AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

ACROMEGALY: A CONTEMPORARY REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT APPROACHES

Ergasheva Gulshan Toxirovna

Asia International University

Abstract: Acromegaly is a chronic neuroendocrine disorder caused by excessive secretion of growth hormone (GH) and elevated insulin-like growth factor-1 (IGF-1), typically resulting from a GH-producing pituitary adenoma. The disease develops insidiously and is often diagnosed late, after irreversible systemic complications have developed. This article provides an expanded, evidence-based overview of the etiology, pathogenesis, epidemiology, clinical manifestations, diagnostic algorithms, and modern management strategies for acromegaly. Acromegaly is a rare disease, caused largely by a growth hormone (GH) pituitary adenoma. Incidence is higher than previously thought. Due to increased morbidity and mortality, if not appropriately treated, early diagnosis efforts are essential. Screening is recommended for all patients with clinical features of GH excess. There is increased knowledge that classical diagnostic criteria no longer apply to all, and some patients can have GH excess with normal GH response to glucose. Treatment is multifactorial and personalised therapy is advised.

Keywords: Acromegaly, growth hormone, pituitary adenoma, somatostatin receptor ligand

Introduction

Acromegaly is one of the most disabling endocrine diseases due to its multisystem involvement. Slow progression, subtle early symptoms, and lack of awareness among non-endocrine specialists contribute to diagnostic delays of 5–15 years. Early detection and adequate treatment significantly improve survival and quality of life. Acromegaly is a chronic disorder characterised by growth hormone (GH) hypersecretion, predominantly caused by a pituitary adenoma.[1] Disease prevalence ranges from 2.8–13.7 cases and annual incidence is between 0.2–1.1 cases/100,000 people; however, real incidence is likely much higher.[2,3] Average age at diagnosis ranges from 40–50 years[4–6] and mean delay in diagnosis is approximately 10–11 years. More than 95% of acromegalic cases are secondary to a pituitary adenoma: somatotrophs or GH-producing cells. In <5% of cases, acromegaly is related to a hypothalamic or neuroendocrine tumours, which secrete GH-releasing hormone, leading to excess GH. Peripheral GH-secreting tumours are exceedingly rare.[1]

GH stimulates synthesis of insulin-like growth factor 1 (IGF-1) from the liver and systemic tissues. Hypersecretion of GH leads to excess production of IGF-1. IGF-1 mediates most of the phenotypic features and metabolic effects of GH, but GH excess also has direct detrimental effects.[1,7] Acromegaly is associated with increased morbidity and mortality, but mortality returns to that of the normal population after appropriate treatment and biochemical normalisation.[8,9] This review focusses on several recent updates related to acromegaly diagnosis and treatment.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Etiology

Approximately 98% of acromegaly cases are caused by sporadic GH-secreting pituitary adenomas. Screening is recommended for all patients presenting with clinical features of acromegaly (such as mass tumour effects, systemic effects of GH/IGF-1 excess, cardiovascular and metabolic features, respiratory and bone/joint manifestations and/or other endocrine consequences). However, screening may also be considered in patients with several medical conditions known to be associated with acromegaly such as type 2 diabetes mellitus, carpal tunnel syndrome, debilitating arthritis, hypertension and sleep apnoea.[10–12] Awareness of these comorbidities is critical for early detection of acromegaly.
Less common causes include:

1. Hypothalamic GHRH-producing tumors

Bronchial carcinoids

Pancreatic neuroendocrine tumors

2. Ectopic GH secretion

Abdominal tumors

Bone marrow tumors (extremely rare)

3. Genetic and hereditary syndromes (≈ 5%)

MEN-1 syndrome (MEN1 mutations)

MEN-4 syndrome (CDKN1B mutation)

McCune–Albright syndrome (GNAS mutation)

Carney complex (PRKAR1A mutation)

Familial Isolated Pituitary Adenoma (FIPA) — often associated with AIP gene mutations

X-linked acrogigantism (X-LAG) (GPR101 gene duplication)

Hereditary forms typically manifest earlier, often with aggressive tumor growth and reduced sensitivity to somatostatin analogues.

Biochemical screening is the first step for an acromegaly diagnosis. Endocrine Society guidelines and experts' consensus recommend using age- and sex-adjusted IGF-1 levels in combination with GH nadir during an oral glucose tolerance test (OGTT) to diagnose and rule out acromegaly.[13,14] Measuring serum IGF-1 is usually the initial screening test. Considerable variation in laboratory results for IGF-1 obtained from different assays,[15] pose a hindrance to diagnosis. For example, these discrepancies may lead to inaccurate exclusion of a diagnosis. This has been reported in up to 30% of patients in different laboratories.[16] Given the methodological differences between assays and to establish accurate laboratory results, interpretation reference intervals must be method-specific, adjusted for age and sex, and stratified according to Tanner

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

stages.[17] Equivocal or elevated IGF-1 levels require further diagnosis confirmation in most patients. An OGTT with 75 g glucose is considered the gold standard for diagnosing acromegaly. However, similar to IGF-1 assays, the GH assay method can impact the absolute GH concentration reported by a laboratory.[18] As a consequence, the assay method may also impact the cut-off for GH suppression following oral glucose load.[19] Current widely used cut-offs for GH after OGTT are 1.0 and 0.4 ng/dL. However, these may not be accurate for all commercial assays, and method-specific values for GH cut-offs must be reported when available.

Pathogenesis

Excess GH stimulates hepatic production of IGF-1, which mediates:

soft tissue hypertrophy

bone enlargement via periosteal growth

metabolic alterations, including insulin resistance

cardiovascular tissue remodeling (leading to cardiomyopathy)

GH secretion is normally inhibited by somatostatin, acting through somatostatin receptor subtypes SSTR2 and SSTR5. These molecular pathways explain the efficacy of somatostatin analogues in treatment.

In 2017, the World Health Organization updated the histological grading of pituitary neuroendocrine tumours.[43] The new grading abandoned the term ‘atypical adenoma’ and emphasised the evaluation of morphology, tumour proliferation and invasion status for prognostication and evaluation of aggressiveness.[44]

GH-producing pituitary adenomas have several histological subtypes, and differ in morphology, clinical and biological behaviour. Classification is derived from the results of hematoxylin-eosin stain, immunohistochemistry, appearance under an electron microscope and transcription factors expressed in cells, and the following subtypes are established:

- GH-producing adenomas:

densely granulated somatotroph adenomas (DGSA) sparsely granulated somatotroph adenomas (SGSA); and intermediate granulated somatotroph adenomas.

- mixed GH/prolactin producing adenomas:

mammosomatotroph adenomas; and acidophil stem cell adenoma.

- plurihormonal adenomas, and silent somatotroph adenomas.[45]

DGSA are found in 40% of acromegaly tumours, while SGSA are found in 30%.[46,47] SGSA are usually larger at diagnosis than DGSA (21.6 mm versus 19.2 mm, respectively), have lower somatostatin receptor subtype 2 positivity (50% versus 100%) and higher Ki-67 proliferation

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

index (>3% in 67% of SGSAs versus <3% in 89% in DGSA).[48] Sparse granulation pattern has been also correlated with adenoma hyperintensity signal on T2-weighted MRI.[49]

Patients with SGSA usually require more surgeries, more radiotherapy, multiple different medications, a higher number of combined treatments and show medication resistance more often than DGSA. In a recent large study, median time for biochemically controlled acromegaly, using age-adjusted IGF-1 levels, was 9.7 years versus 16 years, in SGSA and DGSA, respectively.[50]

Intermediate granulated somatotroph adenomas have similar clinical behaviour to DGSA. Both acidophil stem cell and plurihormonal adenomas have been associated with aggressive behaviour, while clinical behaviour of silent somatotroph adenomas is variable, but often aggressive.[51–53] It is essential that pathology defines the exact type of GH pituitary adenoma in all patients undergoing surgery, as it has been proven to predict both clinical and biochemical outcomes.

Epidemiology

The true prevalence of acromegaly remains underestimated due to diagnostic delays.

Prevalence: ~5.9 per 100,000 population

Incidence: ~3.8 per 1,000,000 population per year

Peak diagnosis age: ~50 years

Actual prevalence may be 15–20 times higher when active screening is used

Mortality: 2–3 times higher without treatment

Life expectancy reduced by ~10 years in untreated patients

Severe obesity, prolonged fasting and malnutrition reduce IGF-1 levels in patients without acromegaly[21,22] and may also impact levels in patients with acromegaly. Random GH level testing is not recommended for diagnosis given the pulsatile nature of secretion.[23] Stress, physical exercise, acute critical illness and fasting state can cause physiological higher peak in GH secretion.[24–26] In pregnancy, homology between GH and placental GH makes GH measurement especially challenging in acromegaly cases.[27] Chronic renal failure can lead to higher GH but IGF-1 remains unchanged or can even decrease.[28] Type 2 diabetes and insulin resistance are associated with higher GH due to impaired suppression by glucose, while chronic hyperglycaemia has shown to be associated with decreased GH release.[29] High GH with low IGF-1 can be observed in states of GH resistance such as systemic inflammation, chronic liver disease, cirrhosis and anorexia nervosa.

Clinical Manifestations

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Changes in Appearance

Enlarged hands and feet

Facial coarsening (broadened nose, thick lips)

Mandibular prognathism

Increased space between teeth (diastema)

Thickened skin and excessive sweating

Neurological Symptoms

Headache (due to mass effect)

Carpal tunnel syndrome

Fatigue and paresthesias

Cardiovascular Symptoms

Hypertension

Biventricular hypertrophy

Cardiomyopathy

Arrhythmias

Congestive heart failure

Respiratory Symptoms

Obstructive sleep apnea

Snoring

Dysfunction of respiratory muscles

Endocrine and Metabolic Disorders

Impaired glucose tolerance

Type 2 diabetes mellitus (up to 50% of patients)

Dyslipidemia

Thyroid gland enlargement

Gastrointestinal Manifestations

Increased risk of colon polyps and colorectal cancer

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Enlarged intestines (dolichomegacolon)

Reproductive Disorders

Menstrual irregularities

Infertility

Erectile dysfunction

Decreased libido

Complications

The most frequent complications based on large cohorts:

Complication	**Frequency**
Cardiovascular diseases	67.6%
Hypopituitarism	26.3%
Sleep apnea	24.9%
Malignancies	22.6%
Arthropathies	19.0%
Skeletal abnormalities	8.2%

Untreated acromegaly significantly increases risks of stroke, heart failure, and gastrointestinal cancers.

Diagnosis

1. Biochemical Diagnosis

a. Elevated IGF-1 level — the primary diagnostic test

Age- and sex-adjusted reference ranges must be used.

Conditions such as diabetes, liver failure, pregnancy, and malnutrition influence IGF-1 levels.

b. GH suppression test (Oral Glucose Tolerance Test — OGTT)

Indicated if IGF-1 is mildly elevated or clinical signs are unclear.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Normal individuals suppress GH < 1.0 ng/mL

High-sensitivity assay cutoff: < 0.4 ng/mL
Lack of suppression confirms acromegaly.

2. Imaging

Pituitary MRI with contrast is the gold standard.
Findings:

Microadenomas (<10 mm)

Macroadenomas (≥10 mm)

Giant adenomas (>40 mm)

If MRI is negative:

CT chest, abdomen, and retroperitoneum to search for ectopic tumors

3. Evaluation of Comorbidities

Fasting glucose & HbA1c

Prolactin

Thyroid hormones (TSH, free T4)

Gonadal hormones

Cortisol

Ophthalmologic examination (visual fields)

Management Strategies

1. Surgical Treatment — First-Line Therapy

Transsphenoidal transnasal adenomectomy is recommended in most patients.

Success rates:

Microadenomas: 80–90% remission

Macroadenomas: 50–75%

Giant invasive tumors: 20% or lower

Success depends heavily on surgeon experience (recommended ≥50 pituitary surgeries/year).

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

2. Pharmacological Therapy

Used when:

Surgery is not possible

Remission not achieved

Tumor recurs

As preoperative therapy in selected cases

a. Somatostatin Analogs (SSAs) — First Line

Octreotide LAR

Lanreotide

Mechanisms:

Inhibit GH secretion

Reduce tumor volume in 30–50%

b. Pegvisomant — Second Line

GH receptor antagonist

Normalizes IGF-1 in >90% of resistant cases

Does not shrink tumor, so regular MRI is needed

c. Cabergoline

Effective in mild IGF-1 elevation

Can be combined with SSAs for partial responders

3. Radiotherapy

Indications:

Persistent disease after surgery + medical therapy

Inoperable tumors

Disadvantages:

Response develops slowly (months–years)

Risk of hypopituitarism (up to 50%)

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Prognosis and Follow-up

With adequate treatment:

Mortality approaches the general population

Quality of life significantly improves

Lifelong monitoring is mandatory

Follow-up includes:

IGF-1 (every 6–12 months)

GH suppression test if needed

Annual MRI for residual tumor

Screening for diabetes, cardiomyopathy, colon polyps

Conclusion

Acromegaly is a complex endocrine disorder requiring early detection, multidisciplinary care, and long-term monitoring. Modern surgical approaches, advanced pharmacotherapies (including pegvisomant), and improved imaging techniques have significantly reduced morbidity and mortality. Raising awareness among general practitioners and specialists is essential to minimize diagnostic delays.

References:

1. 1. Ergasheva, G. (2025). POLYCYSTIC OVARY SYNDROME: A COMPREHENSIVE OVERVIEW AND CURRENT TREATMENT APPROACHES. Modern Science and Research, 4(4), 937-944.
2. Ergasheva, G. (2025). ACROMEGALY: A SEVERE NEUROENDOCRINE DISORDER WITH MULTISYSTEM MANIFESTATIONS. Modern Science and Research, 4(3), 1123-1131.
3. Ergasheva, G. (2024). THE ROLE OF CORRECTIONAL PEDAGOGY IN ORGANIZING THE EDUCATION OF CHILDREN WITH DISABILITIES. Ethiopian International Journal of Multidisciplinary Research, 11(06), 206-207.
4. Toxirovna, E. G. (2024). QALQONSIMON BEZ KASALLIKLARIDAN HASHIMOTO TIREODIT KASALLIGINING MORFOFUNKSIONAL O'ZIGA XOSLIGI. Modern education and development, 16(7), 120-135.
5. Toxirovna, E. G. (2024). REVMATOID ARTRIT: BO'G'IMLAR YALLIG'LANISHINING SABABLARI, KLINIK BELGILARI, OQIBATLARI VA ZAMONAVIY DAVOLASH YONDASHUVLARI. Modern education and development, 16(7), 136-148.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

6. Эргашева, Г. Т. (2024). ОЦЕНКА КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ ОРЛИСТАТА У БОЛЬНЫХ ОЖИРЕНИЕМ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ. Modern education and development, 16(7), 92-105.
7. Ergasheva, G. T. (2024). THE SPECIFICITY OFAUTOIMMUNE THYROIDITIS IN PREGNANCY. European Journal of Modern Medicine and Practice, 4(11), 448-453.
8. Эргашева, Г. Т. (2024). ИССЛЕДОВАНИЕ ФУНКЦИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ ПРИ ТИРЕОИДИТЕ ХАШИМОТО. Modern education and development, 16(7), 106-119.
9. Toxirovna, E. G. (2024). GIPOFIZ ADENOMASINI NAZORAT QILISHDA KONSERVATIV JARROHLIK VA RADIATSIYA TERAPIYASINING UZOQ MUDDATLI SAMARADORLIGI. Modern education and development, 16(7), 79-91.
10. ERGASHEVA, G. T. (2024). OBESITY AND OVARIAN INSUFFICIENCY. Valeology: International Journal of Medical Anthropology and Bioethics, 2(09), 106-111.
11. Ergasheva, G. T. (2024). Modern Methods in the Diagnosis of Autoimmune Thyroiditis. American Journal of Bioscience and Clinical Integrity, 1(10), 43-50.
12. Tokhirovna, E. G. (2024). COEXISTENCE OF CARDIOVASCULAR DISEASES IN PATIENTS WITH TYPE 2 DIABETES. TADQIQOTLAR. UZ, 40(3), 55-62.
13. Toxirovna, E. G. (2024). DETERMINATION AND STUDY OF GLYCEMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH COMORBID DISEASES. TADQIQOTLAR. UZ, 40(3), 71-77.
14. Toxirovna, E. G. (2024). XOMILADORLIKDA QANDLI DIABET KELTIRIB CHIQARUVCHI XAVF OMILLARINI ERTA ANIQLASH USULLARI. TADQIQOTLAR. UZ, 40(3), 63-70.
15. Toxirovna, E. G. (2024). QANDLI DIABET 2-TIP VA KOMORBID KASALLIKLARI BO'LGAN BEMORLARDA GLIKEMIK NAZORAT. TADQIQOTLAR. UZ, 40(3), 48-54.
16. Tokhirovna, E. G. (2024). MECHANISM OF ACTION OF METFORMIN (BIGUANIDE) IN TYPE 2 DIABETES. JOURNAL OF HEALTHCARE AND LIFE-SCIENCE RESEARCH, 3(5), 210-216.
17. Tokhirovna, E. G. (2024). THE ROLE OF METFORMIN (GLIFORMIN) IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS. EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE, 4(4), 171-177.
18. Эргашева, Г. Т. (2024). Эффект Применения Бигуанида При Сахарным Диабетом 2 Типа И Covid-19. Research Journal of Trauma and Disability Studies, 3(3), 55-61.
19. Toxirovna, E. G. (2024). QANDLI DIABET 2 TUR VA YURAK QON TOMIR KASALLIKLARINING BEMOLARDA BIRGALIKDA KECHISHI. ОБРАЗОВАНИЕ НАУКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ, 38(7), 202-209.
20. Эргашева, Г. Т. (2024). СОСУЩЕСТВОВАНИЕ ДИАБЕТА 2 ТИПА И СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ У ПАЦИЕНТОВ. ОБРАЗОВАНИЕ НАУКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ, 38(7), 219-226.