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# ACROMEGALY – ETIOLOGY, SYMPTOMS, TREATMENT. LITERATURE REVIEW

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**ABSTRACT**

Acromegaly is a rare endocrine disorder, typically resulting from a growth hormone (GH)-secreting pituitary adenoma. While these tumors are generally benign, they can sometimes exhibit local invasiveness or resistance to standard treatments. Clinically, the condition manifests through both distinctive physical changes and a range of systemic symptoms that may affect the cardiovascular, respiratory, metabolic, and neurological systems, and may also be associated with an increased risk of neoplastic diseases. Without timely treatment, these complications can significantly raise mortality risk, highlighting the importance of early detection. Initial screening usually includes measuring the levels of insulin-like growth factor 1 (IGF-1). Despite medical advancements, diagnosing acromegaly remains challenging, and delays in diagnosis are common, often resulting in advanced disease and severe complications. The preferred initial treatment is surgical resection of the tumor. For individuals who are ineligible for surgery or do not achieve remission postoperatively, medical therapy using somatostatin analogues is recommended. The primary therapeutic aims include normalization of IGF-1 and GH levels, reduction of tumor size, and management of associated complications.

**KEYWORDS**

Acromegaly, Growth Hormone, Pituitary Adenoma, Insulin-Like Growth Factor 1

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## Introduction

Growth hormone (GH) is released in a pulsatile fashion, with the most significant surges occurring during nighttime sleep. This hormone is produced by somatotroph cells located in the anterior pituitary gland. Its release is tightly regulated by two hypothalamic hormones: growth hormone-releasing hormone (GHRH), which promotes secretion, and somatostatin, which suppresses it (Ershadinia and Tritos, 2022). GH exerts both direct and indirect effects on various tissues, playing a crucial role in metabolic processes and promoting tissue development. The liver is the primary organ influenced by GH, as it produces insulin-like growth factor 1 (IGF-1) in response to GH stimulation. IGF-1 then promotes chondrocyte proliferation within the growth plates, contributing to bone elongation and mineral deposition. Additionally, GH independently stimulates osteoblast activity within bone tissue (Melmed, 2019; Hilczer and Szalecki).

## Epidemiology

Acromegaly is a rare hormonal disorder caused mainly by a pituitary adenoma, leading to chronic growth hormone (GH) excess. Its prevalence ranges from 2.8 to 13.7 per 100, 000, with 0.2–1.1 new cases annually per 100, 000 people (Lavrentaki et al., 2017; Maione and Chanson, 2019). In Poland, rates are slightly higher—up to 70 cases per million, with 3–4 new cases yearly per million (Bolanowski, 2014).

Typically diagnosed around age 45, it affects men and women similarly. Diagnosis is often delayed by years due to slow-onset symptoms like enlarged hands and facial changes, along with conditions like hypertension or diabetes.

Most patients have macroadenomas (>10 mm) at diagnosis—about 75%—a figure unchanged over time, pointing to ongoing challenges in early detection (Maione and Chanson, 2019). Despite better tools and awareness, underdiagnosis remains an issue, stressing the need to screen at-risk individuals with unusual comorbidities.

**Etiology**

Acromegaly is caused by chronic excess of growth hormone (GH), mostly due to a GH-secreting pituitary adenoma. Around 95% of cases are sporadic, with 40% of these tumors carrying GNAS mutations, which activate the cAMP–PKA pathway and promote GH production and tumor growth (Yamamoto and Takahashi, 2022). These GNAS-mutant tumors tend to be smaller and more responsive to first-generation somatostatin receptor ligands (fg-SRLs) (Beckers et al., 2013). Other cases lack GNAS mutations, implying different tumorigenic pathways.

Familial acromegaly involves germline mutations in genes like AIP, MEN1, CDKN1B, PRKAR1A, SDHx, and GPR101 (Hannah-Shmouni et al., 2016). AIP mutations are common in young patients with aggressive macroadenomas, while MEN1 and PRKAR1A mutations cause syndromic forms (MEN type 1, Carney complex). GPR101 microduplications are linked to X-linked acrogigantism (X-LAG), causing early-onset gigantism (Cazabat et al., 2012; Hannah-Shmouni et al., 2016).

Epigenetic factors, especially microRNAs (miRNAs), also play a role in acromegaly by regulating gene expression post-transcriptionally. Altered miRNA levels in tumor tissue and blood affect tumor growth and treatment response, with some reducing somatostatin receptor subtype 2 (SST2) expression, leading to lower fg-SRL effectiveness (Henriques et al., 2022; Trivellin et al., 2014). Abnormal methylation and chromatin changes may also contribute in tumors without clear mutations (Beckers et al., 2013).

Overall, acromegaly arises from a combination of somatic mutations, inherited genes, and epigenetic changes, highlighting the need for personalized diagnosis and treatment, especially in early-onset or resistant cases

**Symptoms**

Acromegaly is a multisystem disease that is often diagnosed with a delay. As a result, many symptoms and comorbidities are already present at the time of diagnosis (Slagboom et al., 2023). Patients usually show enlargement of the distal extremities, especially the hands and feet. The fingers become broader, accompanied by thickening of the soft tissues. Distinct facial characteristics include a prominent forehead, pronounced cheekbones, and a wide, bulky nose. Excessive growth of the mandible and maxilla frequently results in misalignment of the teeth. Skeletal deformities can also involve other parts of the body, and in more severe instances, a kyphotic curvature of the spine along with chest deformities may develop (Chanson and Salenave, 2008).

The skin thickens due to the buildup of glycosaminoglycans such as hyaluronic acid and chondroitin sulfate. There is an increase in sebum secretion, and excessive sweating frequently occurs. Women may experience hirsutism. Additionally, patients commonly develop numerous skin tags and keloid scars (Wang et al., 2023).

Hypertrophic osteoarthritis frequently occurs in acromegaly patients. It begins with an expansion of the joint spaces, but as the disease progresses, these spaces narrow, resulting in the development of osteophytes and other degenerative joint changes. Reducing growth hormone levels can partly prevent this progression, highlighting the significance of early detection (Colao et al., 2004).

Carpal tunnel syndrome is also a common complication. Its mechanism in acromegaly differs from that in the general population, primarily due to swelling of the median nerve. Furthermore, thickened ligaments and other soft tissues may compress the nerve (Giustina et al., 2003; Colao et al., 2004).

An excess of growth hormone adversely impacts both trabecular and cortical bone, increasing the likelihood of fractures in the vertebrae and femoral neck (Giustina, 2023).

Hypertension in acromegaly is probably caused by the proliferation of smooth muscle cells, which raises vascular resistance. Growth hormone also promotes increased sodium reabsorption in the kidneys and expands plasma volume, both contributing to higher blood pressure levels (Lombardi et al., 2006).

Patients often develop acromegalic cardiomyopathy, characterized by left ventricular hypertrophy. This condition further exacerbates hypertension and impairs the heart’s diastolic function (Lombardi et al., 2006; Kamenický et al., 2021).

Arrhythmias linked to acromegaly include paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, ectopic beats, sick sinus syndrome, ventricular tachycardia, and bundle branch blocks (Lombardi et al., 2006; Sharma et al., 2017).

Patients with acromegaly often experience notable respiratory complications. These arise from several structural and functional changes, including hypertrophy of nasopharyngeal soft tissues, increased lung volume (pneumomegaly), abnormal thoracic architecture, and alterations in respiratory musculature. Among the most

prevalent conditions is obstructive sleep apnea, affecting more than half of individuals with the disease. Respiratory insufficiency may also occur. Additionally, central sleep apnea is relatively common and may result from direct involvement of the central nervous system's respiratory regulation (Yousseif et al., 2012; Pivonello et al., 2017; Dineen et al., 2017).

Acromegaly frequently leads to disruptions in both glucose and lipid metabolism. Elevated levels of GH and IGF-1 play a key role in the development of insulin resistance, which in turn increases the risk of type 2 diabetes and abnormal lipid profiles. Even when acromegaly is effectively managed, complete resolution of these metabolic complications is uncommon (Mercado and Ramírez-Rentería, 2018; Ershadinia and Tritos, 2022).

Reproductive dysfunction, including hypogonadism, is frequently observed in individuals with acromegaly. The underlying causes are diverse and include increased prolactin levels, mechanical pressure exerted by a large pituitary tumor on the surrounding glandular tissue—disrupting gonadotropin secretion—and, in women, the metabolic consequences of excess growth hormone. Specifically, elevated GH may contribute to insulin resistance and secondary hyperandrogenism, leading to clinical features that resemble polycystic ovary syndrome (PCOS) (Colao et al., 2004; Zarool-Hassan et al., 2016).

Acromegaly is often associated with various neuropsychological disturbances. Patients may suffer from emotional instability, reduced social engagement, persistent low mood, and elevated stress levels. These symptoms can evolve into clinically significant anxiety or depressive disorders, highlighting the necessity of psychological care as an integral part of comprehensive treatment (Matthesen et al., 2025).

**Diagnosis**

The diagnosis of acromegaly primarily relies on clinical assessment, hormonal testing—particularly elevated serum insulin-like growth factor 1 (IGF-1) levels and insufficient suppression of growth hormone (GH) following glucose intake—and imaging of the pituitary gland using magnetic resonance imaging (MRI) (Ershadinia and Tritos, 2022). Evaluation of GH and IGF-1 levels is central not only to establishing the diagnosis but also to monitoring disease progression and treatment response (Schilbach et al., 2017).

Testing IGF-1 levels is advised in individuals exhibiting signs commonly associated with acromegaly, such as enlarged extremities or distinctive facial changes. It is also appropriate for patients with frequently linked comorbidities, including high blood pressure, persistent headaches, obstructive sleep apnea, irregular menstruation, carpal tunnel syndrome, or type 2 diabetes (Bolanowski et al., 2019; Caron et al., 2019).

If serum IGF-1 levels are elevated beyond age- and sex-adjusted reference ranges, an oral glucose tolerance test (OGTT) should be performed. This test involves administration of 75 grams of glucose, followed by measurement of GH levels to assess suppression. In patients with diagnosed diabetes, where OGTT reliability is reduced, serial GH measurements are preferred (Bolanowski et al., 2019).

Although random GH measurements are not typically used for initial diagnosis, they may still reflect disease activity during or after treatment (Schilbach et al., 2019). A single GH value below 1.0 μg/L is generally considered sufficient to rule out active acromegaly (Katznelson et al., 2014). Unlike GH, IGF-1 concentrations do not vary significantly throughout the day, making it a more stable diagnostic biomarker when GH overproduction is suspected (Ershadinia and Tritos, 2022). However, IGF-1 values should be obtained using standardized and validated assays. If the results are inconclusive or inconsistent with clinical symptoms, repeat testing is advised (Ershadinia and Tritos, 2022).

Active acromegaly is defined by persistently elevated IGF-1 levels combined with failure to suppress GH during OGTT. GH concentrations above 1.0 μg/L—or above 0.4 μg/L when using ultrasensitive assays—confirm the diagnosis (Katznelson et al., 2014; Bolanowski et al., 2019).

While GH and IGF-1 measurements are widely accepted for diagnosis and monitoring, their interpretation is often complex due to physiological and assay-related variability (Schilbach et al., 2017). GH is secreted by the anterior pituitary gland, and in acromegaly, this secretion becomes uncontrolled due to a GH-producing pituitary adenoma. IGF-1, in turn, is produced mainly by the liver in response to GH interaction with hepatic receptors (Schilbach et al., 2017).

Although IGF-1 is typically reflective of GH activity, the levels of both hormones may be influenced by several factors. IGF-1 levels naturally rise during puberty and pregnancy but may be lower in acromegalic patients with severe liver or kidney dysfunction, hypothyroidism, poorly controlled diabetes, malnutrition, or in women using oral estrogen therapies (Melmed, 2019).

After biochemical confirmation of acromegaly, imaging of the pituitary gland using contrast-enhanced magnetic resonance imaging (MRI) is essential to identify the underlying cause. If a pituitary macroadenoma

is detected, visual field testing should also be conducted to assess potential optic pathway involvement (Bolanowski et al., 2019).

MRI evaluation should include analysis of the tumor's T2-weighted signal intensity relative to adjacent brain structures. This feature may offer predictive value regarding the responsiveness to first-generation somatostatin analog therapies (Potorac et al., 2016).

**Treatment**

The primary aim of managing acromegaly is to restore normal levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). These hormone levels are directly linked to symptom severity, the presence of coexisting disorders, and are also used as predictors of life expectancy (Clemmons and Bidlingmaier, 2023).

The only treatment that offers a real possibility of curing acromegaly in the long term is transsphenoidal removal of the growth hormone-secreting pituitary neuroendocrine tumor. Research indicates that over half of the patients undergoing neurosurgery achieve full remission. In many other cases, the procedure significantly lowers GH and IGF-1 levels, which facilitates further biochemical control of the condition (Zamanipoor Najafabadi et al., 2022; Pennlund et al., 2025).

Tumor size is the key predictor of successful surgical outcome, with remission rates 2–3 times higher for microadenomas compared to macroadenomas. For large tumors, especially those with extrasellar extension, preoperative use of long-acting somatostatin analogs is often required to shrink the mass and optimize the patient’s condition before the technically demanding surgery. The transsphenoidal approach can be performed via microscopic or endoscopic techniques. Current evidence does not conclusively favor one method over the other in terms of success or safety, so the decision should be based on tumor characteristics and, most critically, the neurosurgical team’s expertise (Guinto et al., 2024).

Long-acting somatostatin analogs serve as the main pharmacological therapy, especially when surgery is not feasible or as preoperative treatment to decrease tumor volume. Agents such as Octreotide and Lanreotide are commonly used for long-term hormonal control. These drugs are generally effective, helping regulate hormone levels and alleviate clinical symptoms, which leads to an improved quality of life (Störmann et al., 2021; Bolanowski et al., 2021; Ferone et al., 2025).

Somatostatin analogs are typically well-tolerated, though they are associated with side effects such as increased gallstone formation, abdominal discomfort, diarrhea, and occasionally pancreatitis. Gastrointestinal symptoms tend to be milder and less frequent in patients treated with Octreotide (Gezer et al., 2022).

If first-generation somatostatin analogs fail to adequately control GH and IGF-1 levels, other therapeutic agents like Pasireotide or Pegvisomant may be introduced. Pasireotide, a next-generation somatostatin analog, has shown in clinical trials to reduce tumor size and decrease GH concentrations by an average of 0.6 ng/mL (Biagetti et al., 2025).

In select cases, especially in patients with large pituitary tumors, Pasireotide may be considered as a first-line therapy (Olarescu et al., 2025). However, it often causes disturbances in glucose metabolism, requiring close monitoring of blood sugar levels during the initial three months of treatment and after any dose adjustments.

Pegvisomant is a GH receptor blocker that acts on peripheral tissues. It does not affect GH secretion or tumor size, but it is highly effective in reducing IGF-1 concentrations and correcting metabolic abnormalities (Pirchio et al., 2023; MacFarlane and Korbonits, 2024).

Radiotherapy, due to its limited effectiveness and significant risk of inducing hypopituitarism, is not recommended as a first-line option. Stereotactic radiosurgery (e.g., Gamma Knife) may be considered postoperatively, particularly in patients with residual macroadenomas (Slavinsky et al., 2022).

Given the heterogeneity of clinical presentations and the wide range of treatment options, a single standardized therapeutic pathway for acromegaly does not exist. Evidence suggests that individualized treatment strategies result in quicker achievement of biochemical control (Marques-Pamies et al., 2024).

**Conclusions**

Acromegaly continues to pose significant diagnostic difficulties, with diagnosis frequently occurring late, which contributes to the emergence of severe health complications. The disease tends to progress slowly, and its symptoms are commonly misinterpreted or dismissed as signs of unrelated disorders, causing many patients to consult a specialist only when the condition is already advanced. Typical clinical manifestations involve alterations in facial features, increased size of the extremities, joint discomfort, persistent fatigue, and elevated blood pressure. The primary treatment method is surgical excision of the tumor, most often carried out using a transsphenoidal technique. If surgery is not an option or fails to achieve remission, patients are treated pharmacologically, primarily with somatostatin analogs. Treatment aims include the normalization of IGF-1 and GH concentrations, control of disease-related complications, and reduction of tumor size. Successful therapy can markedly enhance patient quality of life and decrease the likelihood of cardiovascular and metabolic issues, which are the leading contributors to the elevated mortality rate associated with acromegaly.

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