Update on Systemic Complications, diagnosis *and remission of Acromegaly*

What's new?!

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Pituitary (2024) 27:7–22
https://doi.org/10.1007/s11102-023-01360-1

Consensus on criteria for acromegaly diagnosis and remission

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Systemic Complications of Acromegaly and the Impact of the Current Treatment Landscape: An Update

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Endocrine Reviews

Introduction

Acromegaly caused by a GH-secreting pituitary adenoma can deleteriously affect QOL and mortality if not diagnosed early and properly treated.

- Acromegaly incidence is slightly higher in **females**.
- **Men** are significantly **younger** at diagnosis, by a median of 4.5 years.
- Women may show both increased incidence and mortality risk.
- **Younger** patients tend to have larger and more aggressive tumors that are diagnosed earlier.
- **Older** patients usually have smaller and less aggressive tumors.

Introduction

- About 50% of patients are partially or totally resistant to available somatostatin receptor ligands (SRLs).

Somatostatin receptor 2 and 5 subtypes are usually expressed in GH-secreting adenomas, and approved SRLs bind preferentially to SSTR2 and, to a lesser extent, SSTR5.

J Clin Endocrinol Metab, January 2015, 100(1):122–131

Morphology classification

Densely granulated adenomas

Perinuclear

- If >70% of the cells had perinuclear.
- Higher SSTR2 expression.
- Exhibit a more favorable SRL response.
- Hypointense adenomas

Sparsely granulated adenoma

- Globular aggregations
- Larger tumors
- Low SSTR2 expression
- Generally are more invasive
- T2-weighted hyperintensity

3 Acromegaly types :

Type 1

- Older (> 50 y) with the longest follow-up.
- Densely granulated
- Non aggressive
  - A **concave MRI** shape
  - **IGF-1** levels at diagnosis are **lower**
  - Mass effects are less commonly seen
  - Resulting in **longer disease duration**
  - Ki-67 index < 3%, indicating lower proliferative activity.

Type 3

- Age at diagnosis (30 y),Female patients
- More aggressive
- Sparsely granulated ,Macroadenomas
- Extend to both the sphenoid sinus and suprasellar regions.
- Commonly encountered optic chiasm compression.
- MRI as a “peanut”or round shape
- shorter disease duration
- The lower expression of SSTR2, Shortest duration with controlled disease.
- Adverse survival , High aggressiveness

J Clin Endocrinol Metab, January 2015, 100(1):122–131

Type 2

- Densely or sparsely granulated.
- Macroadenomas with no invasive features.
- Densely granulated adenomas in this group responded less effectively to treatments than type 1 patients.
- Sparsely granulated tumors in acromegaly type 2 are not invasive.
- Higher IGF-1 levels at diagnosis
- Required more treatments than did type 1 patients.
- flat MRI shape.
- Abundance of SSTR2 are intermediate, as were clinical outcomes.

Mortality
What's new?!

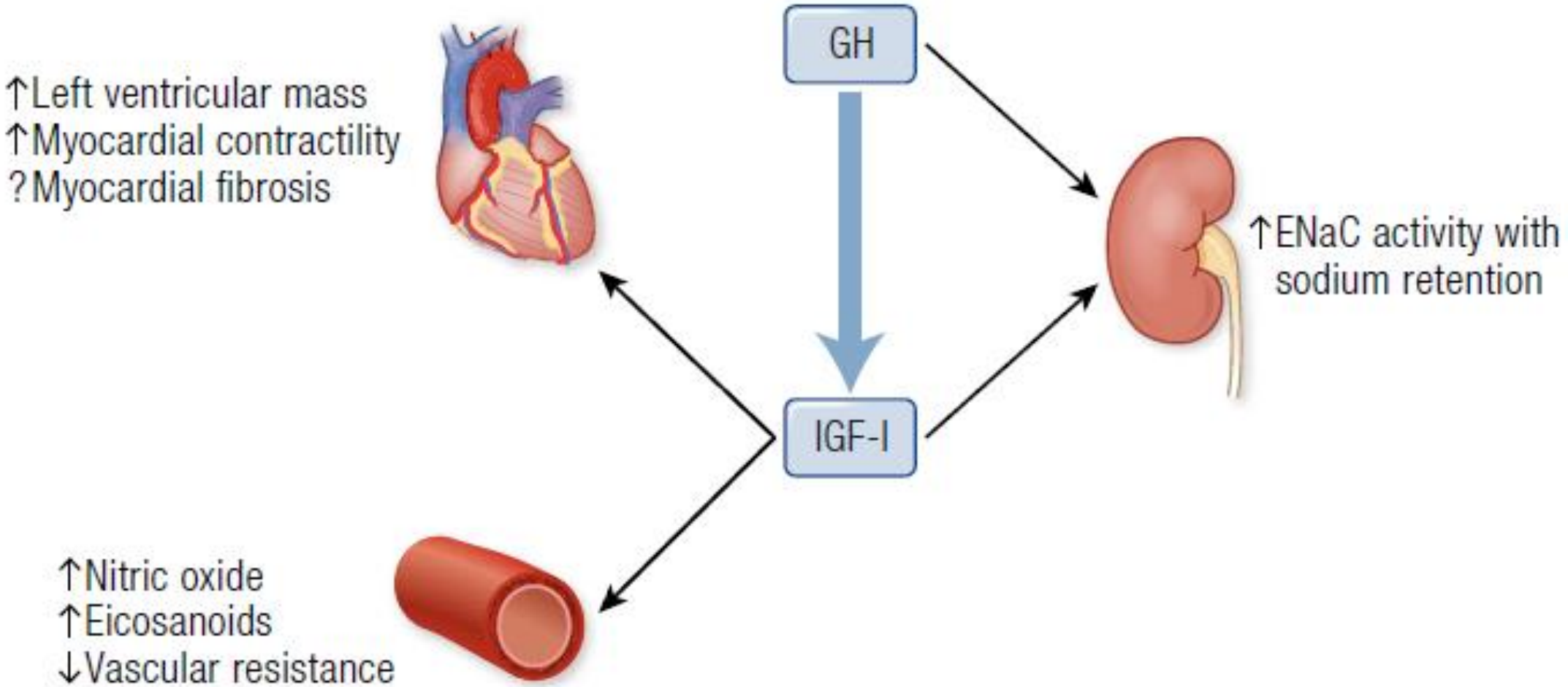
***Excess mortality** reported primarily due to:*

- ***Cerebrovascular disease***
- ***IHD***
- ***Malignancy***

Systemic Complications

GH/IGF-I and the cardiovascular system

- The GHR is expressed at high levels in both **myocardium and vessels**, as is the IGF-I receptor.
- The addition of IGF-I to cultured neonatal rat cardiomyocytes induces cell **hypertrophy without** affecting the number.
- GH and IGF-I also have ***indirect effects*** on the cardiovascular system by regulating peripheral resistance.
- IGF-I–induced vascular resistance is reduced through stimulation of NO release from the endothelium.


↑Left ventricular mass
↑Myocardial contractility
?Myocardial fibrosis
GH
IGF-I
↑ENaC activity with sodium retention
↑Nitric oxide
↑Eicosanoids
↓Vascular resistance

- Frequency of LVH ranging from 11% to 78% when analyzed by **ECHO**.
- MRI the ***gold standard*** for evaluating **LVH and fibrosis**.
- CMRI is a more precise methodology **higher accuracy** than ECHO.
- ECHO has also been shown to overestimate LVH, particularly in patients with AH and cardiomyopathy.

- Diastolic dysfunction : **11% to 58%** of patients when analyzed by ECHO.

- **Systolic dysfunction** is uncommon, Not seen or observed in **<3 %** of the patients in most recent studies that used ECHO.

Therefore, although **diastolic dysfunction** is frequently observed in ECHO studies, it is usually mild and with no **clinical consequence**,

and the **progression to systolic** dysfunction has

generally **not** been described.

Ischemic cardiac disease

- Acromegaly is associated with many known **risk factors** for CHD, such as AH,DM, and dyslipidemia.

- Prevalence of AH was **higher** in patients who suffered an ***MI or stroke*** than in patients who did not ,indicating that **AH** was probably the **main contributor to vascular complications**.

- Although patients with acromegaly display decreased flow-mediated dilatation and **increased carotid intima thickness**, they present lower levels of **CRP and oxidative stress parameters**, indicating that inflammation and oxidative stress are **not** increased in these patients.

- Therefore, in summary, current knowledge indicates that **CHD** does **not** seem to be increased in patients with acromegaly.

Valvular abnormalities:

- Active acromegaly has been associated with **cardiac valvular abnormalities**.
- **Mild to moderate** AR of **31**% in patients with **active** acromegaly, **18%** in patients with **controlled** acromegaly.
- MR **(32% to 60%),** which was only observed in patients with active disease.

Risk factor for valvular disease :

✓Acromegaly duration

✓ Presence of AH

✓Disease activity

Arterial Hypertension

The increased prevalence of AH multifactorial etiology:

✓Increase in plasma volume, secondary to sodium and water retention in the kidney.

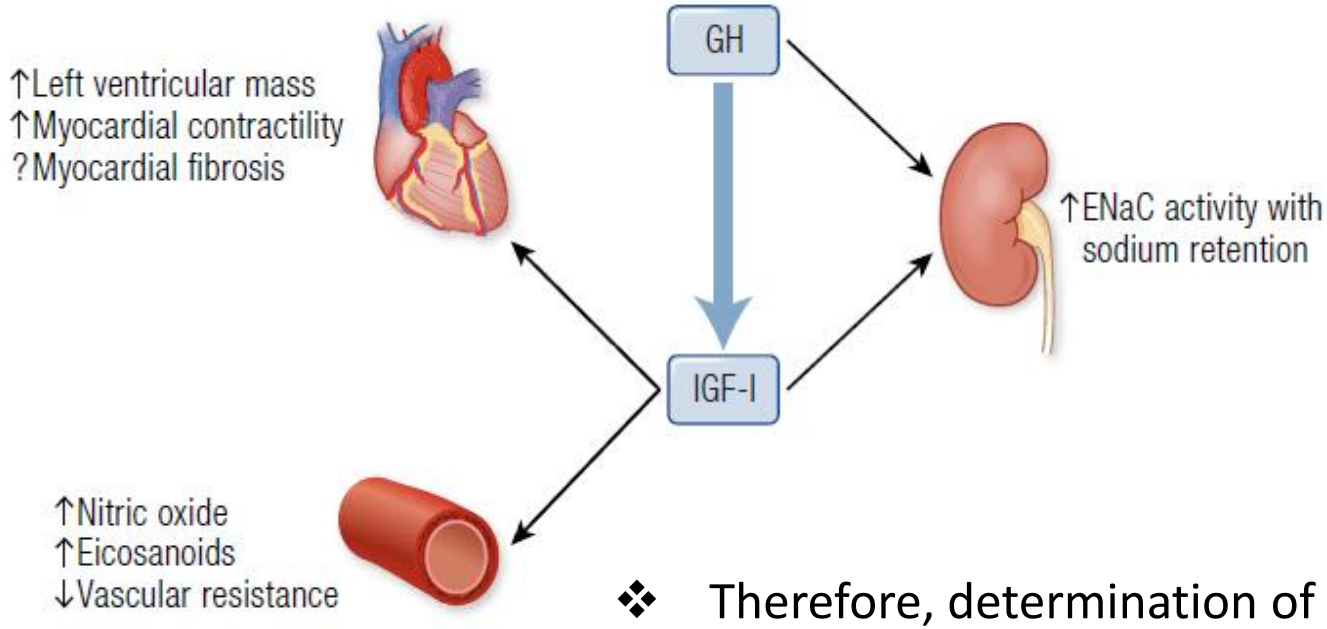
The antinatriuretic effect of GH may be mediated by :

❖The activation of the RAA system, as suggested showing an increase in the levels of renin and aldosterone after a GH infusion.

❖Direct effect of GH on the kidney.

GH **directly stimulates** the epithelial sodium channel subunit in the **cortical collecting ducts**.

Contrary, IGF-I can promote reduction of vascular resistance.



- Therefore, determination of which patient will have AH or not depends probably on the balance between these two opposite effects, but also on the individual predisposition to develop this complication.

- The true prevalence of AH in patients with acromegaly may have been overestimated in studies that used only a clinical **outpatient** BP evaluation.
- An AH rate of ***32.4%*** evaluated using clinical measurement, but the rate was reduced to **29.9% when ABPM** was used.

Patients with acromegaly have a ***higher diastolic*** BP and lower systolic BP than do non acromegaly hypertensive controls.

Recommendations:

- BP measurements are recommended for all patients with acromegaly at diagnosis in the outpatient clinic.
- In patients **with** AH, a 24-hour ABPM might be advisable, as some patients who are identified based solely on the ambulatory measurement will not display AH on ABPM.

- If BP is normal at the first consultation, **subsequent ambulatory measurements** should be performed, particularly in patients with active acromegaly.

Recommendations:

- ✓An ECHO is also recommended at diagnosis for all patients with acromegaly to evaluate **valvular disease**, **diastolic and systolic** function, and the presence of **LVH**.
- ✓If the ECHO is **normal** at diagnosis, no additional screening evaluation is needed in patients whose disease is **controlled** with treatment.
- ✓The examination may be repeated **after 1 year** in patients with a normal ECHO at diagnosis who continue to have active disease.
- ✓Similarly, a **repeat ECHO after 1 year** is recommended for patients with ***ECHO abnormalities*** at the acromegaly diagnosis.

- Although CHD prevalence per se does not seem to be increased in patients with acromegaly based on recent data, patients have many CHD ***risk factors***.
- Therefore, an evaluation of risk factors (AH, glucose abnormalities, and hyperlipidemia) and aggressive treatment to achieve clinical goals are required.
- Evaluations and treatments should be performed according to the recommended guidelines for the normal population.

Respiratory disease:

- Respiratory complications in acromegaly arise from both **structural and functional** changes in the entire respiratory system, resulting in **SAS** and/or **respiratory insufficiency**.

- Accounting for ***10% to 20%*** of **mortality** in acromegaly.

Anatomical changes in the ***craniofacial region*** and upper respiratory:

✓Macroglossia

✓ soft palate, pharyngeal and laryngeal swelling

✓vocal cord thickening

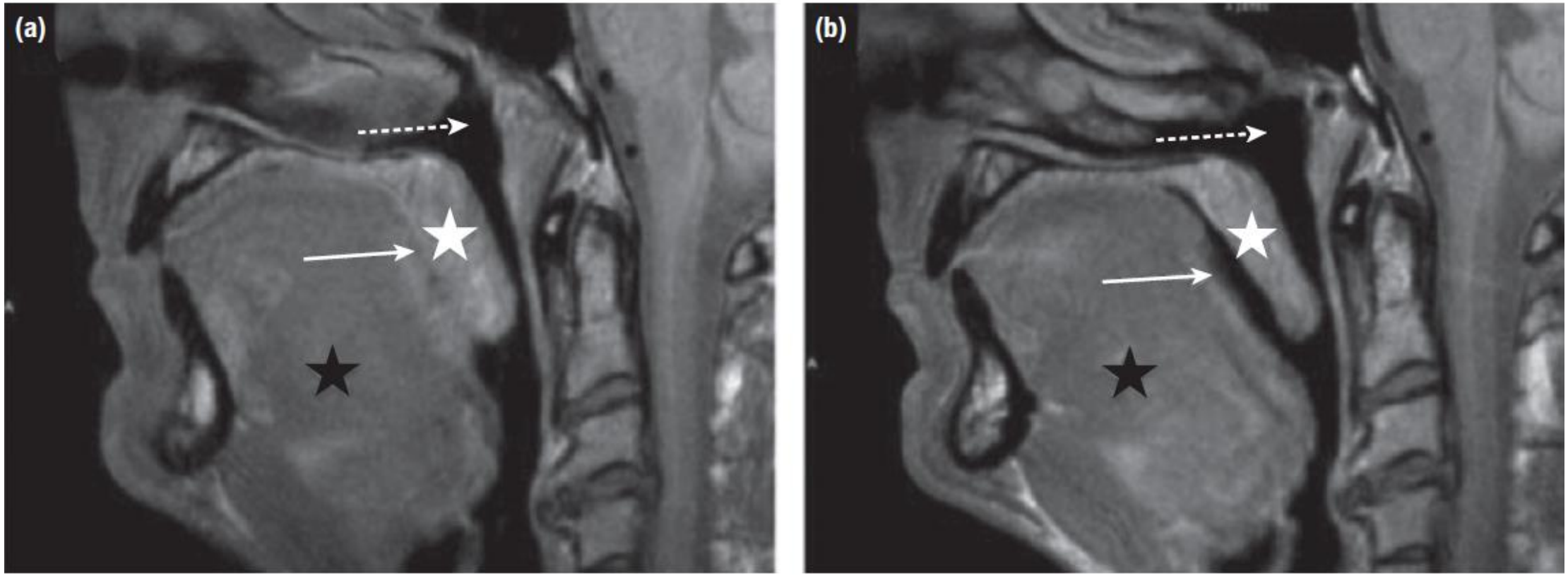
✓ An mandible and maxilla overgrowth

- Up to a third have an additional *central component* of SAS :

  repeated **apneic episodes** *without* any associated **ventilatory efforts**.

- Directly related to *high GH or IGF-I* levels resulting in modulation of central respiratory center function and an **increased ventilator threshold** for carbon dioxide.

- Approximately **70%** of patients with active acromegaly have SAS, representing a significantly higher prevalence than the estimated one in the **general population** at ***5% to 10%.***



Sagittal T1-weighted MRI sequences of the neck before (a) and after treatment (b) of acromegaly in a male patient with OSA.

Treatment of acromegaly resulted in a decrease in tongue (black star), soft palate (white star), and pharyngeal wall thickness, and widening of both the oropharynx space (solid arrow) between the tongue and soft palate and of the posterior nasopharynx (dashed arrow).

Resolution of OSA was seen in this patient after treatment of GH excess.

- **Hypopituitarism** impact on OSA in patients with acromegaly is also notable. **Hypothyroidism** increases OSA prevalence, albeit replacement therapy improves OSA, at least in non obese patients.

- Conversely, several studies demonstrated **OSA exacerbation** of sleep apnea in **eugonadal or hypogonadal men treated** with androgens.

- Therefore, **caution** is needed when commencing ***androgen replacement*** in patients with acromegaly with **severe untreated OSA**.

- Increased lung volumes were first observed on chest radiographs.

✓Increased lung volumes and air trapping, as well as ***small airway resistance and obstruction.***

- Forced vital capacity (FVC), total lung capacity (TLC), and residual volume (RV) have been shown to be greater .
- **Airway resistance was also increased**, reflecting small airway involvement that may be explained by a loss of elastic tissue.

Recommendations:

- All patients be evaluated for SAS at diagnosis , the gold standard for which is polysomnography.
- In patients with *severe SAS*, preoperative treatment with SRLs may be considered, which can potentially reduce upper airway soft tissue swelling, thereby minimizing the risk of intubation-related complications.

Bone complications

- Up to 60% prevalence of radiological VFs has been reported and a substantial risk of incident fractures despite biochemical disease control, which may result in significant pain, morbidity, and poor QoL.

GH, both directly and via systemic and local IGF-I production has an anabolic effect on bone:

- ✓stimulating **osteoblastogenesis**
- ✓ osteoblast **differentiation and function**
- ✓ upregulates **type 1 collagen** transcription and decreases collagen-degrading proteases.

Mechanisms behind increased bone resorption:

- GH- and IGF-I–induced cytokine production (e.g., IL-1, TNF-a)
- ↑ markers of bone resorption compared with bone formation markers in patients with acromegaly .

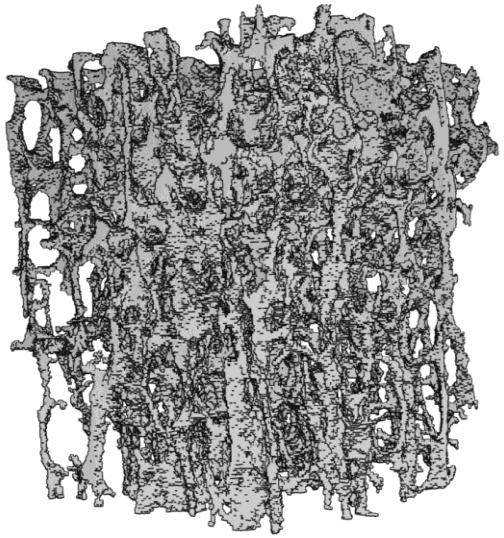
However, increased bone resorption in acromegaly seems to be coupled to bone formation.

Increases **trabecular bone volume**,

but with a ***negative impact on bone microstructure***.

Hypercalcemia: 5% to 10%

Hypercalciuria : 68%



The hypercalciuria frequently observed has been attributed to increased **bone *turnover*** *by GH excess*, and therefore may also be considered a marker of ***skeletal fragility***.

BMD interpretation in the context of acromegaly remains challenging for several reasons:

1. ***Overestimation*** of BMD at the lumbar spine due to **osteophyte formation** and **facet joint hypertrophy**.
2. The effect of **bony enlargement** on two-dimensional areal DXA measurement.
3. Differential effects of GH on cortical and trabecular bone (increased **periosteal ossification** vs **weakened trabecular microarchitecture**), which are variably distributed at different skeletal sites, but are not distinguishable by DXA.

4. Higher femoral neck BMD, but similar lumbar spine BMD, in acromegaly patients compared with controls.

Increased fracture risk appears to be independent of BMD , and the **fracture risk assessment score** has not been shown to be predictive of fractures.

TBS

- Micro-CT, which is another form of high-resolution CT,

metric extraction from lumbar spine DXA images.

TBS : be of value in the evaluation of secondary osteoporosis and of greater utility than BMD in several circumstances:

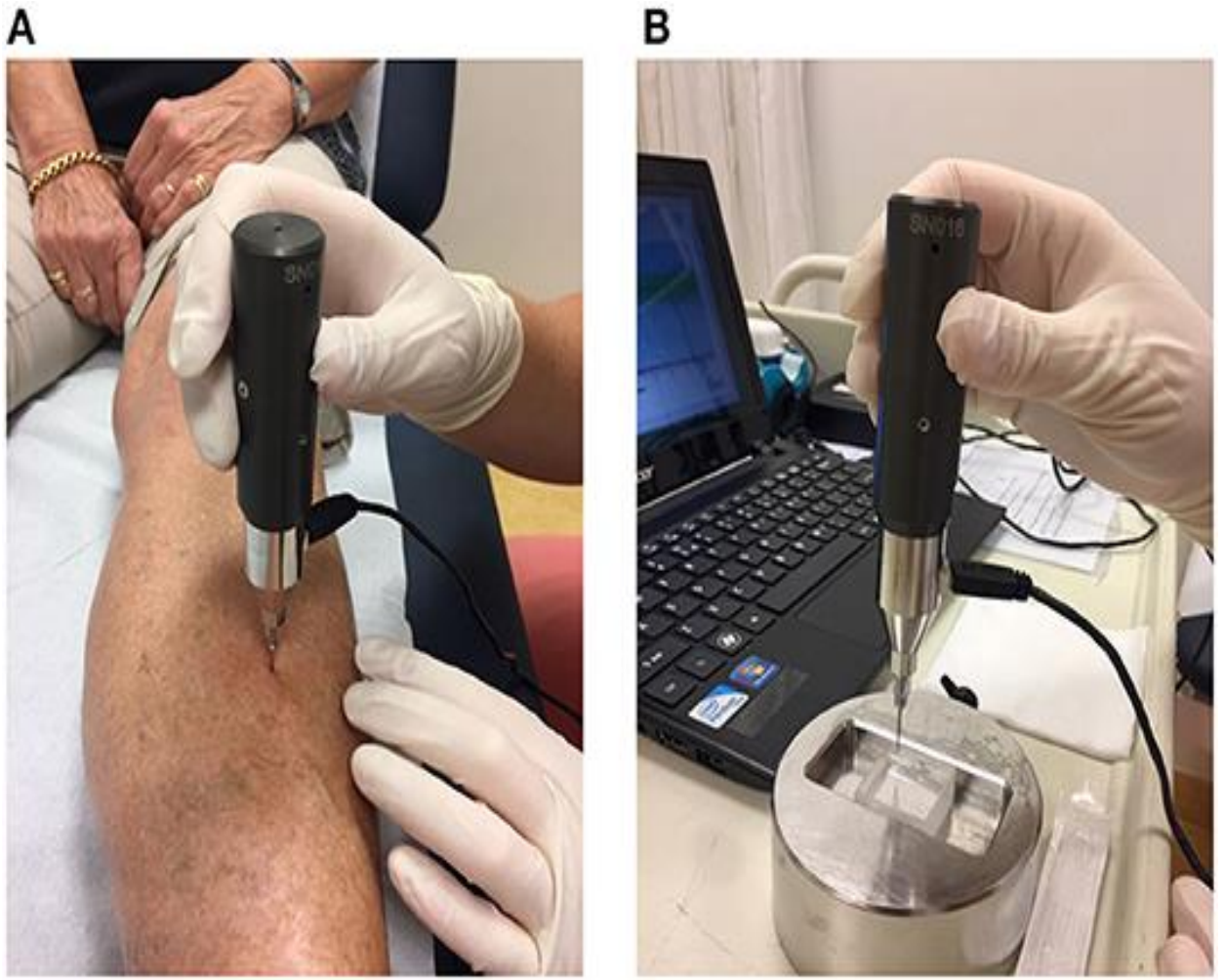
✓DM2

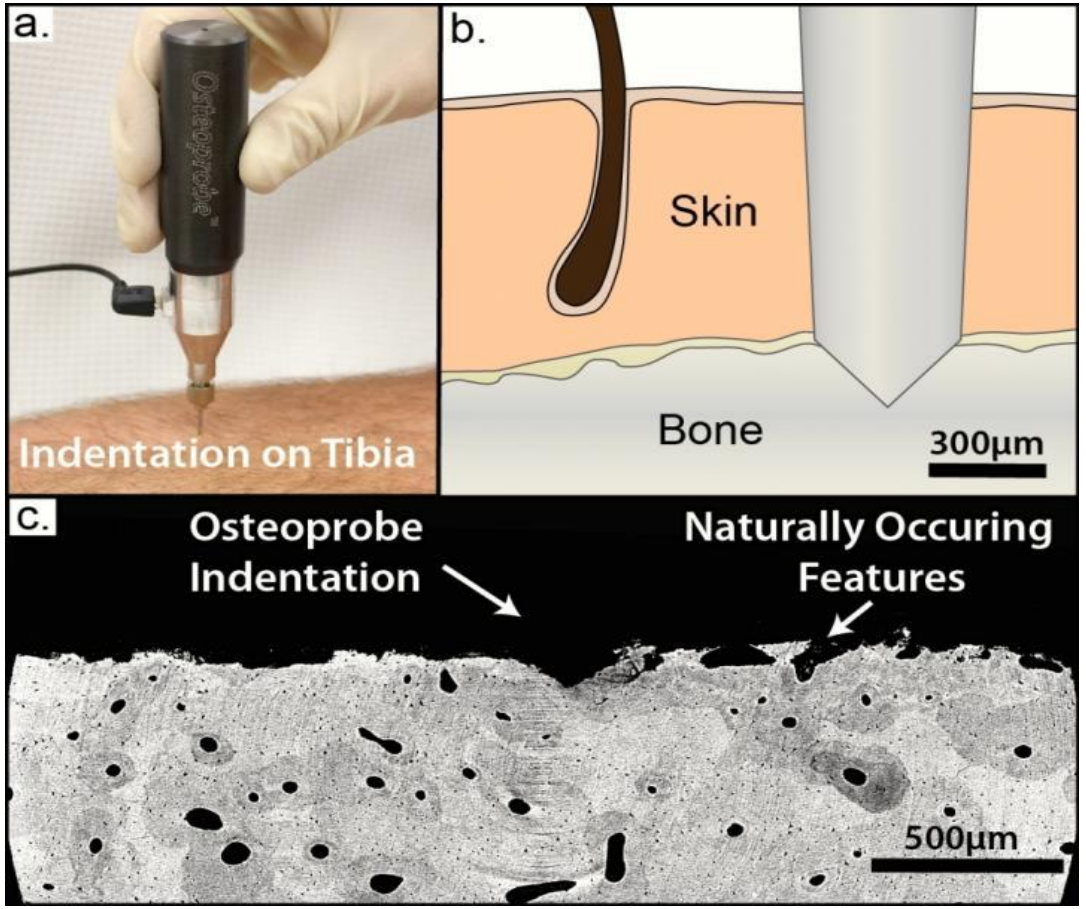
✓GC-induced

More recently, it has been evaluated as a potential **skeletal fragility index** in acromegaly; despite similar BMD values, lower lumbar spine TBS was demonstrated in acromegaly patients compared with controls, especially in hypogonadal patients and women.

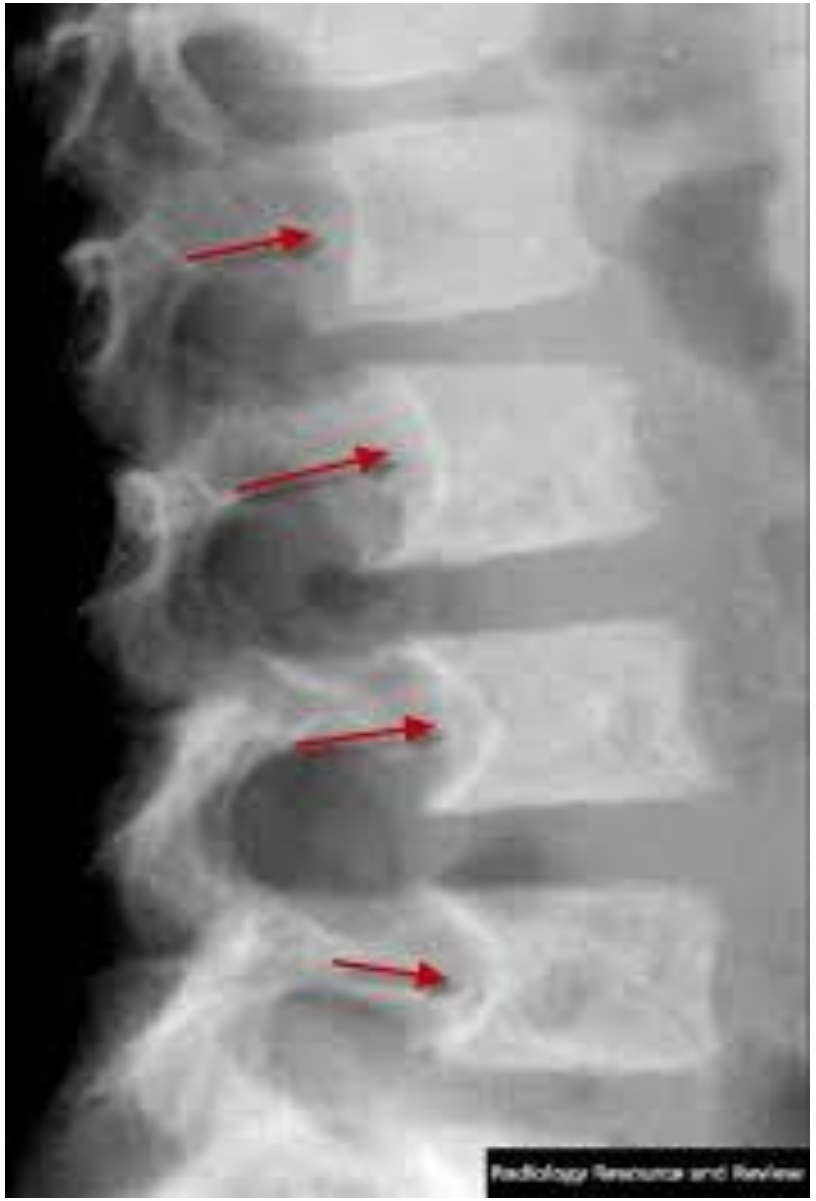
Impact microindentation

- Another novel technique used to acquire ***bone material strength*** index measurements in vivo.
- used as a surrogate to assess tissue-level ***properties of cortical bone.***
- This technique involves insertion of a test probe/indentation tool into *the midshaft of the tibia*.
- The bone ***material strength index*** was significantly lower in acromegaly patients.




a.
Osteoprobe
Indentation on Tibia
b.
Skin
Bone
300µm
c.
Osteoprobe
Indentation
Naturally Occuring
Features
500µm

- Fractures were most frequent in the thoracic spine and occurred as early as 2 to 3 years after diagnosis.
- Greater in patients with active disease (60%) compared with those in biochemical control (25%).
- As expected, hypogonadism was also associated with a higher prevalence of VFs.
- Higher in DM (63%) compared with patients without (28%).
- fracture risk appears to be *independent of BMD*.



The exact role of **antiosteoporosis drugs** in patients with acromegaly remains to be elucidated.

However, in general in patients with **uncontrolled disease**, antireabsorptives drugs (bisphosphonates and denosumab) are preferred owing to *high bone turnover*, resulting from excess GH and IGF-I, especially in the presence of reduced BMD.

Teriparatide might be preferred in patients with **VFs and progression of skeletal fragility** despite controlled acromegaly (and lower bone turnover overall).

Recommendations:

✓We recommend that screening x-rays or VF assessment for thoracic and lumbar spine fractures be undertaken **at diagnosis**, as patients with prevalent fractures are likely to be at highest risk for further fractures.

- **Repeat** imaging is needed although the **exact interval** is not clear. Recommendations suggest:

Every 2 to 3 years when osteoporosis risk factors, kyphosis, or symptoms are present.

Neoplastic complications

- **15% to 24% of acromegaly deaths** were **previously** attributable to cancer, most commonly colorectal cancer, and to a lesser extent, breast, thyroid, prostate, and other cancers.
- Mean cancer prevalence of **10.8%** significantly ***higher*** than in the global population (5-year cancer prevalence estimated at 0.59%).

Current guidelines for screening for colorectal cancer suggest :

At least one colonoscopy should be done at the time of diagnosis, followed by appropriate surveillance depending on findings from initial colonoscopy and disease activity.

✓In younger patients, the age at which screening should start remains controversial.

- Some have proposed that colonoscopy only be offered starting at ***age 40 years*** ,but others suggest that screening at diagnosis be performed **regardless of age**, as up to a **fifth** of acromegaly patients < 40 years of age have been found to have *colonic neoplasia vs* ***5% of controls***.

- If initial colonoscopy is normal, then patients should be screened in a similar manner to the general population every 10 years, provided acromegaly is biochemically controlled .
- More frequent screening may be required in patients with persistently active disease, but the optimal frequency is yet to be determined.

✓Some have recommended colonoscopy every 3 to 5 years in patients with either a polyp or persistently elevated IGF-I.

Thyroid nodules and cancer

- Nodular goiter has been reported in 43% to 75% of patients with acromegaly in ultrasound-based studies.

- Interestingly, unlike in the general population, where thyroid nodules are 3fold to 4 fold more common in women, *the prevalence is comparable in men and women.*

- This is unlikely, as the **natural history** of thyroid cancer in acromegaly does **not** appear to differ greatly from that in the general population; **multifocal**, **aggressive**, or **anaplastic tumors** have only ***rarely*** been reported.
- The most frequently reported thyroid cancer in acromegaly is DTC, ***most commonly PTC***.

In the absence of symptoms, or patient-observed goiter, clinical examination for thyroid nodules should be performed yearly, followed by ***US in those with palpable nodules***.

- **Indications for FNAB** should be guided by guidelines for the investigation of thyroid nodules.

Although current guidelines recommend a cut-off of 1.5 cm as an indication for FNAB in ***low suspicion nodules*** , it may be prudent to consider a 1 cm threshold for FNAB in acromegaly patients.

Other cancers!

- In registry-based studies, breast cancer does not appear to be more prevalent than in the general population , and **insufficient data** are available for prostate and kidney cancer.

- Assessment for other risk factors and adherence to standard age- and gender-based international, local screening guidelines should be emphasized in patients with acromegaly.

Complication	Screening at Diagnosis
Cardiovascular	• Ambulatorial BP
	• 24-h monitoring of BP[a]
	• ECHO
	• Electrocardiogram (if cardiac rhythm abnormality at physical examination)
	• Symptoms: referral to cardiologist
Respiratory	• Epworth scale
	• Polysomnography (if symptoms?)
Bone	• Thoracic and lumbar x-ray or VFA
Articular	• Clinical evaluation
Cancer	• Colonoscopy (especially if >40 y)
	• Thyroid US (only if palpable nodule)
Metabolic	• Glucose levels and lipid profile
Endocrine	• Pituitary function
QoL	• AcroQol (repeat yearly)

Diagnosis
What's new?!

- IGF-1 is used as it does not vary with **sleep patterns**, **exercise**, or throughout the day like GH.
- Increased IGF-1 level confirms GH excess, and imaging should be done next to localize the source.

✓If the *IGF-1 is normal*, acromegaly can essentially be *ruled out* at this point.

✓If the test is equivocal, a **GH suppression** test should be performed.

In 2014, guidelines from the Endocrine Society :

They recommended using IGF-I normalized to **age** but not sex for the diagnosis of acromegaly.

Confirmed by lack of suppression of GH < 1 µg/L during OGTT if necessary,

and

age-normalized IGF-I and random GH < 1.0 µg/L as a therapeutic goal.

Following on studies underscoring the challenges of uniformly applying results of GH and IGF-I assays in the clinic the 14th Acromegaly Consensus Conference held in 2022 in Italy, once again ***revisited the question of how to define biochemical criteria for acromegaly diagnosis and evaluation of therapeutic efficacy.***

Diagnosis
What's new?!

In a patient with typical clinical signs and symptoms of acromegaly, IGF-I > 1.3 times the ULN for ***age*** confirms the diagnosis.

- GH measured after overnight fasting may be useful for informing prognosis or complications, but is **not** required for diagnosis (SR).

Because of the episodic nature of GH secretion, however, serum concentrations may normally **fluctuate** from "undetectable" up to 30 µg/L(V)

- For patients with ***equivocal*** results, IGF-I measurements can be **repeated** using the same validated assay, and OGTT might additionally be useful.

- ***Age-stratified*** reference ranges should be based on adequate numbers of subjects , but sex-stratified reference ranges are likely not required beyond puberty if the normative population is sufficiently large .

- However BMI might influence normal IGF-I ranges, such that patients with high BMI have lower IGF-I levels for their age group.
- Nutritional, genetic, metabolic, and hepatic factors can also impact IGF-I concentrations, often inducing states of GH resistance.

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

Acromegaly: pathogenesis, diagnosis, and management,Lancet

- In a patient with ***typical clinical signs and symptoms*** of acromegaly, ***IGF-I > 1.3×ULN*** for age confirms the diagnosis.
- Random GH measured after **overnight fasting** may be useful for informing prognosis, but is not required for diagnosis.

- For patients with ***equivocal results***, IGF-I measurements can be repeated using the same validated assay, ***and OGTT might*** additionally be useful.

OGTT

- Thus, glucose suppressed GH nadir is effectively an ***indirect assessment of IGF-I*** and a reflection of preserved GH neuroregulation.
- However, there is no cut off for glucose-suppressed GH that **definitively excludes** a diagnosis of acromegaly .

- Furthermore, up to one third of patients with acromegaly may show a **paradoxical increase** in GH following OGTT and may demonstrate up to 50% increase or more in GH levels within 120 min after glucose ingestion.

- In most cases, diagnosis is clear without a need for OGTT, and the interpretative difficulties of OGTT therefore outweigh the potential advantages.

Thus, the consensus recommended :

This test be reserved for patients in whom

baseline hormone levels do not clarify the diagnosis

If OGTT is performed, 75 g glucose should be administered after fasting, and GH nadir assessed after 30, 60, 90, and 120 min.

BMI-based GH nadir cutoffs can be considered for diagnosis, with:

< 0.4 µg/L for BMI < 25 kg/m2

and

< 0.2 µg/L for BMI ≥ 25 kg/m2

- As healthy premenopausal females on estrogen-containing OC have higher GH nadirs, cessation of oral estrogen therapy 4 weeks prior to OGTT may avoid its effects on the GH axis.

- OGTT can **be safely** performed in patients with **IGT or type 2 DM**, with some applying **BMI-based cutoffs**.

- However, due to the ***suppressive effect of hyperglycemia*** on GH levels , particularly in patients with uncontrolled DM, both random and post-OGTT GH levels should be interpreted with caution.
- Measurement of **basal and 120-minute *Bs*** during OGTT is useful for detecting disturbances in glucose homeostasis.

Criteria for remission

- Although **biochemical** remission is the primary assessment of treatment outcome, it is not the only goal of treatment in acromegaly. In all cases, biochemical findings should be interpreted within the ***clinical context*** of acromegaly signs and symptoms.
- Maintaining serum IGF-I level in the **mid to upper half** of the age-related reference range could be considered in clinically controlled patients to avoid induction of **GH deficiency**.

Postoperative remission

There are no definitive studies on the **optimal** assessment for postoperative remission, nor of the **timing** of its evaluation.

- Within 2 hours of successful resection, **metabolic dysfunction** and **soft tissue swelling** start improving.
- **GH levels** are sometimes controlled within an hour.
- **73%** with microadenomas and **61%** harboring macroadenomas achieved GH levels lower than 1.0 µg/L during glucose loading and **normal serum IGF1 levels**.

Predictive of postsurgical remission:

- ✓Experience of the neurosurgeon
- ✓ smaller adenoma size
- ✓ lower Knosp score
- ✓lower preoperative IGF1
- ✓ and GH levels
- ✓Postoperative GH level within 24 hours of surgery

• BOX 7.5 Significant Predictors of Postoperative Biochemical Remission in Acromegaly Patients

Older age
Smaller tumor size
Lower Knosp grade
Lower preoperative GH level
Lower preoperative IGF1 level

Key Recommendation

- IGF-I should be measured at 12 weeks after surgery to determine postoperative biochemical remission.

- Early random GH assessment on day 1–14 and comparison with preoperative GH can inform the degree of ***adenoma removal and subsequent longer-term remission.***
- OGTT assessment may provide further predictive value.

Approximately 60% of patients achieve biochemical remission in the immediate postoperative period when defined as nadir GH < 1 µg/L *during OGTT*, with lower rates in patients with macroadenomas.

- Remission rates fell to approximately **40%** when using stricter criteria of **< 0.4 µg/L** on postoperative ***day 2.***

- **Nadir < 0.4 µg/L at 2–5 days and at 3–6 months** correlated better with remission than did < 1 µg/L.
- Generally, IGF-I normalization measured 12 weeks after surgery defines surgical success.
- However, delayed IGF-I normalization has been seen as late as 24–57 months after surgery.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 18 November 2021
doi: 10.3389/fendo.2021.743052

Check for updates

Postoperative GH and Degree of Reduction in IGF-1 Predicts Postoperative Hormonal Remission in Acromegaly

- Postoperative day 1 **(POD1) GH levels ≥1.55ng/mL predicted failure** to remit from surgical resection alone (59% specificity, 75% sensitivity).
- **Decrease** in corrected IGF-1 levels of at least 37% prognosticated biochemical control (90% sensitivity, 80% specificity).
- Early postoperative assessment at 1 day after surgery predicted **long-term remission**, and others have confirmed that elevated **random GH** on postoperative **day 1 or 2** strongly predicts persistent disease.

- **Discordant GH/IGF-I results :**

✓ ***Mild ongoing disease activity***, reflecting ***dysregulated but persistent*** somatotroph GH secretion and tissue responsiveness.

✓**Delay in IGF-I return** to normalization after surgery potentially determined by ***GH receptor polymorphism***.

Recommendation:

- IGF-I levels should be measured 12 weeks after surgery to determine postoperative biochemical remission.

- Early ***random GH*** assessment on day 1–14 and comparison with preoperative GH levels can inform the degree of adenoma removal and subsequent longer-term remission.

Recommendation

- OGTT as sessment may provide further predictive value.
- As preoperative SRL, used in patients with risk factors for more adverse surgical outcomes , may have carryover effects that continue to ***influence postoperative IGF-I values*** , assessment should be **repeated** at ***3–6 months to confirm remission***.

Recommendation:

- Within the first ***postoperative year***, IGF-I measurements ***every 3–6 months*** may be appropriate to confirm remission and then every ***6–12 months*** to monitor for potential **recurrence**.
- OGTT might be helpful in evaluating patients with **borderline IGF-I** levels and clinical signs of disease activity .

*Remission with adenoma-directed **medical therapy***

- As injectable SRL is administered monthly, timing of assessment for IGF-I could influence determination of biochemical control.

Recommendation:

- IGF-I level measured in the last week before the next injection should therefore be used to determine a need for dose titration or consideration of alternative treatment options if normalization is not achieved.

Recommendation:

- For patients treated with oral SRL administered daily, assessment of IGF-I for the purposes of dose titration should be done after at least 2 weeks of treatment .
- Timing of IGF-I assessment is not critical for patients treated with ***cabergoline*** administered in more than once-weekly intervals; the timing of assessment for patients treated *once weekly has not been systematically investigated*.

Recommendation:

- With all of these agents, random GH assessment is not likely to provide additional information in all patients, *but could be considered for symptomatic patients with IGF-I levels at the* ***higher end of the ULN****.*

For patients who did not achieve postoperative remission

and who are treated with adjuvant SRL, IGF-I should be assessed

3 months after initiation/dose adjustment of **injectable SRL and**

2–4 weeks after initiation/dose adjustment of **oral** SRL to establish an optimal dosing regimen, and **then every 6–12 months** thereafter once biochemical control is achieved.

Effects on Clinical Features:

- More than 70% of patients experience improved general **well-being, and soft tissue swelling** dissipates within several days of treatment.

- **Headache**, a common symptom, usually resolves within minutes of octreotide injection, likely reflecting a specific **central analgesic** effect .
- **Joint function improves and crepitus is reduced**, ultrasound shows evidence of bone or cartilage **repair**.
- After several months, sleep apnea resolves.

- low QOL measures including anxiety and depression may persist.

✓Hypertension

✓ joint space narrowing

✓new-onset vertebral fractures

do not appear to be ameliorated despite controlled GH and IGF1 levels.

The most important determinant of therapeutic responsiveness:

- ✓A higher SST2 to SST5 ratio.
- ✓Containing large, dense intra tumoral GH granules are more responsive to SRLs than are those with sparse GH granules.

(Sparsely granulated adenomas express SST2 less abundantly and more SST5)

*Remission with **peripherally** directed medical therapy:*

- The GH receptor antagonist pegvisomant as first-line medical therapy, 82–92% of patients achieved normalized IGF-I.
- Real-world studies of pegvisomant used mostly as **second- or third-line** medical therapy show approximately 54–64% of patients maintain biochemical control over the long term.

- Nevertheless, regardless of IGF-I control, patients showed consistent ***improvements in QOL*** as well as decreased blood glucose in those *with and without* diabetes suggesting that suppression of peripheral GH action has a **broader effect on disease activity** beyond IGF-I control.

✓Measuring GH is therefore not an efficacy marker and IGF1 measurement is the appropriate marker of patient responsiveness.

- As pegvisomant and cabergoline have a shorter half life than injectable SRL, IGF-I should be assessed every 1–3 months after treatment initiation/dose adjustment to establish the dosing regimen, and then every 6–12 months thereafter.
- GH assessment is not informative in follow-up of pegvisomant and cabergoline and should not be performed.

Radiation Therapy:

- In patients receiving medical therapy as a bridge until radiotherapy effect is seen, IGF-I should be assessed at the intervals appropriate for the medical therapy used.

- With sustained decline of IGF-I within the target range, treatment can be paused at least once each year depending on rapidity of the IGF-I decline to test for the onset of radiation-induced remission.

- IGF1 levels or nadir GH level less than 1 µg/L after an oral glucose.

- New or persistent elevations in IGF-I levels should be interpreted within the context of the *individual clinical scenario* and account or *factors that could affect* results such as **pregnancy, estrogen use, starvation, and metabolic changes.**

- Estrogens and SERMs inhibit hepatic IGF-I production but currently have a limited role in acromegaly management.
- For patients treated with medical therapy that targets the **GH receptor or the estrogen receptor**, efficacy assessment is limited to IGF-I normalization .

With these agents, GH assessment is not informative and should not be performed.

Follow up

- Acromegaly is also a heterogenous disease, With complex treatment

Follow up assessments should be consider:

✓ ***Biochemical*** evaluation of treatment effectiveness.

✓***Imaging*** studies evaluating residual or recurrent mass.

✓Clinical ***signs and symptoms*** of acromegaly complications and comorbidities.

Imaging studies

Recommendation:

MRI should be performed at 3–6 months postoperatively and used as baseline for further assessments.

- Thereafter, MRI should be performed upon:

1. signs of biochemical or clinical disease progression.
2. when a change in therapeutic modality is considered, such as prior to a second surgery or radiotherapy.

11C-methionine PET imaging may aid localization of residual adenoma in patients with persistent GH hypersecretion following primary (and subsequent) therapy when MRI findings are equivocal.

Clinical assessments

SAGIT and ***ACRODAT*** (Acromegaly Disease Activity Tool) are scoring tools that use multiple disease-specific parameters to ***define severity of acromegaly***.

(b)

S	SIGNS & SYMPTOMS	**Which of the symptoms (S) from the list below is your patient experiencing?**	**Score S**	**Score S** *from 0 to 4* *(0 = no Signs & Symptoms ticked)*
		Headache ☐ Sweating ☐ Joint symptoms ☐ Swelling ☐	Sum up the number of symptoms (S) ticked	S = _____
A	ASSOCIATED COMORBIDITIES	**Which of the associated comorbidities (A) from the list below is your patient experiencing?**	**Score A**	**Score A** *from 0 to 6* *(0 = no Comorbidities ticked)*
		Altered carbohydrate metabolism ☐ Hypertension ☐ Sleep apnea ☐ Heart disease ☐ Hypopituitarism ☐ Active malignant tumor ☐	Sum up the number of comorbidities (A) ticked	A = _____
G	GH NADIR WITH OGTT	**Report concentration result of GH nadir with OGTT**	**Corresponding score**	**Score G** *from 0 to 4*
		≤ 0.4 µg/l ○ > 0.4 to < 1.0 µg/l ○ ≥ 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/l ○ ≥ 5 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = _____
	OR	OR	OR	OR
	GH RANDOM OR MEAN CONCENTRATION OF GH SERIES	**Report concentration result from the test (GH random or mean concentration of GH series)**	**Corresponding score**	**Score G** *from 0 to 4*
		≤ 1.0 µg/l ○ > 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/l ○ ≥ 5 to < 10 µg/l ○ ≥ 10 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = _____
I	IGF-I	**Report level relative to age-adjusted upper limit of normal** *(ULN)*	**Corresponding score**	**Score I** *from 0 to 3*
		Normal ○ < 1.3 ULN ○ ≥ 1.3 to < 2 ULN ○ ≥ 2 ULN ○	I = 0 I = 1 I = 2 I = 3	I = _____
T®	TUMOR	**Describe the tumor** *(tick the worst choice by default)*	**Corresponding score**	**Score T** *from 0 to 5*
		No visible tumor ○ Micro tumor intrasellar < 10 mm ○ Macro tumor intrasellar ≥ 10 mm ○ Extrasellar tumor < 40 mm ○ Invasive tumor ○ Giant tumor ≥ 40 mm ○	T = 0 T = 1 T = 2 T = 3 T = 4 T = 5	T = _____

(b)

S — SIGNS & SYMPTOMS

Which of the symptoms (S) from the list below is your patient experiencing?		Score S	Score S *from 0 to 4 (0 = no Signs & Symptoms ticked)*
Headache	☐	Sum up the number of symptoms (S) ticked	S = _____
Sweating	☐		
Joint symptoms	☐		
Swelling	☐		

A — ASSOCIATED COMORBIDITIES

Which of the associated comorbidities (A) from the list below is your patient experiencing?		Score A	Score A *from 0 to 6 (0 = no Comorbidities ticked)*
Altered carbohydrate metabolism	☐	Sum up the number of comorbidities (A) ticked	A = _____
Hypertension	☐		
Sleep apnea	☐		
Heart disease	☐		
Hypopituitarism	☐		
Active malignant tumor	☐		

G — GH NADIR WITH OGTT / OR / GH RANDOM OR MEAN CONCENTRATION OF GH SERIES

Report concentration result of GH nadir with OGTT		Corresponding score	Score G *from 0 to 4*
≤ 0.4 µg/l	○	G = 0	G = _____
> 0.4 to < 1.0 µg/	○	G = 1	
≥ 1.0 to < 2.5 µg/l	○	G = 2	
≥ 2.5 to < 5 µg/	○	G = 3	
≥ 5 µg/l	○	G = 4	
OR		OR	OR
Report concentration result from the test (GH random or mean concentration of GH series)		**Corresponding score**	**Score G** *from 0 to 4*
≤ 1.0 µg/l	○	G = 0	G = _____
> 1.0 to < 2.5 µg/l	○	G = 1	
≥ 2.5 to < 5 µg/l	○	G = 2	
≥ 5 to < 10 µg/l	○	G = 3	
≥ 10 µg/l	○	G = 4	

IGF-I	Report level relative to age-adjusted upper limit of normal *(ULN)*	Corresponding score	Score I *from 0 to 3*
	Normal ○	I = 0	I = ____
	< 1.3 ULN ○	I = 1	
	≥ 1.3 to < 2 ULN ○	I = 2	
	≥ 2 ULN ○	I = 3	

TUMOR	Describe the tumor *(tick the worst choice by default)*	Corresponding score	Score T *from 0 to 5*
	No visible tumor ○	T = 0	T = ____
	Micro tumor intrasellar < 10 mm ○	T = 1	
	Macro tumor intrasellar ≥ 10 mm ○	T = 2	
	Extrasellar tumor < 40 mm ○	T = 3	
	Invasive tumor ○	T = 4	
	Giant tumor ≥ 40 mm ○	T = 5	

With SAGIT, clinicians have the opportunity to standardize scoring to evaluate signs and symptoms, **associated comorbidities**, GH levels, **IGF-I levels**, and adenoma characteristics.

✓**If SAGIT-G = 0, 1, or 2 and SAGIT-I = 0:**

91% of patients' treatment remained unchanged.

✓**If SAGIT-G = 0, 1, or 2 and SAGIT-I = 1, 2, or 3:**

71% of patients' treatment also remained unchanged.

✓ **If SAGIT-G = 3 or 4 and SAGIT-A = 0, 1, or 2:**

70% of patients' treatment had to be intensified or initiated.

✓**If SAGIT-G = 3 or 4 and SAGIT-A = 3, 4, or 5:**

100% of patients, treatment had to be intensified or initiated.

- With ACRODAT, clinicians rate disease activity as stable, mild, or severe based on IGF-I level, **adenoma status**, comorbidities, **symptoms**, and QOL, and the validation study showed that elevated IGF-I and evidence of adenoma growth drove definition of disease severity.

Both instruments may be useful in clinical practice for assessing changes in acromegaly disease severity and progression over time.

Take Home Message:

Diagnosis :

✓***Typical clinical signs and symptoms :*** ***IGF-I > 1.3×ULN*** for age confirms the diagnosis.

✓Random GH measured after **overnight fasting :**prognosis, but is not required for diagnosis.

✓ For ***equivocal results***, IGF-I can be repeated ***and OGTT***

After surgery:

✓IGF-I should be measured at 12 weeks after surgery to determine postoperative remission.

✓Random GH assessment on day 1–14

✓OGTT might be helpful in evaluating patients with borderline IGF-I and clinical signs of disease activity .

Take Home Message:

- SLRs:

✓ *IGF-I*

✓ Random GH assessment is not likely to provide additional information in all patients, *but could be considered for symptomatic patients with IGF-I levels at the* ***higher end of the ULN****.*

Take Home Message:

peripherally directed medical therapy:

✓GH is therefore not an efficacy marker and IGF1 measurement is the appropriate marker of patient responsiveness.

- ***Radiation Therapy:***
- IGF1 levels or nadir GH level less than 1 µg/L after an oral glucose.

- IGF-I should be assessed at the intervals appropriate for the medical therapy used.


Thank you