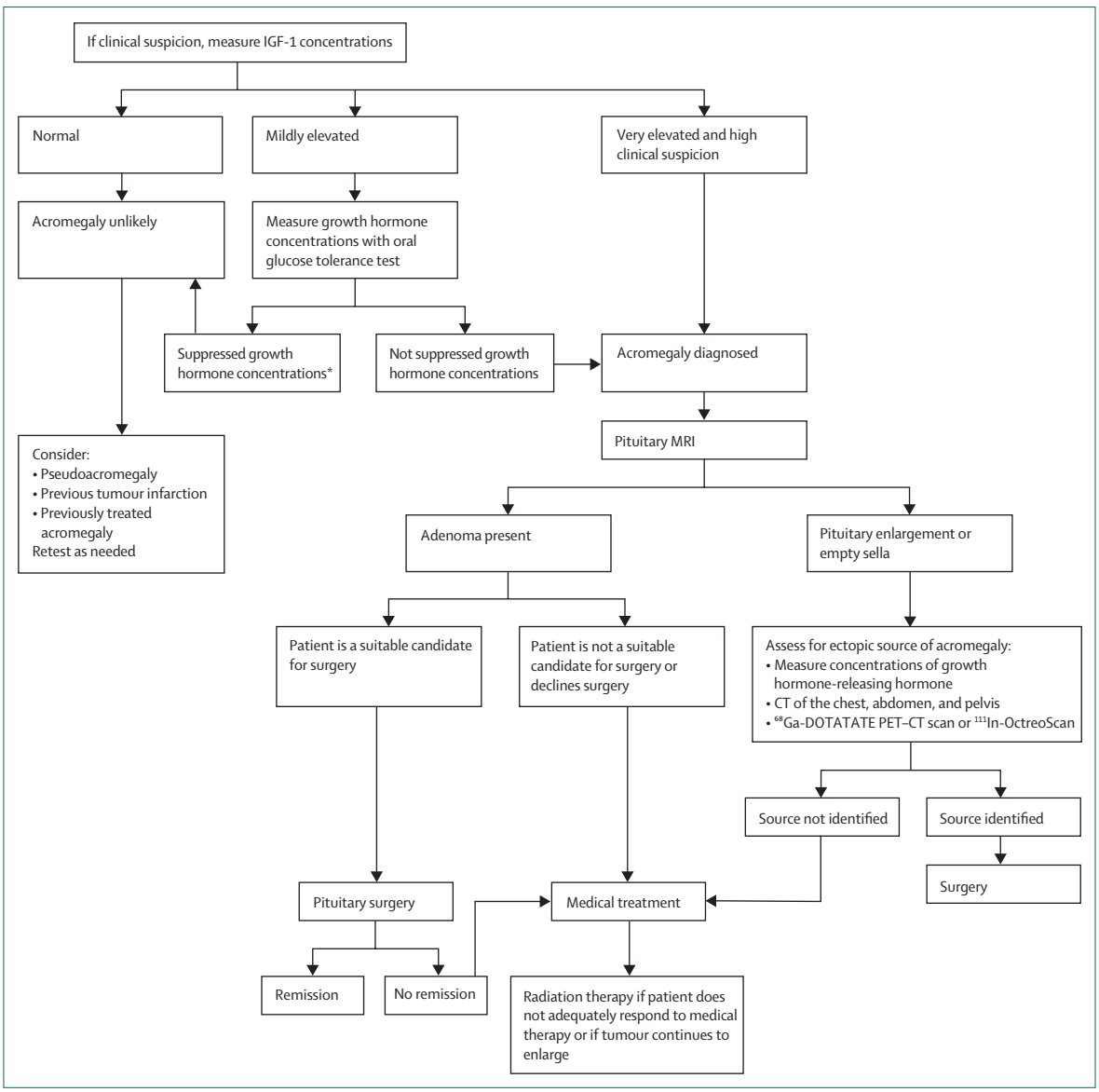


Figure 3: **Algorithm for acromegaly diagnosis and management**
IGF=insulin-like growth factor. *Up to 30% of patients with growth hormone excess might not show growth hormone suppression in response to oral glucose tolerance test.

a variable secretion pattern and a much shorter half-life (approximately 14 min;[45] appendix p 5).[44] Normal (age-specific and sex-specific) IGF-1 concentrations are sufficient in most patients to exclude active acromegaly, whereas very high IGF-1 concentrations in patients with signs and symptoms of growth hormone excess establish the diagnosis (figure 3). However, mildly elevated IGF-1 concentrations should prompt confirmatory testing with OGTT to show absence of growth hormone suppression in response to a glucose load. Both IGF-1 and OGTT have diagnostic caveats, sometimes leading to challenges in diagnosing acromegaly.

Optimal interpretation of IGF-1 and growth hormone testing

IGF-1 concentrations in serum should be interpreted according to established age-specific and, where available, sex-specific reference ranges. Overall, IGF-1 concentrations are slightly lower in female individuals than in male individuals.[46] IGF-1 concentrations decline more rapidly in female individuals after puberty and are higher in male individuals later in life, possibly because of changes in female sex hormones due to menopause.[46] Importantly, reference ranges can differ, despite use of the same calibration standard for IGF-1 assay kits (WHO NIBSC 02/2547), and wide variability

in IGF-1 concentrations might be seen across different assays[47] because of both preanalytical and analytical conditions. Thus, borderline values might lie within or outside the reference range, depending on which assay is used. Inadequately established reference ranges and assay interference commonly lead to falsely elevated IGF-1 concentrations.[48–50]

Several physiological and external factors influence IGF-1 concentrations (table 1). Oral oestrogen and selective oestrogen receptor modulators reduce IGF-1 concentrations as do anorexia, malnutrition, liver and renal disease, uncontrolled diabetes, and acute illness. Higher IGF-1 concentrations are observed during pregnancy and late-stage adolescence, and with hyperthyroidism.[44,51]

A growth hormone nadir cutoff of less than 1 ng/mL on OGTT for acromegaly diagnosis was established before ultrasensitive growth hormone assays became available.[44,51] As more modern assays can now detect lower growth hormone concentrations, the revised suggested cutoff is 0·4–1·0 ng/mL, depending on the assay used.[52] Up to 28% of patients with mild acromegaly (typically microadenomas with baseline growth hormone concentrations of <4·3 ng/mL) had growth hormone concentrations less than 0·4 ng/mL on OGTT,[53] whereas healthy, lean individuals and female individuals taking oral oestrogen might not exhibit growth hormone concentrations less than 0·4 ng/mL.[54] If the diagnosis is unclear, retesting and symptom monitoring are necessary. Importantly, about 25–30% of patients exhibit a paradoxical increase in growth hormone after glucose load, which is potentially related to the release of glucose-dependent insulinotropic polypeptide (GIP) from duodenal K cells signalling through its receptors on the growth hormone-secreting adenoma.[55] Although clinical correlation has not been clearly established, paradoxical growth hormone response has been observed in patients with smaller adenomas and in those who show a greater reduction in IGF-1 concentrations after treatment with somatostatin receptor ligand (SRL).[55]

Imaging

Approximately 70% of somatotroph adenomas are macroadenomas at diagnosis and are readily detected on pituitary MRI.[14] Microadenomas are rarely missed by use of modern MRI techniques such as 3T MRI scans, high-resolution T2-weighted MRI, and dynamic MRI after administration of gadolinium-based contrast agent. Occasionally, patients might show an empty sella on imaging, due to previous pituitary apoplexy, treatment for pituitary adenoma, or, very rarely, ectopic growth hormone or GHRH-secreting adenoma.[41] Both pituitary hyperplasia caused by ectopic GHRH secretion and primary hyperplasia appear as a bulging pituitary gland.[42] Somatotroph adenomas can appear hypointense, isointense, or hyperintense on T2-weighted pituitary MRI (appendix p 7). T2-weighted signal intensity of pituitary adenomas has been associated with histological granulation pattern and SRL clinical response.[56,57]

	IGF-1	Growth hormone
Anorexia and malnutrition	Decrease	Increase
Liver and kidney disease	Decrease	Increase
Poorly controlled diabetes	Decrease	Increase
Critical illness (eg, sepsis or multiorgan failure)	Decrease	Increase
Use of oral oestrogen and selective oestrogen receptor modulators	Increase	Increase
Pregnancy	Increase	Increase
Late puberty	Increase	Increase
Use of parenteral testosterone	Increase	Increase
Age >60 years	Decrease	Decrease
Severe obesity	Decrease	Decrease
Assay inaccuracies (eg, assay interference or inappropriate reference ranges)	Might increase or decrease	Might increase or decrease

IGF=insulin-like growth factor.

Table 1: **Determinants of growth hormone and IGF-1 concentrations**

Rarely, postoperative MRI does not discriminate between residual or recurrent tumour and postoperative changes in the sellar region.[58] In such cases, [^{11}C]methionine ([^{11}C]MET)-PET or [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET in combination with volumetric or thin slice MRI can detect residual adenoma and guide further management, such as repeat surgery or radiation therapy. [^{11}C]MET-PET might have greater sensitivity than [^{18}F]FDG-PET to detect tumours not discernible on MRI,[58] but use of this technique is limited to specialised centres.

Complications: prevalent deleterious systemic effects of growth hormone

Because growth hormone and IGF-1 receptors are ubiquitously expressed, deleterious effects of both IGF-1 and growth hormone excess manifest in multiple organ systems (appendix p 6). Protracted exposures to high growth hormone concentrations before diagnosis amplify these adverse effects,[59] and patients with a diagnostic delay of more than 10 years have been reported to have twice the number of cardiovascular and musculoskeletal comorbidities and higher mortality than patients with shorter delay.[60]

Importantly, signs and symptoms of acromegaly and its associated complications all contribute to disease burden and have a deleterious effect on QoL.[52] Overall, patients with acromegaly have more comorbidities and take more medications than age-matched and sex-matched patients without acromegaly for all related comorbidities.[61] Thus, clinical screening, appropriate diagnosis, and individualised treatment for each

	Cardiovascular	Respiratory	Musculoskeletal	Metabolic and endocrine	Neurological	Neoplastic	Mass effects	Quality of life
Screen	Hypertension, hypertrophic cardiomyopathy, valvulopathy, systolic and diastolic dysfunction, and arrythmias	Obstructive and central sleep apnoea and respiratory insufficiency	Arthropathy, vertebral fractures, and jaw malocclusion	Diabetes or prediabetes, dyslipidaemia (elevated triglyceride and reduced high-density lipoprotein concentrations), hepatic steatosis, polycystic ovary syndrome or hyperandrogenism, and hyperprolactinaemia	Nerve entrapment and headache	Colorectal polyps, thyroid nodules, cancer (colon, breast, thyroid, and renal), and skin tags	Headache, hypopituitarism, and cranial nerve palsy	Negative body image or low self-esteem, cognitive dysfunction, psychological symptoms, pain or headache, treatment burden, and growth hormone deficiency
Test	Blood pressure, echocardiography, and electrocardiogram	Epworth Sleepiness scale and STOP-Bang score (both used for obstructive sleep apnoea), polysomnography, and pulmonary function test	Spine x-rays; dual-energy x-ray absorptiometry, and trabecular bone score; measurement of 25-hydroxy vitamin D concentrations, parathyroid hormone, calcium concentrations in urine, and bone markers if needed; and gonadal hormones	Fasting glucose and oral glucose tolerance test, HbA_{1c} measurement, lipid profile, measurement of alanine transaminase and aspartate transaminase, and prolactin measurement	Electromyography or nerve conduction studies	Colonoscopy, physical examination, and thyroid ultrasound (if palpable nodule)	MRI, visual field testing, and hormonal testing for pituitary deficiency	Quality of life and disease impact
Refer	Cardiologist	Pulmonologist	Bone endocrinologist, rheumatologist, orthopaedic surgeon, and maxillofacial surgeon	Diabetologist and hepatologist for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis	Neurologist	Oncologist, gastroenterologist, and dermatologist	Ophthalmologist, neurosurgeon, and radiation oncologist	Psychotherapist or counsellor, and psychiatrist
Treat	Repeat echocardiography according to general population guidelines and treat with antihypertensive drugs (diuretics, β-blockers)	Continuous positive airway pressure, mouth guard, and uvulopalatoplasty	Intake of calcium and vitamin D, sex hormone replacement therapy, anti-osteoporotic therapy, pain management, joint injections, and joint replacement; avoid over-replacement of glucocorticoids	Metformin, incretin-based therapy, insulin secretagogues, insulin, statins, and monitoring for weight gain after treatment for growth hormone excess	Headache management and octreotide subcutaneous injection if needed	Specific to the disease; follow-up colonoscopy according to general guidelines, unless IGF-1 concentrations are elevated; and fine-needle aspiration for thyroid nodules according to general guidelines	Debulking surgery, radiation therapy, and hormonal replacement	Support groups, reliable educational resources, psychological support, cognitive–behavioural therapies, pain management, and growth hormone replacement for select patients with growth hormone deficiency

IGF=insulin-like growth factor.

Table 2: **Complications of acromegaly**

comorbidity should be an important goal as an adjunct to biochemical control to improve patient outcomes.[1–4,59]

Frequent complications and suggested screening and management strategies are depicted in table 2. Differences in prevalence probably relate to screening procedures, which differ among countries and treating centres.[17,18]

Cardiovascular complications

Cardiovascular disease is present in more than 50% of patients with acromegaly.[13,62] In a large US database study, two-thirds of patients with acromegaly had cardiovascular disease, 40% more than age-matched and sex-matched controls.[61] Cardiovascular complications might triple the risk for admission to hospital for patients with acromegaly and significantly increase annual medical expenses.[63]

Hypertension affects 18–55% of patients, probably mediated by direct kidney growth hormone action. Activation of the epithelial sodium channel and the renin–angiotensin–aldosterone system by growth hormone and IGF-1 increases sodium and water reabsorption;[59,64] IGF-1 also decreases vascular resistance, leading to systolic hypertension with an increase in pulse pressure.[59,65] Risk of hypertension is similar between

individuals with discordant growth hormone and IGF-1 concentration values and individuals considered in remission based on both normal concentrations of growth hormone and IGF-1.[66] In a large observational study including more than 2000 patients treated with pegvisomant, a growth hormone receptor antagonist, cardiovascular disease (p<0·0001) and anterior pituitary deficiencies (p=0·0105) independently predicted mortality in patients with acromegaly who had hypertension.[62]

Hypertrophic cardiomyopathy, including earlier concentric cardiac remodelling, is due to both hypertrophy of myocardial cells and volume overload and is observed in 13–79% of patients on echocardiogram;[13,59,67] however, use of cardiac MRI can result in a much lower frequency (down from 31% to 5%).[67] Hypertrophy (usually biventricular concentric hypertrophy) might be partly reversed in some patients by achieving biochemical control.[52] Diastolic dysfunction is noted in approximately 45% of patients on echocardiography, usually with preserved ejection fraction.[59] Congestive heart failure is rare (<3%) and usually not reversible, even with biochemical control.[68–70] In a large meta-analysis of patients receiving injectable SRLs, individuals with the largest reduction in concentrations of IGF-1 or growth hormone, or both, and younger patients (aged <45 years) showed a decrease in left ventricular mass but did not have a reduced risk of hypertension.[71]

Risk is not necessarily elevated for all types of coronary and cerebrovascular diseases.[59] Stroke risk might be increased in patients who undergo conventional radiotherapy or those with uncontrolled hypertension.[72] A large study showed no increased risk of myocardial infarction in patients with acromegaly.[73] In a prospective cohort, coronary artery calcium content estimated by use of the Agatston score did not offer additional risk stratification.[59]

Arrhythmias, such as atrial fibrillation, are rarely observed and usually occur in individuals with uncontrolled acromegaly, along with structural cardiac changes including atrial dilatation and fibrosis.[59,74] Moderate-to-severe valvular dysfunction is also present in 15–30% of patients;[59,70] aortic regurgitation is the most frequent valvulopathy, occurring in approximately 20–30% of patients,[59,70] possibly related to aortic root dilatation, followed by mitral regurgitation.[70] Acromegaly duration is an independent risk factor for valvular disease. In patients with a long disease history (>16 years), 20% had moderate or more severe mitral regurgitation.[59] Progression of valvular disease is associated with poor biochemical control,[75] and might be an important consideration in patients treated with high-dose cabergoline.[52]

Respiratory complications

Obstructive sleep apnoea is highly prevalent in people with acromegaly, occurring in 27–88% of patients, 7–10 times more frequently than in the general population.[76] Contributing factors include upper airway narrowing caused by macroglossia, swelling of the uvula and pharyngeal wall, and mandibular overgrowth. Central sleep apnoea is also present in up to 30% of patients.[77] Although treatment can induce regression of tissue hypertrophy and tongue volume, it might not suffice to alleviate obstructive sleep apnoea after biochemical control.[59,76] Moreover, growth hormone excess also increases residual lung volume, and leads to small airway obstruction and reduced diffusion capacity.[78] These features, in association with chest wall deformities, adversely affect exercise capacity and physical performance.[79]

Metabolic and body composition complications

Growth hormone and IGF-1 have opposite actions on glucose and lipid metabolism.[69] Growth hormone induces lipolysis and inhibits lipoprotein lipase, whereas IGF-1 increases free fatty acid uptake in adipocytes and hepatocytes.[1] IGF-1 belongs to the family that includes insulin and IGF-2. Each family member has a different affinity for the insulin and IGF receptors, probably explaining some actions of excess IGF-1 on glucose and lipid metabolism.

Growth hormone is a potent inhibitor of insulin receptor signalling, blocking insulin action, decreasing muscle glucose uptake, increasing lipolysis, and enabling an adverse adipokine profile.[80] Upregulation of phosphatase and tensin homolog (PTEN) and suppression of insulin signalling in both skeletal muscle and adipose tissue were found to lead to uncontrolled lipolysis.[81] Overall, growth hormone excess increases insulin resistance and might lead to hyperglycaemia and overt diabetes in approximately 30% of patients.[59,69] Preferred antidiabetic medications, when needed, include metformin and incretin-based agents.[52]

Hyperlipidaemia occurs in 13–80% of patients.[59,82] A typical lipid profile shows hypertriglyceridaemia, low amounts of high-density lipoprotein, and elevated concentrations of apolipoprotein B.[82] A small study reported hepatic steatosis in 66% of patients, of whom 45% had fibrosis.[83]

Uncontrolled acromegaly is characterised by lower mean intrahepatic lipid content than healthy controls matched for age, BMI, and sex.[84] Growth hormone excess also increases expression of proinflammatory cytokine in the adipose tissue,[85] thus exacerbating insulin resistance. Although biochemical control usually improves insulin resistance, one study showed an increase in intrahepatic lipid content and abdominal adiposity and a decrease in muscle mass.[84] Surgical adenoma resection might reverse the lipodystrophy pattern associated with acromegaly, but with differential effects in men and women, with men exhibiting a greater increase in visceral and subcutaneous fat.[86]

Patients with acromegaly and impaired glucose tolerance have increased risk of severe acromegaly cardiomyopathy[87] and patients with acromegaly and diabetes show an increase in Framingham Risk Score, suggesting higher prevalence of cardiovascular disease.[88]

Musculoskeletal complications

Joint pain is common, affecting more than 75% of patients,[59,69] and it is caused by a degenerative joint disease characterised by chondrocyte hypertrophy and osteophytosis. Although any joint might be affected, hip and spine are almost universally involved.[89] Biochemical control might help reduce cartilage thickness, especially in early arthropathy,[90,91] but degenerative disease persists and worsens over time despite normalisation of growth hormone and IGF-1.[92]

Bone disease associated with acromegaly is characterised by altered trabecular architecture and increased cortical bone, predisposing patients to vertebral fractures.[91] Growth hormone excess increases bone resorption, as shown by elevated serum concentrations of biochemical bone turnover markers (eg, C-telopeptide) and hypercalciuria, and further supported by histomorphometry.[59,64,91] Concomitant hypogonadism, diabetes, and differential expression of IGF-binding proteins contribute to the severity of bone disease.[91,93] Risk of vertebral fractures is 3–8 times higher in patients with acromegaly than in controls,[93] affecting approximately 40% of patients.[93] Hypogonadal male patients are at higher risk of vertebral fractures.[94] A higher prevalence of vertebral fractures in patients with acromegaly than in controls (p=0·001), even at diagnosis, suggests that vertebral fractures could be an early consequence of acromegaly directly related to modestly elevated growth hormone concentrations.[95]

Because fractures are frequently mild and asymptomatic, imaging screening for thoracic and lumbar spine fractures is preferred.[93] Notably, bone mineral density measured by use of dual-energy x-ray absorptiometry is often within the reference range (T score >–1 SD), especially at the spine, where the presence of osteophytes misleadingly increases density. The Fracture Risk Assessment Tool, which relies on bone mineral density assessments, is not reliable in assessing risk of vertebral fractures in patients with acromegaly.[96] A more useful measure might be the trabecular bone score as a low score value reflects disrupted and fracture-prone bone microarchitecture.[93] Biochemical control reduces but does not eliminate fracture risk, and 20% of patients show further decrease in vertebral height despite IGF-1 normalisation.[97] Previous vertebral fractures, disease duration, and active disease are among the most relevant factors contributing to skeletal fragility.[93]

Effects of growth hormone excess on muscle function are emerging. In uncontrolled acromegaly, both body cell mass and proximal muscle strength might increase, with reduced grip strength. Biochemical remission normalises body composition and improves hand grip strength, but increases proximal muscle fatigue.[98] Increased thigh muscle adiposity might also be linked to muscle dysfunction, specifically slower gait speed, and poorer performance on the 30 s chair stand.[99]

Neurological complications

Nerve compression as a result of soft tissue hypertrophy and bone overgrowth might cause peripheral neuropathy, including carpal tunnel syndrome, which is observed in 19–64% of patients.[59,100] Headaches, reported in two-thirds of patients, might be due to direct effect of growth hormone excess or due to mass effect of the adenoma from cavernous sinus invasion and irritation of the trigeminal nerve upon stretch of the dura.[101] Biochemical control improves headache in most patients. In addition to the long-term suppression of growth hormone excess, short-acting octreotide might relieve refractory headaches.[101]

Neoplasia

Growth hormone and IGF-1 promote cellular proliferation, potentially leading to carcinogenesis and tumour progression, as shown by in vitro and in vivo animal models.[59,102,103] Biochemical control of acromegaly in patients diagnosed with malignancy is important, because presence of a polyp at the first colonoscopy and uncontrolled acromegaly with persistently high IGF-1 concentrations have been shown to increase risk of new colonic neoplasia at a subsequent colonoscopic screening.[104] Furthermore, in a large retrospective epidemiological cohort study, mortality from all malignant disease and colon cancer was increased in patients with elevated growth hormone concentrations (>2·5 ng/mL) after surgical or medical treatment, but disease duration was not a determinant of cancer development.[105]

Nonetheless, reports are conflicting with regard to cancer incidence in patients with acromegaly.[106] Incidence of both benign and malignant tumours in patients is approximately twice as high than in people without acromegaly,[59] with a US claims database study of 1175 patients with acromegaly showing that the prevalence of malignant tumours in patients was 2·6 times higher than in matched controls.[61] A French registry study showed a non-significant increase in the standardised incidence ratio for incidental cancers, including colorectal cancers.[107] However, in a large Italian cohort, patients with acromegaly had higher incidence of colorectal, kidney, and thyroid cancer than the general Italian population.[108] In this study, multivariate analysis showed that age and family history of cancer were significant predictors of increased risk of cancer, whereas disease duration was not a significant factor.[108]

As colon polyps affect a third of patients,[109] screening colonoscopy is recommended for all patients at diagnosis,[52] with close attention to a distinctive increase

in colon length and hypertrophic mucosal folds.[1] If biochemical control is achieved, recommendations for follow-up colonoscopy are similar to those for the general population. A small exploratory study suggested a protective role of metformin on development of colon polyps.[110] Reported prevalence of thyroid nodules is increased if patients undergo ultrasound screening for thyroid cancer, but the utility of routine imaging has not been shown if no nodules are clinically palpable.[52] Indications for fine-needle aspiration are similar to those for the general population.[52]

Hypopituitarism

Tumour mass effect, hyperprolactinaemia, and direct effect of growth hormone and IGF-1 excess might lead to hypopituitarism; surgery, and especially radiation therapy, further increase risk.[4,59] Assessment for pituitary deficiency of the thyroid, adrenal, and gonadal axes, both at diagnosis and after treatment, is similar to that for other pituitary adenomas.[4,111]

Hypogonadism is present in up to 50% of patients at diagnosis,[112,113] whereas other pituitary deficiencies are rarer. Free testosterone has higher accuracy for diagnosing hypogonadism than does total testosterone because mildly low total testosterone might be normal if adjusted for sex hormone-binding globulin.[84] Even when dysfunction of the hypothalamic–pituitary–adrenal axis is present at diagnosis, recovery after tumour resection is more frequent in patients with acromegaly than in patients with non-functioning adenomas, independent of tumour size and cavernous sinus invasion;[114] frequent postoperative monitoring is therefore needed. Assessment for hypopituitarism is also recommended in patients on medication for growth hormone excess.[4,59,111]

Appropriate hormone replacement is paramount, as both central hypoadrenalism and supraphysiological glucocorticoid doses result in increased mortality in patients treated with radiation.[115] Because the growth hormone–IGF-1 axis also affects cortisol metabolism, glucocorticoid doses should be adjusted according to biochemical control of acromegaly. Untreated central hypothyroidism could increase risk of cardiovascular disease,[111] but over-replacement of thyroid hormone has detrimental effects on bone health,[93,111] which is already altered in patients with acromegaly.[93]

Infertility caused by hypopituitarism or hyperprolactinaemia, or both, is frequent,[25] and growth hormone and IGF-1 excess could inhibit secretion of gonadotropin-releasing hormone or induce polycystic ovary syndrome-like conditions.[112,116]

QoL

QoL is adversely affected in most patients (appendix p 8).[59,117] Major determinants include poor disease acceptance, notably related to frustrations regarding diagnostic delay, changes in facial features and other morphological characteristics leading to negative body image or low self-esteem, and social withdrawal. Prognathism and dental malocclusion can alter chewing functions. Pain related to neuropathy, arthropathy, and headaches is experienced in up to 80% of patients.[118] Increased BMI and depression also might contribute to decreased QoL.[59,119] 81% of patients reported fatigue and short-term memory loss when directly questioned.[120] Growth hormone deficiency induced by surgery or radiotherapy can also adversely affect QoL, and might require growth hormone replacement.[59] There is insufficient evidence that biochemical control in patients with acromegaly improves QoL, because several disease sequelae are irreversible, including skeletal changes and hypertension.

Formal and informal measures exist to assess QoL, either via disease-specific questionnaires such as the Acromegaly Quality of Life Questionnaire (AcroQoL) and the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ), or by informally asking questions about patients' physical and psychological aspects.[121] Overall, improving patient education, offering psychosocial interventions, and inquiring about QoL are important patient care needs.

Mortality: rates are decreasing and aetiology is changing

Mortality in patients with acromegaly is approximately two times higher than mortality in people without acromegaly.[1,122] Two meta-analyses, each comprising nearly 5000 patients and covering approximately 40 years, showed 1·7–2 times higher mortality in patients with acromegaly than in the general population, mainly because of cardiorespiratory causes.[123,124] Older age, supraphysiological replacement of glucocorticoids for adrenal insufficiency, hypogonadism, and history of conventional radiotherapy are associated with increased mortality risk.[59,125,126] However, the traditional method of reporting the last growth hormone measurement rather than calculated cumulative exposure to growth hormone concentrations or IGF-1 concentrations expressed as an IQR might have also inaccurately estimated mortality risk.[127]

With improved care, medical treatment, and management of risks factors, excess mortality risk has decreased,[52,128] and mortality associated with uncontrolled acromegaly is reversed with biochemical control;[128] mortality rates due to cardiovascular disease are now approaching those of the general population.[73,129] Cancer-related mortality is now higher than mortality associated with cardiovascular and respiratory complications of acromegaly, most likely due to increased longevity of acromegaly patients over the past few decades.[12,59,106,130]

Multimodal treatment: expert care is critical

Normalisation of age-adjusted IGF-1 concentrations and reduction of growth hormone concentrations to

Panel: **Predictive factors for incomplete or inadequate response to acromegaly treatment**

Surgery[23,143,144,146]
- Cavernous sinus invasion
- Wider tumour diameter
- Increased preoperative growth hormone concentrations
- Younger age (age varies by study)
- No consistent association between preoperative insulin-like growth factor (IGF-1) concentrations and postoperative remission

Lanreotide or octreotide[56,147–149]
- Sparsely granulated immunohistochemistry pattern and low expression of somatostatin receptor 2
- Age <40 years
- Germline *AIP* mutation (for select patients with familial acromegaly)
- Hyperintensity on T2-weighted pituitary MRI

Pegvisomant[19,150–154]
- Younger age (age varies by study) with aggressive disease
- Increased baseline IGF-1 concentrations
- Increased weight or obesity (increased doses are usually required)
- Female sex (increased doses are usually required)

<1·0 ng/mL (or <0·4 ng/mL with ultrasensitive assays) is the primary therapeutic aim because it is associated with long-term, positive health outcomes.[44,52] Additional treatment goals include tumour shrinkage, relieving symptoms, managing complications, reducing excess morbidity, and improving QoL.[131] A multimodal approach is required to optimally achieve these goals (figure 3).[52]

Surgical resection of the adenoma is the first-line approach for most patients,[44] and it might potentially lead to immediate cure or remission, especially for microadenomas. Even when cure is not possible, debulking surgery results in a rapid growth hormone decline and increases the effectiveness of adjuvant medication.[52,132] Medical treatment is indicated mostly for persistent disease after surgery, whereas radiotherapy is typically reserved as a third-line option in patients who do not respond adequately to medical therapy, or have a large, invasive or expanding tumour remnant.[44,131] Primary medical therapy is increasingly being used in many countries and could play a role in patients who are unlikely to achieve surgical cure.[44,52]

Surgery

Surgical remission is usually achieved in 75–90% of patients with microadenomas and 40–60% of patients with macroadenomas,[133] with higher remission rates reported in specialised high-volume centres. Although a transsphenoidal approach is used in most patients, a transcranial approach might be required for giant extrasellar tumours. Overall, remission rates with endoscopic techniques seem slightly superior to those with microscopic techniques. However, endoscopy might be preferred when a wider field of view facilitates complete macroadenoma excision, especially of those that extend laterally towards the cavernous sinus,[134–136] and better gross total resection outcomes are observed after endoscopic surgery.[137,138] Reported complications are similar after microscopic and endoscopic surgeries, of which cerebrospinal fluid leak (2–3% of patients), hypopituitarism (6–7%), and transient diabetes insipidus (8–9%) are the most common.[134] In a systematic review, initial remission rates of macroadenomas were 46·9% for microscopic and 60·0% for endoscopic surgery, whereas long-term remission rates were 40·2% for microscopic and 61·5% for endoscopic approaches.[134] Although direct comparative studies are scarce, surgical experience remains the main determinant of success.[139,140] Intraoperative MRI might guide the extent of tumour resection, but an MRI-guided complete resection is not equivalent to biochemical remission and is not used routinely in clinical practice.[52,139]

Debulking pituitary surgery for macroadenomas might improve overall outcomes.[141] In a multicentre randomised study,[141] patients who had debulking surgery followed by treatment with SRLs showed higher biochemical control rates after surgery and higher response rates to SRLs than did those treated with octreotide long-acting release (LAR; 30 mg every 4 weeks for 3 months) as primary medical therapy.

Reoperation might also be useful in patients who did not achieve biochemical control despite medical therapy or who have evidence of new tumour growth. However, although a large meta-analysis found that biochemical control rates were similar after reoperation and first-line surgery in patients with microadenomas, reoperation was associated with much lower biochemical control rates for macroadenomas (27·5% *vs* 54·3%) and tumours invading the cavernous sinus (14·7% *vs* 38·5%) than first-line surgery.[142]

Predictive response factors and postoperative assessments

Postoperative remission rates vary widely because of differences in study design, patient population, and definition of biochemical response. Determinants most consistently associated with inadequate surgical response include cavernous sinus invasion, maximal tumour diameter, and high preoperative growth hormone concentrations.[143,144] Lower remission rates are observed in patients with invasive macroadenomas (30–50%) than in patients with non-invasive macroadenomas (70–80%),[133,145] and in patients with radiological Knosp grades 3–4 than in patients with Knosp grades 0–2.[144,146] Presence of extrasellar, suprasellar, or parasellar extension and destruction of the sellar floor might also predict lower remission rates. Remission rates of 86–100% have been reported with preoperative growth

hormone concentrations of 1·5–20 ng/mL and less than 30% for growth hormone concentrations higher than 26–50 ng/mL.[144] In some, but not all studies, younger age has been suggested as an adverse predictor of remission, although age cutoff varies by study (panel).[23,144] Machine-based learning might prove a useful tool for tailoring surgical therapy.[155]

Both random and nadir postoperative growth hormone concentrations during OGTT are associated with long-term remission, although the concentration threshold and optimal timing of growth hormone measurement, ranging from several hours to 7 days postoperative, remain unknown.[156–159] Nadir growth hormone concentrations of less than 0·4 ng/mL 1 week postoperatively showed a positive predictive value higher than 95% for surgical remission,[156] whereas random growth hormone concentration thresholds of 0·9–5·0 ng/mL predicted remission with sensitivity rates of 65–97% and specificity of 77–93%.[144,160]

Preoperative medical therapy is not routinely recommended to improve postoperative remission rates.[44,52,161] Results with this approach are conflicting, with no proven benefit for either early or long-term postoperative remission rates.[162,163] Patients with invasive adenomas, especially in the cavernous sinus (ie, Knosp grade 3), might selectively benefit from preoperative medical treatment, but further evidence is required.[164]

Medical therapy

Medical therapy is indicated in patients with persistent growth hormone hypersecretion after surgery. Primary medical therapy is typically reserved for patients with contraindications to, or who refuse, surgery, although its use has been increasing.[44,52,131] Medical therapies currently available for treatment of acromegaly are summarised in table 3 and agents being investigated in late-stage clinical trials are listed in the appendix (p 3).

Pituitary directed therapy: dopamine agonists and SRLs

Cabergoline, acting on dopamine-2 receptors, has low effectiveness as monotherapy for growth hormone excess.[165] The relatively low cost and oral route of administration are advantages, but wide variations exist in tumour sensitivity to dopamine agonists, and effectiveness is lost over time,[165] thus requiring higher doses with associated increased side-effects. Use of cabergoline as first-line treatment is limited to patients with IGF-1 concentrations less than 1·5–2 times the upper limit of normal.[44,52,131] Dopamine agonists are also used to decrease prolactin concentrations due to adenomas that secrete both growth hormone and prolactin or due to a pituitary stalk effect.

SRLs are available as short-acting (subcutaneous octreotide) or long-acting depot injections (octreotide LAR, lanreotide, and pasireotide LAR), or as an oral formulation (oral octreotide capsules), and they act by signalling through SST receptors to suppress growth hormone secretion and control somatotroph proliferation. Generic versions for both octreotide and lanreotide are available in some countries. SRLs in clinical development are listed in the appendix (p 3).

Lanreotide and octreotide LAR are given once-monthly in most patients, frequently as first-line treatment; effectiveness of both drugs is similar,[3,166] with IGF-1 and growth hormone normalisation achieved in 30–55% of patients,[167,168] and tumour volume reduction higher than 20% achieved in 30–40% of patients. Dose escalation provides additional biochemical control if patients are inadequately controlled, without compromising tolerability.[169,170] Conversely, biochemical control might persist when the interval between lanreotide injections is extended from 4 weeks to 6–8 weeks.[171] Oral octreotide capsules at doses of 40–80 mg/day have been approved for use in the USA. In phase 3 trials, biochemical efficacy persisted in patients switched from injectable SRLs to oral octreotide capsules[172,173] and IGF-1 normalisation was achieved in nearly 60% of patients.[173] The treatment effect does not appear to be dependent on previous injectable SRL dose. When compared head-to-head, maintenance of biochemical control was similar in patients receiving either injectable SRLs or oral octreotide capsules and previously controlled with both therapies.[174] Oral octreotide capsules might be preferred in patients treated with injectable SRL who have breakthrough acromegaly symptoms occurring towards the end of the injection cycle,[172] and use of this agent relieves the burden of monthly injections, potentially increasing treatment satisfaction and QoL for some patients.[174]

In clinical trials, pasireotide LAR is more effective in reducing IGF-1 concentrations than octreotide LAR.[175] Approximately 20% of patients inadequately responding to treatment with either octreotide LAR or lanreotide attained biochemical control and potentially greater tumour volume reduction after switching to pasireotide LAR, with effectiveness observed beyond 5 years.[176–179] The drug is typically used as second-line therapy in patients inadequately controlled despite receiving maximum doses of either octreotide or lanreotide, but it could be considered as first-line therapy in some patients (eg, young patients with fewer metabolic risk factors and patients with large adenomas of concern). Some, but not all, retrospective studies have shown that differential expression of SST2, SST5, SST2/SST5 ratio, AIP, ZAC1, filamin-A, β-arrestin, and E-cadherin could play a role as predictors of SRL response.[147–149,180,181] Germline *AIP* mutations might be associated with attenuated sensitivity to SRLs.[182] Treatment selection might in the future be guided by machine-learning techniques.[183,184]

Safety profile is an important consideration in choice of therapy. Unlike other SRLs, pasireotide LAR is associated with greater frequency and degree of hyperglycaemia-related adverse events.[59,178,185] In a study

	IGF-1 normalisation	Tumour volume reduction (>20%)	Positive response predictors and caveats for use	Selected adverse effects	QoL considerations	Treatment algorithm positioning
Surgery						
Transsphenoidal (endoscopic or microscopic) and transcranial (rarely)	In 75–90% of patients with microadenoma and in 40–60% of patients with macroadenoma	Complete excision or debulking of tumour mass if there is a persistent remnant	Absence of cavernous sinus invasion, reduced maximal tumour diameter, reduced preoperative growth hormone concentrations, and low immediate postoperative growth hormone concentrations	Cerebrospinal fluid leak (2–3% of patients), transient diabetes insipidus (8–9%), and hypopituitarism (6–7%)	Improvement after surgery	First-line therapy in many patients
SRL						
Octreotide (50 µg subcutaneous injection, three times daily), octreotide LAR (10–40 mg intramuscular injection every 4 weeks), and lanreotide (60–120 mg deep subcutaneous injection every 4–8 weeks)	In 30–55% of patients when used as adjuvant medical therapy, and in fewer patients when used as primary medical therapy (estimates vary depending on study)	In up to 50% of patients	Densely granulated adenomas, high SST2 expression, hypointensity on T2-weighted MRI, age >40 years, and absence of *AIP* mutations	Nausea, diarrhoea, gallstones, modest hyperglycaemia, and injection site reactions	End-of-cycle symptoms (approximately 50% of patients), moderate AcroTSQ scores despite biochemical control, and potential injection burden	First-line postoperative medical therapy in most patients and primary medical therapy in patients who are not suitable candidates for surgery or not willing to have surgery
Oral octreotide capsules (40–80 mg/day)	Maintenance of biochemical control in 60–70% of patients switched from treatment with OCT/LAN; if controlled, normalisation persists in the long term	Unknown	Same as injectable OCT/LAN	Nausea, diarrhoea, gallstones, and modest hyperglycaemia	Acromegaly symptoms and QoL improvement	Patients controlled on injectable OCT/LAN who have injection-related treatment burden
Pasireotide LAR (40–60 mg intramuscular injection every 4 weeks)	In approximately 20% of patients who are resistant to treatment with OCT/LAN	In approximately 50% of patients, similar to treatment with OCT/LAN in medically naive patients; and in 11–20% of patients who are resistant to treatment with OCT/LAN	Better response than treatment with OCT/LAN if expression of SST2 and SST5 is high, if adenoma appears hyperintense on T2-weighted MRI, or if adenoma is sparsely granulated	Nausea, diarrhoea, gallstones, and injection site reactions; in patients switched to pasireotide LAR, new-onset hyperglycaemia (42% of patients), and new-onset diabetes (24% of patients); in patients naive to medical therapy, hyperglycaemia-related adverse events were more common with pasireotide LAR (57% of patients) than with octreotide LAR (22% of patients)	Improved AcroQoL global and especially physical domains and reduced fatigue and headache	Second-line or third-line medical therapy in most patients, but first-line in select patients with predicted resistance to OCT/LAN, tumour growth or headache not responsive to OCT/LAN, or non-response or intolerance to pegvisomant or OCT/LAN–pegvisomant combination
Dopamine agonist						
Cabergoline (up to 2·5–5 mg/week oral administration)	In 30–40% of patients but with subsequent loss of effectiveness	Unknown	IGF-1 concentrations less than 1·5–2 times the upper limit of normal; and baseline concentrations of serum prolactin or positive immunohistochemistry expression of prolactin and D2R that is inconsistent with response to treatment	Postural dizziness and gastrointestinal intolerance	Oral formulation and relatively inexpensive	IGF-1 concentrations less than 1·5–2 times the upper limit of normal (most experts suggest <1·5)
Growth hormone receptor antagonist						
Pegvisomant (10–30 mg/day, up to 40 mg/day, subcutaneous injection)	In approximately 90% of patients treated in clinical trials and in 60–70% of patients treated in real-world settings	Stable tumour volume in approximately 70% of patients and tumour volume increase in approximately 3–7% of patients	Increased doses required in patients with obesity, in patients with elevated IGF-1 concentrations at baseline, and in younger patients (age varies by study)	Transient aminotransferase elevation more than three times the upper limit of normal (3% of patients) and lipodystrophy at the injection site (2% of patients)	Improved scores on AcroQoL and PASQ	Second-line medical therapy in most patients and first-line medical therapy in select patients with predicted resistance to treatment with OCT/LAN and no tumour concern

(Table 3 continues on next page)

	IGF-1 normalisation	Tumour volume reduction (>20%)	Positive response predictors and caveats for use	Selected adverse effects	QoL considerations	Treatment algorithm positioning
(Continued from previous page)						
Combination medical therapy						
SRL–pegvisomant	In 60–90% of patients; monthly treatment with OCT/LAN plus weekly or bi-weekly pegvisomant has high efficacy and is cost-effective; 50% pegvisomant-sparing effect in patients controlled on combined OCT/LAN–pegvisomant	In 13–19% of patients treated with combined OCT/LAN–pegvisomant; data on treatment with combined pasireotide LAR–pegvisomant are scarce	Similar to individual drugs	For treatment with combined OCT/LAN–pegvisomant, adverse effects are similar to those associated with individual drugs and aminotransferase concentrations might increase transiently; for treatment with combined pasireotide LAR–pegvisomant, there is a 70–80% incidence of hyperglycaemia in patients who switched from treatment with combined OCT/LAN–pegvisomant to monotherapy with pasireotide LAR or to therapy with combined pasireotide LAR–pegvisomant	Improvement in QoL in patients with persistent symptoms and biochemical control, and a cost-effective option enabling pegvisomant dose reductions	Treatment with combined OCT/LAN–pegvisomant is favoured if tumour volume is large, patient has headache, control on SRL is inadequate, or diabetes is inadequately controlled with SRL or pegvisomant monotherapy; treatment with combined pasireotide LAR–pegvisomant is often third-line medical therapy and is favoured if symptoms are relieved with SRL but patient is inadequately controlled on OCT/LAN–pegvisomant, if large tumour volume is non-responsive to OCT/LAN–pegvisomant, or if patient does not have diabetes
SRL–cabergoline	In 30–40% of patients	Scarce data available	IGF-1 concentrations less than two times the upper limit of normal	Similar to individual drugs	Unknown	Mildly elevated IGF-1 concentrations on SRL monotherapy
Cabergoline–pegvisomant	In 28–68% of patients (based on scarce data available)	Scarce data available	Unknown	Similar to individual drugs	Unknown	Rarely used
Radiation therapy						
Stereotactic (usually single-fraction)	In 50–60% of patients at 5 years, increasing to 80% at 10 years	Tumour growth arrest in >90% of patients	Unknown	New hypopituitarism in 17% of patients who received single-fraction stereotactic radiotherapy and in up to 50% of patients treated with fractionated radiotherapy, new visual deficits (<3% of patients), secondary malignancies, and neurocognitive deficits (rare)	Decreased QoL, mostly if associated with growth hormone deficiency	Third-line therapy if tumour growth is persistent or if disease is refractory to maximum dose of medical therapy; radiation therapy might be considered earlier in patients with poor medication access

Most frequently used doses and schedules are shown. AcroQoL=Acromegaly Quality of Life Questionnaire. AcroTSQ=Acromegaly Treatment Satisfaction Questionnaire. IGF=insulin-like growth factor. LAR=long-acting release. OCT/LAN=octreotide or lanreotide. PASQ=Patient-Assessed Acromegaly Symptom Questionnaire. QoL=quality of life. SRL=somatostatin receptor ligand. SST=somatostatin.

Table 3: **Summary of treatments available for acromegaly: surgery, medications, and radiation therapy**

of patients naive to medical therapy, hyperglycaemia-related adverse events were more common in those treated with pasireotide LAR (57·3%) than with octreotide LAR (21·7%);[175] in another study of patients who switched to pasireotide LAR from octreotide LAR or lanreotide, new-onset hyperglycaemia was observed in 42% of patients and diabetes in 24% of patients.[186] Baseline glycaemic control is an important predictor of development of hyperglycaemia-related adverse events;[59,187–189] therefore, baseline glycaemic assessment and proactive monitoring for adverse effects is advocated, especially in the first 3 months of therapy or with dose escalation.[179,190,191] Younger patients (aged <40 years) and those without hypertension or dyslipidaemia have more favourable glycaemic responses to pasireotide LAR.[189] Metformin alone or in combination with other glucose-lowering agents might be required.

Treatment with SRLs should be initiated for most patients with persistent disease, with responses

assessed typically after 3–4 months. Timing of IGF-1 measurement relative to injection cycle is also important, as measurement closest to the injection is the least predictive of biochemical control.[192] Partial resistance is observed in approximately 50% of patients receiving either octreotide or lanreotide and complete resistance (ie, growth hormone and IGF-1 reduction <20%) is observed in 10% of patients.[183,193] Definitions of resistance vary, but they should include biochemical resistance (elevated growth hormone and IGF-1 concentrations) and tumour resistance, evidenced by an increase in tumour size (either by volume or longest diameter) or a decrease less than 20% compared with baseline measurements after at least 12 months of treatment.[193] However, few response predictors that are clinically relevant have been established so far (panel).[56,147–149]

Growth hormone receptor antagonist

Pegvisomant is a PEGylated recombinant growth hormone analogue that competitively blocks growth hormone receptor signalling, resulting in reduced IGF-1 production.[44,52,131] Although more than 90% of patients receiving monotherapy in clinical trials achieved biochemical control,[194] reported efficacy was 66% at 5 years and more than 70% at 10 years in real-world surveillance studies.[195,196] Pituitary adenoma remained stable in most patients, and transient aminotransferase elevation of more than 3 times the upper limit of normal has been reported in 3% of patients.[196] Adequate uptitration is required for biochemical control.[196] When used as a second-line monotherapy, weight, age, and baseline IGF-1 concentrations are favourable response predictors (panel).[19,150–154]

In contrast to the effect of either octreotide or lanreotide on glycaemic control, which is overall proportional to growth hormone and IGF-1 reduction,[197] pegvisomant improves fasting glucose, glucose tolerance, and HbA_{1c} concentrations independent of disease control. Long-term use induces visceral and subcutaneous fat mass increases, with injection site lipohypertrophy observed in 2% of patients.[198,199]

Therefore, in select patients with predictors of resistance to either octreotide or lanreotide and in patients with small residual adenomas or pre-existing diabetes, or both, pegvisomant might be considered as first-line medical therapy.[183,200]

Combination therapy

In a large single-centre study, SRL–pegvisomant combination led to IGF-1 normalisation at any point in 97% of patients,[201] whereas other surveillance studies reported end-of-study efficacy of 60–70%.[202–204] Substantial tumour volume reduction of more than 20% has been reported in 13–19% of patients.[201] Combination treatment is preferred in patients with large tumour volumes or persistent headache,[205] or in patients who require further treatment to maintain biochemical control but have good symptom control while taking SRL. SRL might worsen glycaemia whereas pegvisomant might improve it; therefore, SRL–pegvisomant combination might have a neutral effect on glycaemic control, benefiting patients with diabetes who are inadequately controlled on either SRL or pegvisomant as monotherapy,[198,202] and it allows for pegvisomant dose reduction.[203,204] Low-dose lanreotide (60 mg) or octreotide LAR (10 mg) combined with weekly pegvisomant (40–160 mg) is cost-effective, with more than 95% of patients achieving biochemical control.[206]

A pegvisomant-sparing effect is also observed with pasireotide LAR–pegvisomant combination. In patients who achieved biochemical control with octreotide LAR or lanreotide plus pegvisomant, switching to pasireotide LAR–pegvisomant allowed for pegvisomant dose reduction of 66% at 24 weeks and 52% at 48 weeks.[187,188] Patients with higher pituitary T2 signal intensity achieved more favourable IGF-1 responses.[207] Case series show the potential of pasireotide LAR–pegvisomant combination for managing giant, invasive, treatment-resistant tumours. Hyperglycaemia remains the main limitation of treatment with pasireotide LAR–pegvisomant combination.[188,208] Diabetes incidence doubled in patients switched from treatment with octreotide LAR or lanreotide plus pegvisomant to treatment with combined pasireotide LAR–pegvisomant, and it increased to more than 75% of patients at 48 weeks of treatment.[187,188] This combination seems most suitable for patients with normoglycaemia who have either persistent tumour growth or acromegaly symptoms while on other treatment regimens.[190,191]

Adding cabergoline to either octreotide or lanreotide to reduce IGF-1 concentrations is limited to patients with mildly elevated IGF-1 concentrations (<2 times the upper limit of normal).[165] Fully oral combination of oral octreotide capsules and cabergoline is an attractive option for reducing treatment burden, but further studies are needed.[174] Data on cabergoline–pegvisomant combination are scarce, with a prospective trial showing greater efficacy of combination therapy than either drug as monotherapy.[209]

Oral oestrogen in women[210] and clomiphene in men[211] (which are rarely used) in addition to SRL could further decrease IGF-1 concentrations in select patients, but long-term safety should be considered. These combinations could offer cost-saving benefits. Temozolomide in combination with SRLs in aggressive tumours has also rarely been used.[52]

Primary medical therapy

In select patients, primary medical therapy can be considered, with the goals of long-term tumour growth control and growth hormone and IGF-1 normalisation

without surgery.[4,131] Biochemical control in patients receiving primary therapy is, overall, lower than in patients treated with surgery before adjuvant medical therapy,[212] and rates of tumour volume control might also be reduced. Among 90 patients treated with lanreotide (120 mg), 63% of patients achieved more than 20% reduction in tumour volume by week 48,[213] and normalisation of IGF-1 was achieved in 50% of patients at week 48, with female sex, increasing age, and lower baseline IGF-1 concentrations increasing the likelihood of biochemical control.[214] Growth hormone and IGF-1, but not tumour response at 12 weeks, was associated with a higher likelihood of biochemical control and a clinically significant tumour reduction at last study visit.[214]

Radiation therapy

Radiotherapy is reserved generally for third-line treatment of patients with persistent disease or tumour growth despite surgery and medical therapy, or for patients who are not suitable candidates for surgery.[44,52] Stereotactic radiotherapy, either delivered in a single fraction or fractionated, is increasingly replacing conventional radiotherapy.[215] Tumour growth arrest is usually observed,[216] with biochemical control achieved in 50–60% of patients, and increasing over time; full response might not be observed for 5–10 years.[216–218] In a large cohort study, the 10-year remission rate was 52% in patients who received single-fraction stereotactic radiotherapy and 48% in patients treated with fractionated radiotherapy, and mean time to IGF-1 normalisation was approximately 2 years for single-fraction stereotactic radiotherapy and 3 years for fractionated radiotherapy.[219] In a large random effects meta-analysis, crude tumour control rate was estimated at 97% and crude endocrine remission rate at 44%, with no association with margin dose.[215]

The most common adverse effect is hypopituitarism, which also increases over time; nearly 30% of patients treated with single-fraction stereotactic radiotherapy and at least 50% of patients with conventional radiotherapy develop hypopituitarism within 10 years of treatment, and therefore lifelong monitoring of pituitary function is required.[44,52,217] Other rare side-effects include visual impairment, radiation-associated secondary intracranial tumours and malignancies (eg, meningioma, glioma, or sarcoma), and neurocognitive deficits. Single-fraction stereotactic radiotherapy does not appear to increase risk of cerebrovascular damage,[220] but it is yet unknown whether it confers a mortality advantage over conventional radiotherapy.

Assessing improvements in QoL: integrating treatment and patient-reported outcomes into the clinic

Instruments developed to specifically assess patients' symptoms and quality of life include AcroQoL and PASQ, which assess physical and psychological symptoms, and the Acromegaly Treatment Satisfaction Questionnaire (AcroTSQ), which is specific to monthly injectable SRLs (appendix p 8).[221] Surgery improves QoL, especially if postoperative remission is achieved.[222] Although both symptoms and QoL improve with treatment,[223] biochemical disease control per se is not directly associated with better patient-reported outcomes.[224]

Pegvisomant improves QoL,[225] and patients with diabetes especially reported improvement over time, regardless of IGF-1 control, as assessed by use of PASQ.[224] SRL–pegvisomant combination can improve QoL in both uncontrolled and controlled patients but symptomatology might persist.[225] Increased HbA_{1c} concentrations and BMI are associated with reduced QoL in some subject area domains.[226]

In addition to biochemical control, treatment effects on glycaemic control and weight need to be considered when tailoring personalised therapy. Several studies suggest that weight and diabetes might be important determinants of QoL. Because some symptoms and complications persist despite biochemical control, further elucidation of which aspects more greatly affect QoL is needed.

Monitoring and clinical goals

Close biochemical, imaging, and clinical monitoring for acromegaly (figure 2) and its complications (table 2) are needed for patients with this rare and challenging disorder, preferably by a multidisciplinary team. Biochemical normalisation of both growth hormone and IGF-1 is an important goal. However, a third of patients could have discordant growth hormone and IGF-1 concentrations.[44,52] Optimal management of hypopituitarism also remains paramount.[59,111] Patients might require corrective cosmetic or functional surgery; moderated patient support groups, educational materials, and counselling have been shown to be helpful in addressing decreased QoL.

Disease activity and outcome can be assessed by clinician-reported instruments including the Acromegaly Disease Activity Tool (ACRODAT) and the Signs and symptoms, Associated comorbidities, GH levels, IGF1 levels and Tumour profile (SAGIT).[3,227]

Special considerations: acromegaly and pregnancy

Fertility and pregnancy should be discussed with female patients soon after acromegaly diagnosis.[228] Symptomatic adenoma growth in pregnant women with acromegaly occurs in approximately 7% of patients and risk for diabetes and hypertension is increased.[229]

Surgery is the first-line treatment in patients with newly diagnosed acromegaly who want to become pregnant.[25] However, in patients with mild growth hormone excess, normal ovulation, and no comorbidities,

Search strategy and selection criteria

We searched PubMed for articles published in English from Jan 1, 1980, to May 1, 2022, using the terms "acromegaly", "GH-secreting pituitary adenoma", "diagnosis", "complications", "quality of life", "pituitary surgery", "somatostatin receptor ligands", "dopamine agonists", "growth hormone receptor antagonists", "radiation", and "genetics". To provide an updated review on acromegaly, we selected mainly articles published between Jan 1, 2016, and May 1, 2022, and highly referenced articles published before Jan 1, 2016.

guidelines suggest that medical or surgical treatment can be postponed until after delivery.[229] Octreotide, lanreotide, and cabergoline can be used until pregnancy confirmation and the few available reports of continued treatment suggest risks are probably low.[229] Fewer patients have been treated with pegvisomant. After stopping treatment, many pregnant women will exhibit normalised IGF-1 concentrations because of increased growth hormone resistance; however, treatment can nevertheless be restarted if needed for either symptom or tumour mass control. Close biochemical and imaging monitoring after delivery are needed because IGF-1 concentrations can rebound soon thereafter. Breast-feeding is not contraindicated, but individualised decisions should be made on the basis of tumour size and need for medical treatment for growth hormone excess.

Conclusions

Acromegaly remains a challenging endocrine disorder to recognise in clinical practice, and screening all patients with clinical suspicion or associated comorbidities would shorten the delay in diagnosis. Accurate diagnosis requires rigorous assessment based on biochemical, imaging, and pathological markers. Pituitary adenoma size, predictors of response and remission, treatment side-effects, and complications of disease should all be considered when implementing an optimal management approach. Patients often require multimodal treatment including surgical, medical, and radiation therapy to optimally achieve treatment goals, reduce excess morbidity, and improve overall patient's QoL. Future directions for improved strategies in diagnosis and monitoring, treatment, and monitoring of QoL are detailed in the appendix (p 4).

Contributors

All authors contributed equally to the literature review, writing of the manuscript, and development of tables, figures, and panels. All authors reviewed and approved the final version of the manuscript and made the decision to submit for publication.

Declaration of interests

MF has received grants to their institution from Amryt/Chiasma, Crinetics, Ionis, Novartis, and Recordati; has received consulting fees from Amryt/Chiasma, Ionis, Ipsen, Novartis, Pfizer, and Recordati; has served as an adviser to Recordati, Amryt/Chiasma, and Crinetics; and has served as a member of the Board of Directors (non-compensated) for the Pituitary Society. FL has received honoraria for presentations from Pfizer and Recordati, has served as an adviser to Novartis and Recordati, and has served as a member of the Continuing Medical Education Committee for AMEQ (Association des Médecins Endocrinologues du Québec). SM has received grants to their institution from Pfizer and consulting fees from Ionis and Ipsen; has served as an adviser to Ipsen, Recordati, Crinetics, and Amryt/Chiasma; and serves as Secretary (non-compensated) for the Pituitary Society. All other authors declare no competing interests.

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