Croatian Endocrine Society Consensus Statement on Diagnosis and Management of Acromegaly

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SUMMARY

Acromegaly is a rare pituitary disorder with significant morbidity. This consensus statement aims to provide evidence-based diagnostic and management recommendations adapted to the Croatian setting. A multidisciplinary panel systematically reviewed international guidelines and evidence, applying the GRADE approach to assess certainty and strength of recommendations. Recommendations cover diagnosis, imaging, surgery, pharmacotherapy (first- and second-generation somatostatin receptor ligands, pegvisomant, dopamine agonists, combination therapy), radiotherapy, follow-up, and comorbidity management. A graded summary table provides practical guidance. These consensus recommendations offer standardized, evidence-based guidance for the diagnosis and management of acromegaly, aiming to improve patient outcomes and harmonize care across Croatia.

KEYWORDS

Acromegaly; Insulin-like growth factor 1 (IGF-1); Growth hormone; Pituitary neoplasms; Therapy; Croatia

Introduction

Acromegaly is a rare hormonal disorder caused by excessive production of growth hormone (GH), typically due to a benign pituitary adenoma. If not diagnosed and treated in a timely manner, it may result in severe health consequences, significantly impairing quality of life and reducing life expectancy[1,2]. This consensus statement aims to provide standardized, evidence-based guidance tailored to the Croatian healthcare system, while aligning with and critically comparing to international guidelines, particularly the 2024 Pituitary Society consensus[3] and Endocrine Society Clinical Practice Guidelines[4]. The intent is to ensure that recommendations are implementable within the Croatian Health Insurance framework while preserving evidence-based care.

Regarding the access model and centers of expertise, management should be centralized in tertiary centers with neurosurgery, pituitary imaging, and endocrine expertise. Subspecialist confirmation and multidisciplinary review for initiation or escalation of high-cost therapies is typically required (e.g., somatostatin receptor ligands (SRLs), pasireotide, pegvisomant). Prior authorization cycles usually span 6-12 months and require timely renewal with documented biochemical response.

First-line pharmacotherapy SRL-first generation (SRL-fg), octreotide LAR and lanreotide autogel are generally accessible with prior authorization when surgery is contraindicated, has failed to achieve remission, or when used temporarily to control disease while awaiting therapeutic effect of radiotherapy. Dose escalation to octreotide 30-40 mg monthly or lanreotide 120 mg every 4 to 8 weeks is usually permitted when insulin-like growth factor 1 (IGF-1) remains above the upper limit of normal (ULN), provided adherence and injection technique are verified. Octreotide is usually the first choice of therapy due to its lower cost compared to lanreotide.

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For pasireotide long-acting release (LAR) (SRL-second generation) coverage is typically restricted to patients with inadequate control on SRL-fg and/or with clinically significant tumor progression or symptoms. Given its diabetogenic potential, a plan for glucose monitoring and management is warranted; switching from SRL-fg to pasireotide *versus* combining with pegvisomant should be justified by clinical profile (tumor growth, symptom burden, glycemic risk).

Pegvisomant is reimbursed after failure or intolerance of SRLs (± cabergoline) and persistent IGF-1 elevation. In patients with diabetes or intolerable hyperglycemia on pasireotide, pegvisomant may be favored. Combination therapy (low-dose SRL + pegvisomant) can be effective, but documentation should include IGF-1 levels and magnetic resonance imaging (MRI) finding stability, given that pegvisomant does not reduce tumor size.

As a low-cost oral option, cabergoline is typically accessible and useful for mild biochemical activity (IGF-1 <1.5× ULN) or mixed growth hormone/prolactin (GH/PRL) adenomas.

Stereotactic radiosurgery is available in designated centers; documentation on surgical ineligibility/failure and inadequate biochemical control on medical therapy is required. Medical therapy is continued during the latency period to remission and may be tapered if radiation response occurs.

Practical implications for sequencing: surgical resection should be the initial approach whenever feasible. If not in remission, SRL-fg with dose/interval optimization should be initiated. If IGF-1 remains >ULN or tumor grows: (a) switch to pasireotide if tumor control is prioritized and glycemic risk is acceptable; (b) add pegvisomant if biochemical control is the priority or pasireotide is poorly tolerated; (c) add cabergoline when disease activity is mild or PRL is elevated. Radiosurgery for residual/invasive disease unresponsive to medication should be considered.

Documentation checklist for prior authorization should encompass: (i) diagnosis with age adjusted IGF-1 levels; (ii) oral glucose tolerance test (OGTT) results if applicable; (iii) MRI with revised Knosp grade; (iv) surgical and multidisciplinary notes; (v) histopathology report from surgical specimens, if available; (vi) prior therapies, doses, and adherence; (vii) IGF-1 trends over time; and (viii) comorbidity profile (especially glycemia, liver tests, cardiac valves). A summary table of graded recommendations is shown in Table 1.

Epidemiology and pathophysiology of acromegaly

Epidemiology of acromegaly shows a prevalence of 40 to 70 cases *per* million people and an annual incidence of 3 to 4 cases *per* million. Different studies have recorded a prevalence from 2.8 to 13.7 cases *per* 100,000 persons[5,6]. A systematic review and meta-analysis published in 2021 demonstrated a pooled prevalence of 5.9 cases *per* 100,000 persons and an incidence rate of 0.38 cases *per* 100,000 person-years[7]. It typically affects middle-aged adults and is slightly more common in men than women. Signs and symptoms include enlargement of hands, feet, facial features, and organs, as well as joint pain, thickened skin, and carpal tunnel syndrome. Over time, patients may develop complications such as diabetes mellitus (DM), hypertension, cardiovascular disease, sleep apnea, and arthritis[7]. The etiology is mainly associated with pituitary adenomas, but it can also result from ectopic GH secretion[8]. It can also be caused by genetic disorders including *AIP* mutations in familial isolated pituitary adenomas (FIPA), GPR101 duplications in X-linked acrogigantism (*X-LAG*), *GNAS* mosaic mutations in McCune-Albright syndrome, *MEN1* and *CDKN1B (MEN4)* syndromes, *PRKAR1A* in Carney complex, and *SDHx* gene mutations in the '3Pas' syndrome (pituitary adenomas with paragangliomas/pheochromocytomas)[9,10]. Genetic (hereditary or mosaic) forms of acromegaly should be suspected in individuals presenting unusually early, particularly in childhood or adolescence, with large or aggressive pituitary tumors, especially when there is a family history of pituitary adenomas, or when acromegaly occurs as part of a syndromic constellation (e.g., MEN1 features, cutaneous findings, paragangliomas/pheochromocytomas, or Carney complex manifestations). When suspicion is raised, the workup should include germline genetic testing (e.g., sequencing and multiplex ligation-dependent probe amplification (MLPA) for genes such as *AIP*, *MEN1*, *CDKN1B*, *PRKAR1A*, *GPR101* duplications,

Table 1. Graded recommendations for diagnosis and management of acromegaly

Domain	Recommendation	Evidence/grade
Diagnosis	Measure age-adjusted serum IGF-1 using validated assays (02/254 standardization); IGF-1 >1.3×ULN confirms acromegaly in typical phenotype.	Moderate, strong
	Repeat IGF-1 and/or perform OGTT when IGF-1 is equivocal; confirm diagnosis if GH fails to suppress to <1 μg/L (or <0.4 μg/L with ultra-sensitive assays).	Low-moderate, conditional
	OGTT not required when IGF-1 is clearly elevated.	Moderate, strong
	Use BMI-adjusted GH nadir cut-offs (<0.4 μg/L if BMI <25; <0.2 μg/L if BMI ≥25) for specificity.	Low-moderate, conditional
	Use standardized assays (IGF-1 02/254; GH 98/574); maintain longitudinal consistency with same lab.	Moderate, strong
Imaging and pathology	Perform gadolinium-enhanced pituitary MRI with modified Knosp grading for staging and surgical planning.	Moderate, strong
	Pathologic evaluation: GH±PRL IHC, granulation pattern, Ki-67; consider SSTR 2/5 when available for predicting SRL response.	Low-moderate, conditional
Care organization	Refer equivocal or refractory cases to centralized pituitary multidisciplinary centers.	Moderate, strong
Surgery	Transsphenoidal surgery is first-line therapy in resectable adenomas and suitable surgical candidates.	High, strong
	Expected biochemical remission rates: microadenomas ≈80%, macroadenomas ≈50-60% (lower with invasion).	High-moderate, strong
	Early post-op GH (~day 1) ≈1.55 ng/mL predicts remission (sensitivity 75%, specificity 59%).	Moderate, —
Medical therapy – first generation SRLs	SRL-fg (octreotide LAR, lanreotide autogel) normalize IGF-1 in ~40-60% of patients; effective for tumor shrinkage ≥20% in a substantial proportion.	Moderate-high, strong
	Indicated after unsuccessful surgery when surgery contraindicated, or preoperatively in high-risk patients.	High, strong
	Gastrointestinal adverse events, gallstones, and bradycardia are usually mild-moderate; monitor as indicated.	Moderate, strong
Medical therapy — oral SRL	Oral octreotide capsules maintain biochemical control in ~58% (IGF-1) and 78% (GH <2.5 ng/mL); suitable for maintenance after SRL response.	Moderate, conditional
Medical therapy — second generation SRL	Pasireotide LAR for SRL-resistant disease or aggressive tumor biology; achieves ~15-20% normalization; tumor shrinkage in majority; monitor for hyperglycemia.	Moderate, conditional (risk of hyperglycemia)
Medical therapy – GH receptor antagonist	Pegvisomant normalizes IGF-1 in up to 75% long-term (10 years); most effective agent for biochemical control.	High, strong
	Monitor liver function (LFT >3×ULN ~3%); lipohypertrophy 1-15%.	Moderate, —
	Improves glycemia in diabetes; favorable metabolic profile.	Moderate, strong (in diabetes mellitus)
	Tumor growth rare (~3-7%); MRI intervals individualized (annual not mandatory).	Moderate, —

Table 1. [Continued]

Domain	Recommendation	Evidence/grade
Medical therapy – dopamine agonists	Cabergoline monotherapy or add-on: ~10-30% IGF-1 normalization, best in mild disease (IGF-1 <1.5×ULN) or GH/PRL co-secretion.	Low, conditional
	Valvulopathy risk low at endocrine doses; consider echo with higher cumulative exposure.	Low-moderate, —
Combination therapy	SRL + pegvisomant: improved IGF-1 control *vs*. SRL alone; may reduce pegvisomant dose.	Low-moderate, conditional
	Pasireotide + pegvisomant: high biochemical control but increased hyperglycemia; select carefully.	Very low-low, conditional
	SRL + cabergoline: modest additional IGF-1 lowering; useful near target or mild disease.	Low, conditional
Radiotherapy	Consider stereotactic radiosurgery (SRS) or conventional radiotherapy only in refractory/unresectable disease or when medical therapy fails.	Moderate, conditional
	Long-term remission ≈50-60% at 10-15 years; hypopituitarism common (50-100%).	Moderate, —
	Lifelong pituitary axis surveillance required post-radiation.	Moderate, strong
Remission criteria	Age-adjusted normal IGF-1 and nadir GH <1 µg/L (or <0.4 µg/L ultra-sensitive assay) post-OGTT define remission.	Moderate, strong
Follow-up	Postoperative IGF-1 at 6-12 weeks; early random GH (day 1-14) prognostic of remission.	Moderate, strong
	MRI at 3-6 months post-op; repeat as clinically indicated; annual MRI not required on stable pegvisomant.	Moderate, strong
	IGF-1 every 3-6 months in year 1, then every 6-12 months; more frequent if therapy changes.	Moderate, strong
Comorbidity management	Cardiovascular: regular blood pressure, ECG, echocardiogram; treat hypertension, arrhythmias, cardiomyopathy.	Moderate, strong
	Metabolic: screen fasting glucose/HbA1c; OGTT as needed; monitor closely with pasireotide.	High (screening), moderate (drug-specific), strong
	Respiratory: screen for sleep apnea; CPAP improves QoL and cardiovascular risk; reassess even if biochemically controlled.	Moderate, strong
	Neoplasia: colonoscopy at baseline; adapt interval to IGF-1 status; thyroid ultrasound if nodules present.	Moderate, strong/conditional
	Skeletal: screen for vertebral fractures, osteoporosis, arthropathy.	Moderate, strong
	Endocrine: monitor for hypopituitarism and other hormonal deficits.	Moderate, strong
	Quality of life: include QoL assessment in routine management.	Moderate, strong

GH = growth hormone; IGF-1 = insulin-like growth factor 1; ULN = upper limit of normal; OGTT = oral glucose tolerance test; BMI = body mass index; IHC = immunohistochemistry; PRL = prolactin; SSTR = somatostatin receptor; SRL = somatostatin receptor ligand; SRL-fg = somatostatin receptor ligand-first generation; MRI = magnetic resonance imaging; LAR = long-acting release; LFT = liver function test; SRS = stereotactic radiosurgery; QoL = quality of life; CPAP = continuous positive airway pressure

SDHx), with pituitary MRI surveillance, especially in asymptomatic carriers – starting around age 10 and repeated periodically through early adulthood in *AIP*-positive families[11]. This genetic evaluation aids in early diagnosis, targeted surveillance, and better outcomes for both index cases and at-risk relatives[10]. The pathophysiology involves excess GH leading to increased IGF-1 levels, causing abnormal tissue growth and metabolic effects. Uncontrolled acromegaly can lead to severe, life-threatening complications, resulting in a 2- to 3-fold increase in mortality compared to the general population. This highlights the importance of early diagnosis and treatment[12].

Methodology

A panel of experts was convened, including endocrinologists, neurosurgeons, radiologists and internal medicine subspecialists representing all Croatian tertiary centers. Experts were selected based on ≥10 years of clinical experience in pituitary disease, academic activity, and endorsement by the Croatian Endocrine Society. Participants were assigned specific topics related to acromegaly diagnosis and follow-up and conducted comprehensive literature searches for English-language papers published up to November 2024. Search terms included "acromegaly", as well as terms associated with various aspects of acromegaly, including pathophysiology, diagnostic criteria, treatment options, and prognosis. Emphasis was put on high-quality studies and systematic reviews to ensure robustness of the evidence. The first structured discussion took place during the Online Regional Experts' Meeting on Acromegaly, Cushing's Syndrome, and Neuroendocrine Tumors (NETs), held on November 8-9, 2024 in Osijek, Croatia. The second meeting was part of the 12th Croatian Endocrine Society Meeting with International Participation, held on March 6-9, 2025 in Šibenik, Croatia. At these meetings, brief presentations were delivered to the entire group on each topic, followed by breakout group discussions focused on current practice and recommendations. Consensus recommendations were developed based on all presentations and discussions, and all participants voted on each recommendation. After the meetings, members of the Scientific Committee graded both the quality of the supporting evidence and the consensus recommendations, following established principles for grading evidence. Conflicts of interest were declared and managed in accordance with the Croatian Endocrine Society policy. Evidence quality and recommendation strength were graded using the GRADE approach[13,14]. The final recommendations were drafted, reviewed, and revised by the panel, with an emphasis on practicality, feasibility, and alignment with international standards.

Diagnosis of acromegaly

All individuals with a newly diagnosed pituitary tumor should have IGF-1 measurement. Patients with typical clinical signs or symptoms of acromegaly, for example, acral enlargement and orofacial alterations, warrant IGF-1 screening, especially if they coexist with other systemic manifestations such as ventricular hypertrophy or sleep apnea[3].

Diagnosis is based on a combination of biochemical testing, imaging, and clinical evaluation. The primary biochemical test is serum IGF-1, interpreted using age-specific reference ranges, calibrated to international standards (02/254 for IGF-1 and 98/574 for GH) (Fig. 1)[15]. IGF-1 levels are first assessed, as they remain consistently elevated in acromegaly despite fluctuations in random GH. Normal IGF-1 levels vary with age and reference ranges must be adjusted accordingly. Elevated IGF-1 levels above the age-matched reference range strongly

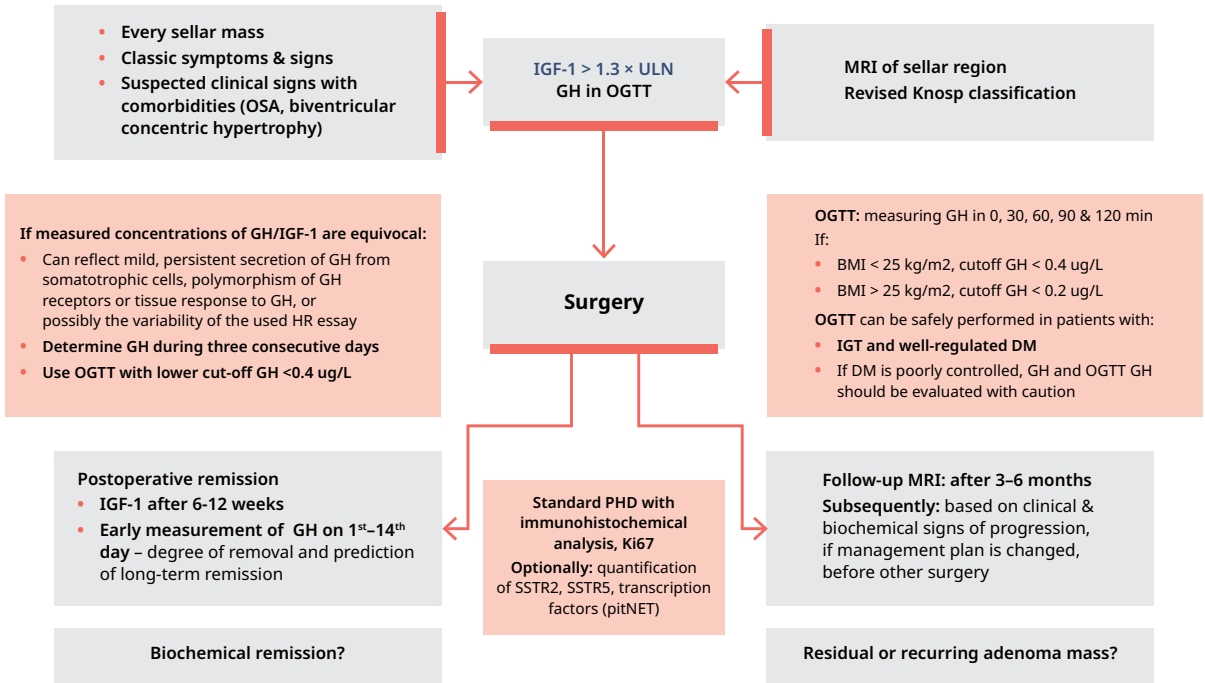

Fig. 1. Diagnostic and therapeutic algorithm for acromegaly.
Patients with suspected acromegaly undergo IGF-1 measurement, followed by GH suppression testing (OGTT) if elevated. Pituitary MRI confirms the diagnosis. Transsphenoidal surgery is first-line treatment, with postoperative biochemical reassessment and individualized management of persistent or recurrent disease.
IGF-1 = insulin-like growth factor 1; OGTT = oral glucose tolerance test; MRI = magnetic resonance imaging

suggest acromegaly. Most centers in Croatia use fully automated chemiluminescent immunoassays on high-throughput platforms – commonly Roche Elecsys IGF-1 (ECLIA) on cobas e analyzers – while some laboratories may use alternative automated assays (e.g., Siemens Immulite, DiaSorin LiaisonXL IGF-1 immunoassay), so clinicians should interpret results with the laboratory reference intervals and, ideally, follow patients in the same lab to avoid inter-assay shifts. In a patient with typical clinical signs and symptoms of acromegaly, IGF-1 >1.3×ULN for age confirms the diagnosis. Measuring random GH is not warranted to confirm diagnosis, although it can be useful in predicting prognosis and complications.

An OGTT can be performed if measured concentrations of IGF-1 are equivocal due to mild, persistent secretion of GH from somatotrophic cells, polymorphism of GH receptors, or tissue response to GH or possibly variability of the GH assay used. In OGTT GH levels are measured after a 75 g glucose load; 75 g glucose should be administered after 8-12 hours of fasting, and GH nadir assessed after 30, 60, 90, and 120 min. A value >1 ng/mL after an OGTT confirms acromegaly[16,17]. GH levels measured by ultrasensitive assays may lower this threshold to 0.3 µg/L. Body mass index (BMI)-based GH nadir cutoffs of < 0.4 µg/L for BMI <25 kg/m^2 and <0.2 µg/L for BMI ≥25 kg/m^2 can be considered[18]. Some conditions can affect random/nadir GH and IGF-1 levels such as pregnancy, liver and renal failure, malnutrition, diabetes, oral estrogens, and critical illness[16,19,20]. Cessation of oral estrogen therapy 4 weeks prior to OGTT may avoid its effects on the

GH axis[21]. A nadir GH ≥ 0.4 μg/L after OGTT may be used to diagnose acromegaly in patients with impaired glucose tolerance, impaired fasting glucose, or relatively well-controlled DM with glycated hemoglobin <8%, according to a recent study by Dobri *et al*. using modern, highly sensitive GH assays[22]. However, in patients with uncontrolled diabetes, both random and nadir GH levels should be interpreted with caution; therefore, OGTT should be postponed after achieving good glycemic control[16]. Medications (especially insulin or insulin secretagogues such as sulfonylureas) can alter glucose curve, potentially affecting reliability of the test in triggering the appropriate GH response. Metformin can also affect GH and IGF-1 levels and may confound test results. Therefore, it is generally recommended to withhold antidiabetic medications on the morning of the test[3,23].

Furthermore, MRI with gadolinium contrast of the sellar region is mandatory at diagnosis. A revised Knosp grade must be included in reports[24], whereas pathology reports should include immunohistochemistry assessment for pituitary hormones and Ki67 (optionally: quantification of somatostatin receptor subtypes SSTR-2 and SSTR-5, as well as transcription factors (pitNET))[25]. Histopathology confirms the diagnosis and provides prognostic information. The World Health Organization (WHO) 2022 classification designates these lesions as somatotroph pituitary neuroendocrine tumors (PitNETs) to reflect their neuroendocrine nature and potential for local invasion. They are subtyped as densely or sparsely granulated based on cytokeratin pattern, which may predict SRL responsiveness. Emphasis is put on lineage-specific transcription factors (PIT-1, SF-1, T-PIT) as mandatory in pathology work-up. Also certain subtypes (e.g., sparsely granulated somatotroph PitNETs) are recognized as potentially more aggressive, whereas clinical aggressiveness should be reported based on a combination of histological features (Ki-67 ≥3%, elevated mitotic index, extensive p53 staining) and clinical course[26]. Essential report elements include: WHO 2022 diagnosis and subtype; immunohistochemistry: PIT-1 positivity, GH staining ± PRL co-expression; proliferation markers: Ki-67 index, mitotic count, p53; resection margins. Optional/extended report elements include: SSTR-2/SSTR-5 expression to guide SRL choice; additional hormones for plurihormonal tumors; GNAS mutation status (more common in densely granulated subtype)[26]. Figure 1 shows diagnostic and initial management algorithm.

Treatment goals

Treatment goals for acromegaly are the following: control of hormonal hypersecretion meaning normalization of serum IGF-1 (for the age-specific reference range), reduction of pituitary tumor bulk or its GH-secreting remnant, and reduction or eradication of symptoms and comorbidities associated with the disease[27]. Remission in acromegaly is defined differently depending on the treatment modalities due to their distinct mechanisms of action. After transsphenoidal surgical resection, biochemical remission is typically defined by normalization of age-adjusted IGF-1 levels combined with a nadir GH level during an OGTT (GH<1 μg/L or <0.4 μg/L with ultrasensitive assays)[27]. Random GH <1 μg/L in the early postoperative period (day 1-14) could provide additional information on long-term remission. In contrast, in patients treated with injectable SRLs, remission is primarily determined by achieving normal IGF-1 levels while random GH measurements are less reliable for definitive remission. When it comes to pegvisomant, GH assays are inherently unreliable because the medication blocks GH receptor signaling without reducing circulating GH levels. Therefore, remission is assessed exclusively based on normalization of IGF-1 levels, alongside periodic monitoring of tumor status *via* imaging[28]. The most precise description for the

biochemical therapy outcome goals in acromegaly is “remission”, which denotes the state in which active disease cannot be detected, even though it may still exist. In the majority of patients, remission can be determined by measuring IGF-1 levels six weeks after surgery; however, those with slightly raised IGF-1 may still return to normal by three to six months[3]. Maintaining serum IGF-1 levels in the mid to upper half of the age-related reference range may be important to prevent the possible development of GH insufficiency[3].

Surgical treatment

Surgery is often considered as the first-line treatment.

Surgical treatment: transsphenoidal surgery

Transsphenoidal surgery is the preferred first-line therapy for most patients with acromegaly, especially when the underlying cause is a pituitary adenoma, ideally performed in high-volume pituitary centers. The goal of surgery is complete tumor resection, which can lead to the normalization of GH and IGF-1 levels and, if successful, can result in remission of acromegaly[4].

Indications for surgery

Microadenomas (<10 mm): these smaller tumors are more likely to be entirely resectable. Surgery has a high success rate in these cases, with remission rates exceeding 80% in expert hands.

Macroadenomas (≥10 mm): for larger tumors, surgery is often more challenging, but it remains the preferred first-line treatment. Remission rates are lower (around 50-60%) due to incomplete tumor removal, particularly if the adenoma has invaded surrounding structures such as the cavernous sinus[29-31]. Remission rates cited above refer to outcomes in experienced centers, where complication rates are lower and the likelihood of remission is higher.

Beyond biochemical control, surgery is indicated for mass-effect symptoms, including visual field deficits/optic chiasm compression, pituitary apoplexy, progressive headaches attributable to the lesion, and other compressive manifestations (e.g., ophthalmoplegia); in these settings, timely decompression takes priority[4].

Benefits of surgery

Immediate GH reduction: although definitive remission cannot be confirmed immediately after surgery, successful adenoma removal typically leads to a rapid decline in GH levels because of its short half-life. Postoperative GH concentrations decrease significantly within hours to the first day after surgery and help predict long-term outcomes. For example, a postoperative day 1 GH threshold of around 1.55 ng/mL is associated with a higher likelihood of non-remission, with 75% sensitivity and 59% specificity[32].

Tumor debulking: even when complete resection is not achievable – especially in macroadenomas with cavernous sinus invasion – surgical debulking can alleviate mass-related symptoms such as headaches and visual field impairments. Importantly, debulking may improve the effectiveness of adjuvant therapies (e.g., somatostatin analogs or radiotherapy) by reducing tumor volume and associated hormonal burden[33].

Improvement of comorbidities: surgical control of acromegaly can significantly ameliorate associated comorbidities. Lowering GH and IGF-1 through surgery may improve hypertension, glucose metabolism (diabetes), and some aspects of cardiomyopathy; however, up to about 40% of patients continue to experience persistent sleep apnea despite biochemical control. Nonetheless, reducing disease activity generally lowers overall morbidity and mortality risk including cardiovascular disease, diabetes, and sleep apnea[34].

Surgical success and outcomes

The success of surgery depends on factors such as tumor size, location, and surgeon's expertise. While smaller tumors have higher remission rates, larger or more invasive tumors are more challenging in terms of complete removal. Post-surgical monitoring of GH and IGF-1 levels is critical, as these determine whether additional treatments are required. About 30-40% of patients with larger adenomas may require follow-up medical therapy or radiotherapy[29,30].

Risks and complications

While transsphenoidal surgery is generally safe, potential risks include damage to the surrounding pituitary gland, potentially causing hypopituitarism, which may require hormone replacement; hyponatremia; cerebrospinal fluid leakage which can lead to meningitis; and damage to nearby structures such as optic nerves or carotid arteries, though this is rare with experienced surgeons[35,36]. New onset hypopituitarism occurs in ~5-10% of cases overall (some series ~4-5%); hyponatremia – especially delayed hyponatremia – is common, in pooled analysis ≈10-12% (reported range ~9-31%); postoperative cerebrospinal fluid leak is present in ~2-7% of cases across series; meningitis is uncommon, ~0.4% (generally <1%); clinically significant injury to nearby structures is rare, with internal carotid artery injury below 0.5% and permanent visual worsening exceptionally uncommon while death or major disability is ~0.3% in large tertiary-center series[37-42].

Pharmacotherapy

While surgical resection of the GH-secreting pituitary tumor remains the first-line treatment in many cases, medical therapy plays a crucial role in managing patients who are not candidates for surgery, have incomplete surgical resection, or require additional control of GH levels post-surgery[4].

The main classes include SRL-fg, second-generation SRLs (pasireotide), GH receptor antagonists (pegvisomant), and dopamine agonists (cabergoline). Detailed mechanisms, indications, dosing, side effects, and a comparative summary are provided in Table 2, while Table 3 outlines evidence-based pharmacotherapy sequencing and combination strategies adjusted to the Croatian healthcare system.

Somatostatin receptor ligands

Somatostatin receptor ligands are the cornerstone of pharmacotherapy in acromegaly, used to inhibit GH secretion by mimicking somatostatin, a natural inhibitor of GH. These drugs effectively lower both GH and IGF-1 levels, and can also reduce tumor size in some patients[43]. Currently, registered somatostatin receptor ligands primarily act on SSTR-2 and SSTR-5, which, upon activation, reduce the secretion of GH from the adenoma. Pasireotide is a new-generation multiligand drug affecting other somatostatin subtype receptors, with the highest affinity for SSTR-5, compared to SRL-fg primarily targeting SSTR-2.

Treatment with SRLs is indicated:

- if the disease was not controlled by surgical treatment;
- in a time interval until reaching the maximum radiotherapy effect;
- if there are contraindications for surgical treatment; and
- preoperatively, for 3 to 6 months in patients with a high operative risk due to comorbidities[44].

Octreotide (Sandostatin LAR): significantly reduces GH secretion in the majority of patients, and remission defined as IGF-1 normalization or 50%

Table 2. Comparative summary of pharmacotherapy for the management of acromegaly

Drug/class	Mechanism	Indications	Efficacy	Key side effects	Monitoring
Octreotide (SRL-fg)	Somatostatin receptor 2/5 agonist	First-line if surgery not possible or unsuccessful; bridge to radiotherapy; pre-op in high-risk cases	IGF-1 normalization in 50-70%; ~20% tumor shrinkage in 65% of patients	GI symptoms, gallstones, injection site pain, glucose intolerance	IGF-1: 3 months after initiation or dose adjustment; stable biochemical control every 6-12 months.; HbA1c /glucose if metabolic risk; MRI for tumor size
Lanreotide (SRL-fg)	Somatostatin receptor 2/5 agonist	Similar to octreotide; option for long-acting and extended dosing intervals	Comparable efficacy to octreotide; IGF-1 normalization in 50-70%; tumor shrinkage possible	GI symptoms, gallstones, injection site reactions, possible hyperglycemia	IGF-1: 3 months after initiation or dose adjustment; stable biochemical control every 6-12 months; glucose/HbA1c monitoring; MRI surveillance
Pasireotide (SRL-sg)	Somatostatin receptor 5 > 2,3,1 agonist	Resistant to SRL-fg ± pegvisomant; tumor progression; clinically aggressive adenomas	IGF-1 normalization in ~20% resistant cases; tumor shrinkage ~40% in 80% treated patients	Hyperglycemia, QT prolongation, bradycardia, GI effects	IGF-1: 3 months after initiation or dose adjustment; stable biochemical control every 6-12 months; baseline glucose/HbA1c ± OGTTIIII; weekly glucose x4 weeks after initiation or dose change; HbA1c every 3 months; ECG monitoring
Pegvisomant	GH receptor antagonist	SRL resistance; diabetics intolerant to pasireotide; combination with SRLs for partial responders	>70% IGF-1 normalization; improves glycemia in diabetics; no effect on tumor size; possible GH increase post-administration	Liver enzyme elevation, injection site reactions	IGF-1 every 4-6 weeks during titration; stable biochemical control every 6-12 months; LFTs every 4 to 6 weeks for 6 months, then periodically; MRI for tumor size stability
Cabergoline	Dopamine D2II receptor agonist	Mild disease (IGF-1 <1.5× ULN); mixed GH/PRL adenomas; adjunct with SRLs	IGF-1 normalization in 10-30%; more effective in PRL co-secreting tumors	Nausea, dizziness, headaches, valvular heart disease (high dose/prolonged use)	IGF-1 every 1-3 months during titration; stable biochemical control every 6-12 months; consider periodic echocardiogram

SRL-fg = somatostatin receptor ligand-first generation; SRL-sg = somatostatin receptor ligand-second generation; SRL = somatostatin receptor ligand; GH = growth hormone; D2 = dopamine 2; PR = prolactin; IGF-1 = insulin growth factor-1; GI = gastrointestinal; LFT = liver function test; MRI = magnetic resonance imaging; OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin

reduction compared to baseline levels is achieved in about 50-70% of cases[45-47]; 20% reduction of tumor growth is seen in 65% of patients[45,48]. The approved starting octreotide LAR dose is 20 mg monthly, with dose titration every 3-6 months down to 10 mg or up to 40 mg monthly[49].

Lanreotide (Somatuline Depot): another long-acting SRL, lanreotide is comparable in efficacy to octreotide, with similar rates of GH and IGF-1 control. For lanreotide autogel/depot, the approved starting dose is 90 mg monthly, with dose titrations down to 60 mg or up to 120 mg monthly[50].

Table 3. Pharmacotherapy sequencing aligned with the Croatian healthcare system

Clinical scenario	Preferred option (GRADE)	Reimbursable pathway (typical)	Notes/clinical considerations
Postoperative persistent disease	Start first-generation somatostatin receptor ligand – octreotide long-acting release or lanreotide autogel (high quality/strong recommendation)	Octreotide long-acting release usually preferred because of lower cost; lanreotide autogel; both with prior authorization	Optimize dose and interval before switching; ensure correct injection technique
Partial response to first-generation somatostatin receptor ligand	Add cabergoline for mild biochemical activity (moderate quality/conditional); or switch to pasireotide long-acting release when tumor size/control is the priority or there is documented growth or in case of persistent symptoms (moderate quality/conditional)	Cabergoline generally accessible; pasireotide requires criteria such as failure of first-generation somatostatin receptor ligand and clinically significant tumor progression or symptoms	Cabergoline is most effective when insulin-like growth factor 1 is <1.5 × upper limit of normal or in mixed growth hormone/prolactin adenomas; pasireotide provides stronger antitumor effect but has higher risk of hyperglycemia – plan structured glucose monitoring
Inadequate response to or intolerance of somatostatin receptor ligands	Initiate or transition to pegvisomant (high quality/strong recommendation)	Pegvisomant reimbursed after failure or intolerance of somatostatin receptor ligands with or without cabergoline	Titrate to normalize IGF-1 (typical maintenance 10-30 mg/day); combine with low-dose somatostatin receptor ligand when residual tumor mass is a concern; consider pegvisomant preferentially in patients with diabetes or when hyperglycemia limits pasireotide
Radiological or clinical tumor progression while on first-generation somatostatin receptor ligand	Switch to pasireotide long-acting release (moderate quality/conditional)	Pasireotide reimbursed with documentation of failure of first-generation somatostatin receptor ligand	Preferred over radiosurgery as next option in case of tumor growth; consider hyperglycemia and glucose management plan
Refractory disease after failure of surgery and multiple medical therapies	Consider stereotactic radiosurgery (moderate quality/strong recommendation in selected cases)	Requires documentation of surgical ineligibility or failure, and inadequate biochemical control with medication	Radiosurgery considered as third-line therapy; continue medical therapy during latency period; discuss risk of hypopituitarism
Stable biochemical remission on lanreotide 120 mg every 4 weeks	Consider interval extension to every 6-8 weeks (moderate quality/conditional)	Interval extension permitted in selected patients according to payer policy	Reduces injection burden; revert to monthly dosing if IGF-1 rises or symptoms recur

IGF-1 = insulin-like growth factor 1

The lanreotide autogel/depot 120-mg dose may be administered in up to 8-week intervals, depending on biochemical response[32,33]. In addition to standard monthly dosing (60-120 mg) with a typical starting dose of 90 mg, extended-interval dosing (EID) can be used in well-controlled patients – 120 mg every 6-8 weeks – to maintain biochemical control while reducing injection burden[51-53].

For partial responders, literature also supports high-dose/high-frequency strategies (e.g., 120 mg every 3 weeks or higher monthly cumulative doses), normalizing IGF-1 in roughly one-third of patients with acceptable safety in selected cases[54]. In Croatia, the most commonly prescribed first-line medication is octreotide due to significantly lower cost compared to lanreotide.

Side effects: common side effects include nausea, vomiting, bloating, abdominal pain, gallstones, diarrhea, and constipation. Additionally, some individuals may experience headaches, fatigue, and pain at the injection site. Somatostatin analogs can also affect blood glucose levels, requiring adjustments in diabetes medications[55].

Pasireotide (Signifor): a newer SRL with broader receptor affinity, pasireotide is often effective in patients resistant to SRL-fg. It targets SSTR-1, SSTR-2, SSTR-3, and SSTR-5 with a high affinity compared to SRL-fg which predominantly bind to SSTR-2[56].

Pasireotide LAR is indicated in the following cases:

- in young patients with tumor growth while on SRL-fg therapy;
- in patients with tumor growth while on first-generation plus pegvisomant therapy;
- in patients with symptoms while on SRL-fg and/or pegvisomant therapy (such as headaches, sweating, arthralgia, fatigue);
- after unsuccessful SRL-fg treatment with a large tumor remnant or severe headaches;
- in patients with clinically aggressive tumors (high Ki67) with proximity to the chiasm or cavernous sinus (surgical treatment not warranted); and
- if the pegvisomant treatment is not tolerated or not effective[44,57].

With the use of pasireotide, IGF-1 normalization is seen in 20% of patients who are resistant to SRL-fg therapy, according to the results of clinical trials[56]. Additionally, compared to SRL-fg, pasireotide LAR had a stronger antitumor efficacy, lowering tumor size by 40% in around 80% of treated patients[58]. Moreover, over 70% of patients reported persistent symptoms while treated with SRL-fg[59]. In the PAOLA clinical trial, treatment with pasireotide after unsuccessful therapy with octreotide led to improvements in most acromegaly symptoms up to 5.8 years of treatment[56]. These findings were confirmed in several real-world studies[60-67]. The initial dose of pasireotide LAR is 40 mg monthly, while 60 mg is the maximal monthly dose[68]. Several real-world cohorts reported dose de-escalation to 20 mg in responders (e.g., after IGF-1 over-suppression or adverse events) with control maintained in those selected patients[69,70].

Pasireotide, especially doses ≥40 mg monthly, often causes hyperglycemia *via* SSTR-5-mediated insulin suppression. Therefore, at baseline fasting glucose and HbA1c should be performed, and an OGTT if high diabetes risk is present. After initiation or dose change, glucose level should be checked weekly for 4 weeks, HbA1c at 3 months, then every 3-6 months and fasting glucose at each visit for 6 months, especially after titration from 40 mg to 60 mg. If dose is reduced (e.g., to 20 mg or 40 mg) due to hyperglycemia, glucose should be monitored weekly for 2-4 weeks to assess improvement[71-73].

Side effects: pasireotide is associated with a higher risk of hyperglycemia than SRL-fg, primarily due to its high affinity for SSTR-5 on pancreatic β-cells, leading to marked suppression of insulin secretion. In addition, pasireotide inhibits incretin hormone release, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), resulting in impaired glucose-stimulated insulin secretion and postprandial hyperglycemia. Insulin sensitivity is generally preserved, indicating that dysglycemia is driven mainly by β-cell and incretin dysfunction rather than increased insulin resistance. These mechanisms support the preferential use of incretin-based antidiabetic therapies (DPP-4 inhibitors or GLP-1 receptor agonists) in the management of pasireotide-induced hyperglycemia, alongside careful glucose monitoring[72]. Other possible side effects include hypertension and hypotension, sinus bradycardia, and prolonged QT interval[74].

Predictors of response to somatostatin receptor ligand therapy

Response to somatostatin receptor ligand therapy in acromegaly can be partially predicted by tumor biological and radiological characteristics. Favorable response to SRL-fg is associated with densely granulated somatotroph pituitary neuroendocrine tumors, high SSTR-2 expression, lower baseline IGF-1 levels, smaller and noninvasive tumors, and hypointense or isointense signal on T2-weighted MRI, whereas sparsely granulated tumors, *AIP* mutation-associated adenomas, and cavernous sinus invasion are linked to reduced efficacy[25,26,44]. In contrast, pasireotide may be effective in patients resistant to SRL-fg, particularly in tumors with higher SSTR-5 expression, sparsely granulated histology, and persistent tumor growth or mass effect despite prior therapy[56-59]. Recognition of these predictors may assist in individualized treatment selection and earlier optimization of medical therapy.

Growth hormone receptor antagonists

Growth hormone receptor antagonists directly block the effects of GH on peripheral tissues, preventing the production of IGF-1. The primary drug in this class is pegvisomant, a pegylated recombinant GH analog and selective antagonist of GH-receptor (GHR)[28]. It is used as a second-line medication therapy or as part of combination therapy.

Pegvisomant (Somavert): this drug is highly effective in normalizing IGF-1 levels, achieving biochemical control in over 70% of patients[75]. However, it does not affect tumor size or lower circulating GH levels and must be administered daily *via* subcutaneous injection.

Pegvisomant is indicated:

- in patients who are resistant to SRLs, particularly in patients with diabetes not threatened by the size of the residual tumor; and
- when SRLs alone are insufficient for controlling IGF-1 levels[44,57].

In patients with DM, pegvisomant improves glucose control independently of IGF-1 levels but has no effect on glycemia in patients without DM[76].

Pegvisomant is available in doses of 10 mg, 15 mg, 20 mg, 25 mg and 30 mg for subcutaneous (sc) injection once daily. An initial daily dose of the drug is 10 mg, and maximal dose is 30 mg daily. Titration is based on IGF-1 levels: IGF-1 is measured every 4-6 weeks and the drug is adjusted by 5 mg/day increments or decrements until normalization; typical maintenance dose is 10-30 mg sc daily (maximal dose 30 mg/day). The maximal IGF-1-lowering effect of a fixed dose is reached within ~4-6 weeks[4,44,77,78].

Side effects: pegvisomant is generally well-tolerated but can cause transient liver enzyme elevation. Liver function tests should be monitored regularly every 4 to 6 weeks during the first six months of treatment and discontinued if liver enzyme levels are five times above the upper limit of the reference range[79].

Dopamine agonists

Dopamine agonists, particularly cabergoline, are used in the treatment of acromegaly, though they are less effective than SRLs and GH receptor antagonists.

Dopamine agonists can be considered:

- in patients with IGF-1 <1.5 ULN;
- mixed somatotroph/lactotroph pituitary adenoma, before surgery or if remission is not achieved by surgery; and
- as add-on treatment in patients partially responding to SRL-fg[4,28,44].

Cabergoline: it is the most commonly used dopamine agonist in acromegaly, with oral administration, more effective than bromocriptine. It is less effective than SRLs, normalizing IGF-1 levels in only 10-30% of patients, but it is a cost-effective option, especially for patients with mild disease or as an adjunct to other treatments[80,81]. Cabergoline shows more efficacy in co-secreting GH/PRL pituitary adenomas and in mild form of acromegaly[82,83]. It is often combined with SRLs to enhance overall efficacy[80,84]. The average dose of cabergoline is 2.5 mg weekly (ranging from 1 to 7 mg)[80].

Side effects: side effects are usually mild but can include nausea, dizziness, and headaches. Higher doses have been associated with valvular heart disease, so careful monitoring is required[85-87].

Combination therapy

In many cases, a combination of pharmacological agents is required to achieve optimal control of acromegaly (Table 3).

Low-dose octreotide LAR or lanreotide plus pegvisomant: this combination is often used when SRLs alone are insufficient. It allows better control of IGF-1 levels and reduces the dosage of each drug, potentially minimizing side effects[88,89].

A combination of pasireotide plus pegvisomant can result in biochemical control rates over 70%, allowing a significant pegvisomant-sparing effect but at the expense of a higher rate of pasireotide-induced hyperglycemia[90]. According to international guidelines, this regimen should be reserved for selected patients – typically those with inadequate control on pegvisomant alone and intolerance or resistance to SRL-fg, given the metabolic risk profile[28].

SRLs plus cabergoline: combining these agents can be effective in patients with mild to moderate disease, particularly if the adenoma secretes both prolactin and GH; however, efficacy is still debatable according to the latest observational study[91,92].

Radiotherapy

Radiotherapy is often considered when surgical removal of the adenoma is incomplete or not feasible, or when medical therapy fails to control GH and IGF-1 levels adequately. It can be delivered using two primary methods, i.e., conventional fractionated radiotherapy (CRT) and stereotactic radiosurgery (SRS)[28].

However, in recent years with the discovery of new drugs, radiotherapy has been used less often in the treatment of acromegaly. It represents the third line of therapy, in patients resistant to all previously mentioned treatment modalities, and is usually reserved for patients who:

- have residual or recurrent tumor after surgery;
- are not candidates for surgery due to medical risks;
- do not achieve biochemical control with medications such as somatostatin analogs, GH receptor antagonists, or dopamine agonists; and
- prefer to avoid or discontinue long-term medical therapy due to side effects or cost[4].

Conventional fractionated radiotherapy

Conventional fractionated radiotherapy (CRT) involves delivering small doses of radiation over multiple sessions (typically 5 days a week for 5-6 weeks).

Efficacy: CRT can result in a significant reduction in GH and IGF-1 levels, but the effects are gradual, often taking up to 15 years to achieve normalization. Studies suggest that about 50-60% of patients achieve disease control over the long term (within 10-15 years)[93,94].

Adverse events: hypopituitarism is the most common late complication, occurring in 50-100% of patients within 5-10 years[95]. Optic neuropathy occurs in <2%, usually with older techniques or high-dose exposure[96]. Rare risk of secondary brain tumors has been reported in <2% of long-term survivors[97].

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a more targeted, high-dose form of radiotherapy delivered in a single or few sessions (e.g., Gamma Knife or CyberKnife). It offers precise targeting of the tumor with minimal exposure to surrounding brain tissue, making it an attractive option for smaller, well-defined adenomas. Efficacy: SRS tends to have a faster onset of action compared to CRT, with some patients achieving biochemical control within 3-5 years. Success rates are similar to CRT, with around 50-70% of patients experiencing normalized GH and IGF-1 levels over time[98-100].

Adverse events: hypopituitarism develops in 20-50% of patients, often within 2-5 years[101]. Cranial nerve injury or optic neuropathy are rare (<2%) but possible, particularly if the tumor abuts critical structures[102,103].

Monitoring after radiosurgery

Monitoring requires measuring IGF-1 for 3-6 months during the first 2-3 years (the effect of SRLs is gradual), then every 6-12 months once the disease is stable or under control; screening for new hypopituitarism should be performed at ~6 months, 12 months, then at least annually thereafter (earlier if symptomatic/biochemical clues exist); and MRI assessment is recommended at 6 months post-treatment, then annually; however, intervals should be adjusted based on biochemistry and/or clinical course of disease. Earlier imaging is indicated in case of rising IGF-1/GH, new visual/neurologic symptoms, or when changing therapy (e.g., before re-operation or additional radiotherapy)[44,104].

Long-term outcomes and considerations

While radiotherapy is effective in controlling GH and IGF-1 levels in the long term, it is not a first-line treatment due to its delayed effects and potential for complications. Because the full effects of radiotherapy take years to manifest, close monitoring of hormone levels and tumor size is essential. Patients may require interim medical therapy to control their symptoms while awaiting the delayed effects of radiation[4,95,105]. Lifelong follow-up with endocrine, imaging, and ophthalmologic assessment is essential.

Follow-up

In follow-up assessment, biochemical evaluation of therapy success, imaging studies assessing residual or recurring adenoma mass, and clinical signs and symptoms of acromegaly, along with associated consequences and comorbidities, should be considered (Fig. 2).

Postoperative remission

IGF-1 should be measured 6 to 12 weeks after surgery to assess postoperative biochemical remission. To determine the extent of adenoma excision and subsequent longer-term remission, early random GH testing on days 1-14 and comparison with preoperative GH are warranted. Random GH below 1 μg/L is indicative of remission. Within the first postoperative year, IGF-1 measurements every 3-6 months may be appropriate to confirm remission, and then every 6-12 months to monitor for potential recurrence. OGTT assessment may provide further predictive value. In patients treated with preoperative SRL, assessment should be repeated at 3-6 months to confirm remission. When assessing

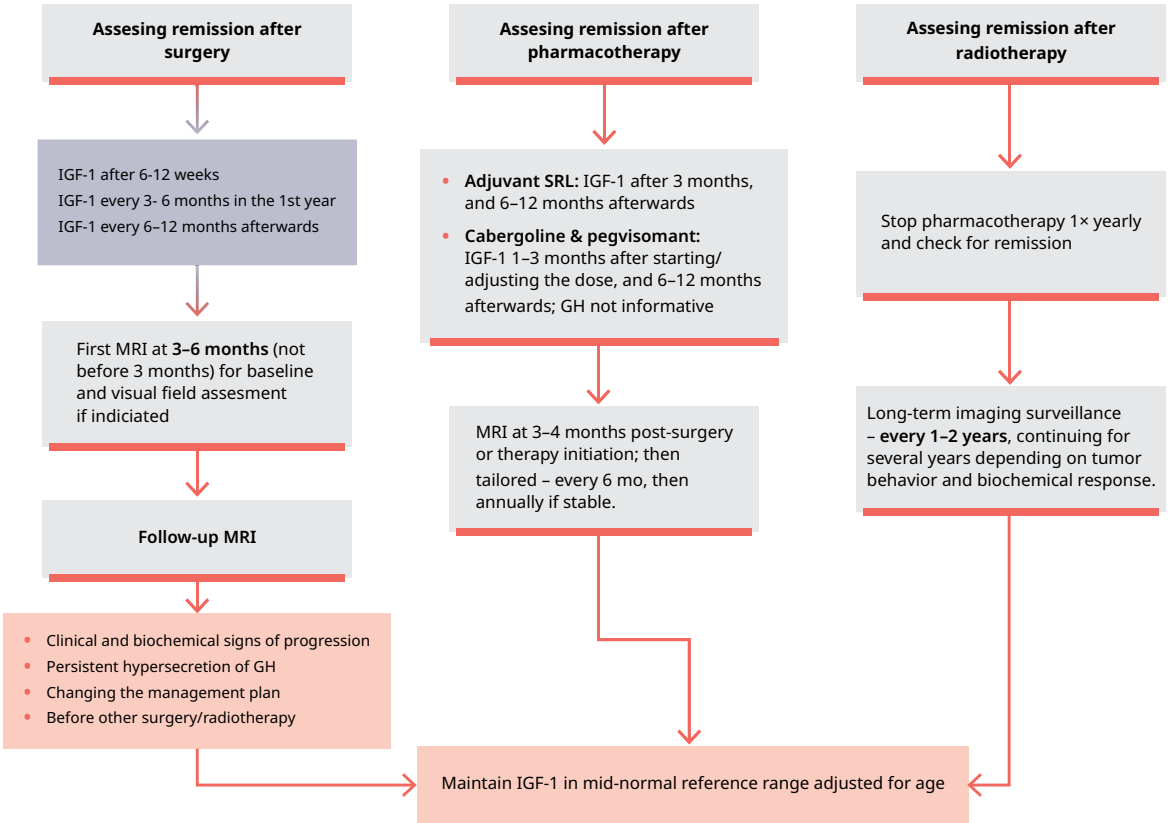

Fig. 2. Follow-up and treatment algorithm for persistent or recurrent acromegaly.
Patients without biochemical remission after surgery require reassessment of disease activity and tumor status. Management includes medical therapy (somatostatin receptor ligands, growth hormone receptor antagonists, or dopamine agonists), repeat surgery in selected cases, or radiotherapy. Treatment is individualized based on biochemical control, tumor characteristics, and comorbidities, with regular long-term monitoring.
IGF-1 = insulin-like growth factor 1; SRL = somatostatin receptor ligand; MRI = magnetic resonance imaging

patients with borderline IGF-1 levels and clinical indications of disease activity, OGTT may be useful. Suppressed GH after OGTT predicts long-term remission, although rates depend on assay cut-off and reproducibility, timing of postoperative measurement, and patient/adenoma phenotype. A nadir GH <1 ng/mL (or <0.4 ng/mL in ultrasensitive assays) is indicative of remission[32,106-110].

Remission with medical therapy

The level of IGF-1 should be measured three months after the start of/dose adjustment of injectable SRL for patients who did not achieve postoperative remission and who are receiving adjuvant SRL. Once biochemical control is attained, IGF-1 should be measured every 6-12 months[111].

As pegvisomant and cabergoline have a shorter half-life than injectable SRL, IGF-1 should be assessed every 1-3 months after treatment initiation/

dose adjustment to establish dosing regimen, and then every 6-12 months thereafter. GH assessment is not informative in the follow-up of pegvisomant and cabergoline and should not be performed[112].

Medical therapy serves as a temporary solution for patients undergoing radiation therapy until the radiation effect is observed. IGF-1 should be measured in these individuals at intervals suitable for the medication being administered. Depending on how quickly IGF-1 declines and if it declines steadily within the therapeutic range, treatment can be stopped at least once a year to check for the development of radiation-induced remission[113]. Ideally, the same well-validated IGF-1 test should be utilized on all evaluations.

Imaging follow-up

An MRI should be performed 3-6 months after surgery to assess residual tumor and guide further management[4,111]. In patients with visual field impairment at diagnosis, a neuro-ophthalmologic evaluation should be part of routine follow-up, as it provides a detailed assessment of both visual fields and optic nerve function beyond what standard perimetry can detect[114]. Visual field testing is recommended every 6 months if deterioration is present or suspected, and annually when visual function is stable[114,115]. Neuro-ophthalmologic follow-up is also indicated when new visual symptoms develop, before interventions that may affect the optic pathway (e.g., radiation therapy or repeat surgery), and in long-term surveillance of patients with tumors abutting the optic chiasm[115,116]. If there are clinical or biochemical signs of disease progression, or if treatment changes are being considered, an MRI should also be obtained[3,4,111].

Clinical assessment and management of comorbidities

Patients with acromegaly often present with multiple comorbidities requiring structured, evidence-based management. Early recognition and active management of these complications are essential to improve outcomes. Key domains include cardiovascular health, metabolic control, skeletal integrity, oncologic surveillance, and sleep disorders[4,15,28,117,118]. Recommendations for baseline and follow-up monitoring are summarized in Table 4.

Cardiovascular complications

Excess GH and IGF-1 exert direct trophic effects on cardiomyocytes, stimulating protein synthesis and hypertrophy, while also promoting interstitial fibrosis and impaired diastolic relaxation. These mechanisms result in concentric biventricular hypertrophy, diastolic dysfunction, and predisposition to arrhythmias[119,120]. Endothelial dysfunction, increased arterial stiffness, and sympathetic overactivity further drive hypertension and atherosclerosis. Hypertension, left ventricular hypertrophy, arrhythmias, and cardiomyopathy are common and contribute to the excess mortality seen in uncontrolled disease. Biochemical control of GH and IGF-1 can partially reverse these changes, though long-standing cardiac damage may persist. The progression of acromegaly to systolic dysfunction with overt congestive heart failure is now an uncommon clinical outcome. Despite the increased prevalence of conventional cardiovascular risk factors in this population, the incidence of clinically significant coronary artery disease and arrhythmia does not appear to be elevated. Valvular abnormalities, attributable to fibrotic remodeling, generally persist irrespective of biochemical disease control; however, current evidence does not support an association between cabergoline

Table 4. Baseline and follow-up evaluation of comorbidities in acromegaly

Comorbidity	At diagnosis	Follow-up frequency	Notes
Cardiovascular	Blood pressure, ECG, echocardiography	Blood pressure every 6 months; ECG/echocardiography annually if abnormal	Assess for hypertension, cardiomyopathy, valvular disease
Metabolic	Fasting glucose, glycated hemoglobin, lipid profile	Every 6 months	Higher risk of diabetes/dyslipidemia in active disease and in patients receiving SRLs
Endocrine	Full pituitary profile: TSH, free T4, cortisol ± ACTH stimulation. Male sex hormones: total testosterone, SHBG, prolactin; free testosterone if interpretation is unclear. Female sex hormones: LH, FSH, estradiol, prolactin. Serum calcium; if elevated check PTH levels and consider MEN1, check 24 h urinary calcium especially in case kidney stones are present	Annually for all; ACTH test if suspected AI Annually in premenopausal women with menstrual disturbances or fertility concerns	Adjust for treatment-induced hypopituitarism
Oncologic	Colonoscopy (all patients, regardless of age); thyroid ultrasound if nodules are present	Colonoscopy every 10 years if normal; earlier if↑IGF-1, abnormal findings, family history; thyroid ultrasound follow-up as indicated	↑risk of colorectal neoplasia and thyroid nodules
Musculoskeletal	DXAII scan; vertebral imaging if fracture risk present	DXAII every 2 years; vertebral imaging annually in high-risk patients or in asymptomatic patients with hypogonadism or long-standing disease	Hypogonadism, GH excess increase fracture risk
Sleep disorders	Screen for OSA: Epworth sleepiness scale or polysomnography if symptomatic	Repeat if symptoms recur or after major weight changes or persistence of disease	OSA is common and worsens CV risk
Quality of Life	AcroQoL questionnaire	Annually	Supports patient-centered care

ACTH = adrenocorticotropic hormone; AcroQoL = Acromegaly Quality of Life questionnaire; AI = adrenal insufficiency; CV = cardiovascular; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; OSA = obstructive sleep apnea; PTH = parathyroid hormone; SRLs = somatostatin receptor ligands; TSH = thyroid-stimulating hormone

therapy and increased valvular pathology. Collectively, therapeutic advances in the management of acromegaly over recent decades have substantially mitigated cardiac morbidity, such that cardiovascular complications no longer represent the principal cause of mortality in affected patients. Regular blood pressure monitoring, electrocardiogram, and echocardiography are recommended at baseline and follow-up[1,7,9,121-123].

Metabolic disorders

Growth hormone acts as a counter-regulatory hormone, antagonizing insulin by promoting lipolysis and increasing circulating free fatty acids, which interfere with insulin signaling in skeletal muscle and liver. It also stimulates hepatic gluconeogenesis and reduces peripheral glucose uptake. While IGF-1 has insulin-sensitizing properties, the net effect of chronic GH/IGF-1 excess is insulin resistance, impaired glucose tolerance, and DM. Dyslipidemia is also frequent, driven by increased hepatic

very-low-density lipoprotein production[124,125]. Up to one-third of patients develop DM, which significantly worsens cardiovascular outcomes. In addition, pasireotide therapy may exacerbate hyperglycemia by reducing insulin secretion *via* somatostatin receptor subtype 5. Screening with fasting glucose, HbA1c, or OGTT should be performed at diagnosis and repeated periodically, especially after therapy changes[1,4,15].

Endocrine disorders

Endocrine comorbidities are highly prevalent in acromegaly and significantly contribute to morbidity and reduced quality of life. Hypopituitarism, particularly hypogonadism, is observed in up to 50% of patients, often resulting from tumor mass effects or concomitant hyperprolactinemia[15]. Careful hormonal evaluation at diagnosis and throughout follow-up is essential, including thyroid, adrenal, and gonadal axes[28]. Free testosterone or indices should be assessed in males with active disease due to reduced sex hormone-binding globulin, which can mask hypogonadism if only total testosterone is measured[15]. Appropriate hormone replacement therapy is crucial but must be carefully balanced, as both under- and over-replacement can worsen metabolic and cardiovascular risk[15]. Moreover, the interplay of gonadal steroids with the GH/IGF-1 axis means that replacement choices, particularly estrogen route of administration, can influence disease activity[4]. Long-term monitoring is required, especially in patients who have received radiotherapy, given their higher risk of progressive pituitary deficits[1,2,6,9].

Respiratory disorders

Soft-tissue hypertrophy of the tongue, pharyngeal walls, and larynx, combined with craniofacial bone overgrowth (e.g., mandibular prognathism), leads to airway narrowing and collapsibility. These anatomic changes explain the high prevalence of obstructive sleep apnea (OSA) in acromegaly, reported in up to 70% of patients. Respiratory muscle weakness and thoracic cage deformities may further contribute to hypoventilation. Patients often present with loud snoring, daytime somnolence, and OSA, which can persist despite normalization of GH/IGF-1. Polysomnography should be considered when symptoms are present. Continuous positive airway pressure is frequently required even after biochemical remission[15,126-130].

Musculoskeletal and neurologic complications

Excess GH/IGF-1 stimulates periosteal bone growth and cartilage proliferation, initially widening joint spaces but eventually leading to cartilage fissuring, osteophyte formation, and secondary osteoarthritis[131]. Despite normal or elevated bone mineral density, altered bone microarchitecture reduces bone strength and might increase fracture risk; however, data are inconsistent. It seems that bone loss and fragility are primarily caused by secondary panhypopituitarism and menopause[132-134]. In addition, soft-tissue hypertrophy in confined spaces (e.g., carpal tunnel) leads to nerve compression and peripheral neuropathies. Arthropathy, chronic back and joint pain, vertebral fractures, carpal tunnel syndrome, and neuropathies are frequent, and musculoskeletal symptoms often persist despite adequate biochemical control[135]. Targeted imaging, vertebral fracture assessment, DXA and neurologic evaluation (e.g., EMG for neuropathy) are warranted in symptomatic patients[15,28].

Neoplasia and cancer risk

Insulin-like growth factor 1 is a potent mitogen with anti-apoptotic properties, acting through PI3K/AKT and MAPK signaling pathways to promote cell proliferation and survival. Chronic IGF-1 elevation

has been implicated in increased cancer risk, particularly colorectal neoplasia, while evidence for thyroid, breast, and prostate cancers is less consistent. Baseline colonoscopy is recommended at the time of diagnosis for all patients. Subsequent surveillance should be individualized according to risk factors, with repeat colonoscopy at 10-year intervals if findings are normal. Earlier repetition is advised in the presence of persistently elevated IGF-1 levels, abnormal colonoscopy findings, or a family history of colorectal cancer. Thyroid ultrasound may be performed in the presence of nodules, while follow-up depends on initial findings. Cancer surveillance should be incorporated into long-term follow-up, even in patients achieving biochemical remission[1,15,117,118,136,137].

Quality of life

Quality of life (QoL) is a fundamental treatment goal in patients with acromegaly, complementing traditional clinical endpoints such as biochemical control and tumor size reduction. Despite achieving normalization of GH and IGF-1 levels, many patients continue to experience significant QoL impairments, particularly in the areas such as body image, musculoskeletal symptoms, headaches, and psychological well-being[138,139]. Multiple studies emphasize that depression and anxiety often exert a stronger influence on QoL than biochemical markers, highlighting the need of integrated, patient-centered care that addresses mental health alongside endocrine treatment[139,140]. Furthermore, although successful therapy can lead to QoL improvements, full normalization is rare, underscoring the importance of ongoing psychosocial support and complementary interventions – such as exercise and cognitive behavioral therapy – as essential components of comprehensive acromegaly management[139,140]. Therefore, QoL assessment should be performed at baseline and annually[15].

Mortality

The cumulative burden of cardiovascular, metabolic, and respiratory complications drives the historically observed 2- to 3-fold increase in mortality among patients with uncontrolled acromegaly[141]. Advances in surgery, pharmacotherapy, and radiotherapy have improved survival, and patients who achieve biochemical remission now often reach near-normal life expectancy[2,12].

Conclusion

This consensus statement provides a comprehensive, evidence-based framework for the diagnosis, treatment, and long-term management of acromegaly within the Croatian healthcare system. By integrating international standards with national healthcare realities, these recommendations aim to harmonize clinical practice, improve timely diagnosis, and optimize individualized therapy. Centralizing care in experienced multidisciplinary centers, ensuring equitable access to effective therapies, and maintaining systematic follow-up will reduce morbidity and mortality while improving patient quality of life. Ultimately, this document underscores the importance of collaboration among endocrinologists, neurosurgeons, radiologists, and allied specialists in advancing care standards and outcomes for patients with acromegaly across Croatia.

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SAŽETAK

Konsenzusne preporuke Hrvatskoga endokrinog društva za dijagnostiku i liječenje akromegalije

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Akromegalija je rijedak poremećaj hipofize koji je povezan sa značajnom smrtnošću. Cilj ove konsenzusne izjave jest pružiti preporuke za dijagnostiku i liječenje temeljene na dokazima, prilagođene hrvatskom zdravstvenom sustavu. Multidisciplinarni panel stručnjaka sustavno je pregledao međunarodne smjernice i dostupne dokaze primjenjujući pristup za procjenu razine sigurnosti dokaza i snage preporuka GRADE. Preporuke obuhvaćaju dijagnostiku, slikovne metode, kirurško liječenje, farmakoterapiju (somatostatinske analoge prve i druge generacije, pegvisomant, dopaminske agoniste te kombiniranu terapiju), radioterapiju, praćenje bolesnika te upravljanje supostojećim bolestima. Tablica sa sažetim i rangiranim preporukama pruža praktične smjernice za kliničku primjenu. Ove konsenzusne preporuke nude standardizirane, na dokazima utemeljene smjernice za dijagnostiku i liječenje akromegalije s ciljem poboljšanja ishoda liječenja bolesnika i unaprjeđenja te usklađivanja skrbi na nacionalnoj razini.

KLJUČNE RIJEČI

Akromegalija; Inzulinu sličan čimbenik rasta 1 (IGF-1); Hormon rasta; Neoplazme hipofize; Liječenje; Hrvatska