

Update to acromegaly management guidelines



What's new?!

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A Pituitary Society update to acromegaly management guidelines

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Presentation

- 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.
-

GH-secreting tumor behavior is heterogeneous and differs between patients.

- Some patients may harbor small **localized micro**adenomas.
 - Whereas others have large **invasive** macroadenomas.
 - Some patients seek medical attention **shortly** after symptoms start.
 - Most exhibit **symptoms for many** years before diagnosis.
-

- **Younger** patients tend to have **larger** and **more aggressive** tumors that are diagnosed earlier.
- **Older** patients usually have **smaller** and **less aggressive** tumors.

Age at diagnosis and **disease duration** appear to be determinants of disease **outcome**, likely reflecting exposure to high circulating levels of GH and IGF-1.

- 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.

Treatment resistance correlates:

inversely with SSTR2 abundance and may also be associated with heterogeneous SSTR type **expression** or **signaling** defects .

Morphology classification: Dense or Sparse granulation patterns.

Based on the density of secretory granules in the cytoplasm of the adenoma cells.

Densely granulated adenomas: Perinuclear

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

Morphology classification: Dense or Sparse granulation patterns.

Sparse granulated adenoma:

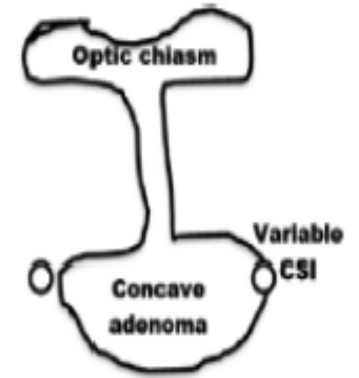
- Globular aggregations
 - **Larger** tumors
 - Low SSTR2 expression
 - Exhibit **no** positivity or **weak** positivity for GH.
 - Generally are more **invasive**
-

Clinical, radiological, and histopathological characteristics are used to classify **three acromegaly types** :

- Tumor aggressiveness
 - Treatment responsiveness
 - Expression profile of somatotroph surface receptors
 - Disease outcomes
-

Type 1 patients:

- Older patients (> 50 y) with the longest follow-up.
- **Densely** granulated
- **Non** aggressive micro and macro adenomas.
- Tumors extended to the **sphenoid sinus more** frequently than the suprasellar region.
- when suprasellar extension occurred, optic chiasmatic compression was **rarely** encountered.



Type 1 patients:

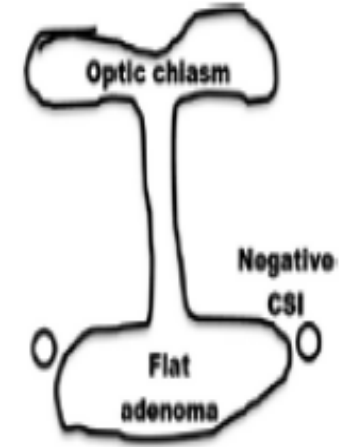
Because tumor extension occurs mainly to the sphenoid sinus, these tumors are more **accessible for debulking** and likely explain why **only one** surgical procedure was needed in most of these patients.

Type 1 patients:

- Higher proportion, Ki-67 index $< 3\%$, indicating **lower proliferative activity**.
 - Expression of SSTR2 and treatment responsiveness :
higher outcomes were more favorable in terms of **lower** hazard ratio for **active disease** at follow-up.
 - Higher median number of years with **normal IGF-1 levels**.
-

Type 2 patients

- 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**.

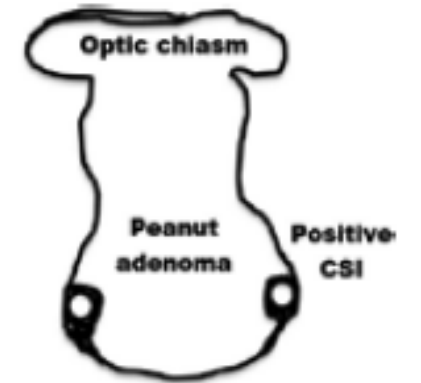


Type 2 patients

- **Higher** IGF-1 levels at diagnosis
- Required **more** treatments than did type 1 patients.
- May be identified with a **flat MRI shape**.
- Abundance of **SSTR2 are intermediate**, as were **clinical outcomes**.

Type 3 patients

- Age at diagnosis (30 y)
- Female patients
- More **aggressive**
- Sparsely granulated
- **Macro**adenomas
- Extend to both the **sphenoid** sinus and **suprasellar** regions with
- Commonly encountered **optic chiasm** compression.
- MRI as a “**peanut**” or round shape.



Type 3 patients

- Symptoms and mass effects are **more severe**.
- **shorter** disease duration before biochemical diagnosis.
- **Prolactin** levels were increased, but not tumor prolactin immunoreactivity
Stalk-section rather than a mixed somatotroph/lactotroph tumor.

Comorbidities

- Risks of complications and comorbidities associated with acromegaly are lower in patients who are biochemically controlled.

The observed **decline** in reported mortality among acromegaly patients is likely due to:

- More effective therapies
 - Higher biochemical control rates
 - Reduce the likelihood of developing respiratory and cardiovascular comorbidities that increase mortality.
-

ORIGINAL ARTICLE

Association between biochemical control and comorbidities in patients with acromegaly: an Italian longitudinal retrospective chart review study

A. Colao¹ · L. F. S. Grasso¹ · M. Di Cera² · P. Thompson-Leduc³  · W. Y. Cheng³ · H. C. Cheung³ · M. S. Duh³ · M. P. Neary⁴ · A. M. Pedroncelli⁵ · R. Maamari⁴ · R. Pivonello¹

Methods Medical charts of adults with confirmed acromegaly and ≥ 6 months of follow-up at an Italian endocrinology center were reviewed. Patients were followed from the first diagnosis of acromegaly at the center until loss to follow-up, chart abstraction, or death. Biochemical control status was assessed annually and defined as IGF-1 \leq the upper limit of normal, or GH ≤ 2.5 $\mu\text{g/L}$ in the few cases where IGF-1 was unavailable. Time-varying Cox models were used to assess the association between biochemical control status and comorbidities.

Results Among 150 patients, 47% were female, average age at diagnosis was 43.1, and mean length of follow-up was 10.4 years. Biochemical control was significantly associated with a lower hazard of diabetes (HR = 0.36, 95% CI 0.15; 0.83) and cardiovascular system disorders (HR = 0.54, 95% CI 0.31; 0.93), and a higher hazard of certain types of arthropathy (HR = 1.68, 95% CI 1.04; 2.71); associations for other comorbidities did not reach statistical significance.

The risks of developing arterial hypertension and myocardial hypertrophy were not different. An increased risk of arthropathy was also noted, suggesting that, once established, structural changes are less likely to be influenced by biochemical control.

Acromegaly treatment **improves glucose** metabolism
even if IGF-I is not normalized.



Preoperative Fasting C-Peptide Acts as a Promising Predictor of Improved Glucose Tolerance in Patients With Acromegaly After Transsphenoidal Surgery: A Retrospective Study of 64 Cases From a Large Pituitary Center in China

Surgical tumor remission, although achieved in only 41% of 64 treatment-naïve patients.

- ✓ Reduced DM rate, from 28% before surgery to 8% after.
- ✓ Normal glucose tolerance increased from 29% to 62.5%.






Preoperative fasting C-peptide were determined to be the predictors for improved glucose tolerance status after surgery.

Through ROC analyses, FCP >2.445 ng/ml was the best independent predictor, with an 86.6% PPV and a 74.5% NPV.

- Decreased IR and increased insulin sensitivity will be obtained in most patients after surgery **regardless** of their **preoperative glucose tolerance status** or whether they **achieved acromegaly remission**.
 - **OGTT and HbA1c** should be reassessed regularly after surgery for acromegaly patients with abnormal glucose tolerance, and management should be adjusted as needed based on the patient's **latest glucose tolerance status**.
-



Acromegaly in the elderly patients

Maria Rosaria Ambrosio¹ · Irene Gagliardi¹ · Sabrina Chiloiro ² · Ana Gonçalves Ferreira³ · Marta Bondanelli ¹ · Antonella Giampietro ² · Antonio Bianchi ² · Laura De Marinis ² · Maria Fleseriu ⁴ · Maria Chiara Zatelli ¹

Received: 25 October 2019 / Accepted: 14 January 2020 / Published online: 14 February 2020

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Older age confers the same increased risk for **DM, hypertension, sleep apnea, and cancer as in the general population** while **left ventricular hypertrophy is more frequent** among elderly patients with acromegaly.

Acromegaly and Vertebral Fractures

GH and IGF-1 are among the most **important regulators** of bone metabolism.

When they are **overproduced**, **increased bone turnover** is observed with subsequent deterioration of **cortical and trabecular bone structure**.

Acromegaly and Vertebral Fractures

Peculiarities of acromegalic osteopathy are that VFs are **common** but **not** explained by **low BMD** being related to disease **duration and activity**, and occurring **even after remission**.

- VF progression was also documented in **20%** of **biochemically controlled** patients, especially in **men**.

Prevalence

- VFs of the **lower thoracic and lumbar spine** are prevalent in acromegaly
 - Reported in **up to 60%** of patients (recent metaanalysis).
 - A **3–8-fold** increased prevalence with respect to the general population.
 - Increased prevalence in **males versus females**.
-

Morphometric VFs: Clinical Significance and General Methodological Aspects

- VFs are a **marker of skeletal fragility** and are

Associated with high risk of **subsequent fracture, decreased survival, and poorer QOL.**

Since few VFs are actually clinically diagnosed, **radiological** and **morphometric approaches** have become the **gold standard** for assessing **prevalence and incidence** of VFs in at-risk groups.

VFs can be assessed on **thoracic–lumbar spine or lateral chest X** rays, or on DXA with a **morphometric approach** that consists of qualitative and quantitative **evaluations of vertebral shape**.

VFs are defined with vertebral body height ratio decreases:

- ✓ Mild:20–25%
- ✓ Moderate:25–40%
- ✓ Severe > 40%

What Is the Value of BMD Measurement?

- BMD may be **normal** on standard DXA.
- Therefore, not only does it not reliably **predict fracture risk**, but it can be misleading in reassuring clinicians about the **preserved bone health** of the patient.
- Even the **FRAX score**, has been shown to be **an inaccurate** predictor of fracture for patients.

- In treated patients, VF progression is not related to BMD level or changes over time .
- However, since **decreased femoral neck BMD** has been observed in acromegaly patients **developing VFs** , DXA BMD measurements at **baseline** and during **follow-up** may have some additional value for the prediction of VFs.
- The **Trabecular Bone Score**, a DXA-derived parameter of bone microarchitecture, has also been found to be **decreased** in patients with acromegaly.

How Do Bone Morphometric Studies Help in Management?

- Imaging studies to perform **vertebral morphometry** are suggested in **all** patients with acromegaly at **diagnosis**, **regardless of disease status**, since this is currently the **only reliable marker** of bone damage in acromegaly.
 - During subsequent follow-up, morphometry should be repeated, in particular, in patients with **prevalent VFs** or **untreated hypogonadism** and **not only**, if biochemically uncontrolled.
-

DXA

Vertebral morphometry on thoracic x-ray,
thoracic and lumbar spine x-ray

- ❖ **Every 2 years** particularly if osteopenia/osteoporosis is present.
- ❖ Annually, particularly if history of **vertebral fracture**, decrease in BMD, **kyphosis**, symptoms of vertebral fracture, **untreated hypogonadism**, and no biochemical control of acromegaly.

- Prevalence of **vertebral fracture** is higher in **eugonadal men** with acromegaly than in healthy controls.
 - Hypogonadism is a significant independent risk factor.
 - **Replacement therapy** should be considered in hypogonadal men and women.
-

Datas suggest, that particularly in **uncontrolled** patients, morphometric VFs may be able to **influence medical choice** .

Pasireotide may be more effective in preventing VFs than pegvisomant.

Biochemically active disease is generally associated with a higher risk of vertebral fractures (VF).



2020 Mar.

Effects of Pegvisomant and Pasireotide LAR on Vertebral Fractures in Acromegaly Resistant to First-generation SRLs

study involved **55 patients** treated with **pasireotide** long acting release (LAR) or **pegvisomant** who had been previously **uncontrolled on octreotide LAR or lanreotide** for at least 6 months, **42% of whom had VFs at baseline**. After a median of **36 months follow-up**, **67%** of patients treated with **pasireotide** LAR and **77%** treated with **pegvisomant** achieved disease control.

Intriguingly, among those **with active disease**, incident VFs were significantly **less frequent** among those treated with **pasireotide than with pegvisomant** (78% vs 25%, $p = 0.04$), regardless of IGF-I level during follow-up.

The mechanisms underlying this finding are **unclear**, but may include **differential impact** of pegvisomant vs pasireotide on GH

An **independent effect** of somatostatin receptor ligands (SRL) on bone turnover.

Vitamin D

- Patients with **active acromegaly** as well as those treated with **somatostatin analogs** have been found at **high risk** of hypovitaminosis D.
 - Moreover, **elevated vit DBP** and **low levels of free vit D** have been reported .
- ❖ Assessment of **baseline vitamin D status** and **vitamin D supplementation** in patients with **low 25-OH vitamin D** may be helpful in acromegaly to prevent skeletal complications.

No controlled studies on bone **active agents in the prevention and treatment** of vertebral fractures are available.

➤ Selective estrogen receptor modulators

May prove a particularly interesting option due their potential **dual effect** on both **bone** health and **acromegaly** control.

- The role of **estrogens** in **reducing IGF-1** generation is well known.
- Women of fertile age usually need **higher doses of GH** to achieve a similar IGF-1 response when compared to men.

Clomiphene citrate is a SERM that possesses **positive estrogenic** effect on the **periphery** and a **negative effect** at the **hypothalamus and pituitary** levels, **thus increasing LH and FSH** secretion and improving hypogonadism and fertility outcomes.

Clomiphene Citrate for Treatment of Acromegaly Not Controlled by Conventional Therapies

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Study Design: In this prospective, open-label, single-center trial, CC (50 mg/d) was added to previous medical treatment for 3 months. Hormonal assessment was performed before and during the intervention.

Patients: Sixteen male patients (median age, 52.8 y; range, 36–79 y) met the following criteria: IGF-1 above the upper limit of normal range for at least 1 year despite the use of available medical therapies, and T levels within or below the third inferior tertile of normality.

Results: Serum IGF-1 levels decreased by 41% (mean \pm SD, 424 ± 108 to 250 ± 83 ng/mL; $P < .0004$), leading 44% (seven of 16) of the patients to achieve normal IGF-1 levels. Total serum T levels increased by 209% (282 ± 201 to 497 ± 310 ng/dL), reaching normal levels in 67% (four of six) of those patients considered hypogonadal.

Conclusions: Addition of CC should be considered an option in male acromegaly patients not controlled by current available options, with a considerable cost-saving benefit. Furthermore, improvement of T levels can be obtained in those patients with concurrent central hypogonadism. (*J Clin Endocrinol Metab* 100: 1863–1869, 2015)

Mortality

What's new?!

- Over the past decade, disease control has improved due to enhanced therapeutic strategies, leading to **reversal of the increased mortality** risk traditionally associated with acromegaly.

Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis

F Bolfi¹, A F Neves¹, C L Boguszewski² and V S Nunes-Nogueira¹

Increased mortality in 17 studies published **before 2008** (standardized mortality ratio [SMR] 1.76, $p < 0.00001$).

Mortality was strikingly **not** different from the general population in 9 studies published **after 2008** (SMR 1.35; 95% CI 0.99, 1.85).

Mortality

What's new?!

Excess mortality reported in **earlier studies** was primarily due to:

- **CVD** (SMR 2.95; 95% CI 2.35, 3.55), including:
 - ✓ IHD (SMR 2.00; 95% CI 1.35, 2.66)
 - ✓ Cerebrovascular disease (SMR 3.99; 95% CI 2.42, 5.55)
- **lesser** effect from **malignancy** (SMR 1.76; 95% CI 1.27, 2.26)

Mortality

What's new?!

- In recent studies,

Cancer has been reported as the leading **cause of death** in acromegaly, likely related to **longer life expectancy** due to better control of the disease and its related **comorbidities** rather than a **specific increased risk of cancer**.

Natural History of Acromegaly: Incidences, Re-operations, Cancers, and Mortality Rates in a National Cohort

Cohort from **Taiwan** including **1195 patients**.

- followed from 1997 to 2013 showed **87 newly diagnosed cancers**.
- with an incidence rate of 10.6 per 1,000 person-years.
- The **two cancers** most associated with acromegaly, namely **colon and thyroid** cancer suggest that this risk might **not be clinically significant**.

Clinicopathological features of colorectal polyps and risk of colorectal cancer in acromegaly

Methods: The study participants were 178 patients who underwent Hardy's operation and perioperative colonoscopy at our hospital between April 2008 and September 2016. For the control group, we randomly selected 356 age- and sex-matched patients who underwent colonoscopy at our hospital during the same period. The incidence, size, location, and histology of the colorectal polyps detected were compared between the groups.

Results: Colorectal polyps were detected in 66.8% of the acromegaly group and 24.2% of the control group ($P < 0.001$). The average number and size of the polyps were 2.44 and 4.74 mm, respectively, in the acromegaly group and 1.77 and 3.89 mm in the control group ($P = 0.001$). Polyps in the acromegaly group were more likely to be in the rectosigmoid region ($P = 0.006$). In the acromegaly group, the frequency of polyps ≥ 5 mm was 34.3% and that for polyps ≥ 10 mm was 15.2%; the respective values were 7.6% and 2.2% in the control group ($P < 0.001$). We found no evidence of between-group histopathological differences in the polyp specimens resected by endoscopy.

Conclusions: Patients with acromegaly are at an increased risk of colorectal polyps, especially in the rectosigmoid region. However, there is no pathological evidence that they are at greater risk of colorectal cancer than the general population.

Thyroid cancer

What's new?!

- The 2014 Endocrine Society Clinical Practice Guideline for patients with acromegaly recommends:

A thyroid ultrasound if there is a **palpable thyroid nodule**.

NO BENEFIT OF DEDICATED THYROID NODULE SCREENING IN PATIENTS WITH ACROMEGALY

*Ngan Betty Lai, MD^{1,2}; Dave Garg, MD^{1,2}; Anthony P. Heaney, MD, PhD¹;
Marvin Bergsneider, MD³; Angela M. Leung, MD, MSc^{1,2}*

- A retrospective chart review was performed of all patients with acromegaly (n=221) between **2006-2015** within the University of California, Los Angeles health system.
- Thyroid **cancer** was present in **8.5%** of all nodules observed in patients with acromegaly, which is **similar** to that of the general U.S.

Over two-thirds of the patients who obtained a thyroid ultrasound were found to **have thyroid nodules**, consistent with prior literature demonstrating **higher rates of thyroid nodules** in patients with acromegaly compared to the general population .

Thyroid cancer

What's new?!

- These findings suggest that **routine thyroid ultrasonography** upon a diagnosis of acromegaly is indicated **only** when a thyroid nodule is **palpated**.
- In line with the screening recommendations for the **general population** by the **ADA**, as well as the **Endocrine Society** Clinical Practice Guideline for patients with acromegaly.

Thyroid cancer

What's new?!

❖ Follow-up and screening **for all other cancers** should be performed according to **national/regional guidelines** for the general population.

Assays (Reference GH nadir levels)

What's new?

- As **GH and IGF-I** assessments remain the **standard for measuring acromegaly disease activity** at **diagnosis and follow-up**, strategies are being developed to improve current assays.

Reference nadir levels of GH (IDS-iSYS GH assay) using the during OGTT that account for:

BMI

sex

Estradiol-containing oral contraceptives (OC) have been empirically established.

Assays

What's new?

525 non - acromegalic individuals into cohorts: GH nadirs :

➤ BMI < 25 vs \geq 25 kg/m²:

leaner group : more than **twice** as high as the heavier (0.22 vs 0.09 μ g/L,
p < 0.0001)

➤ **Pre-** but not postmenopausal women:

had **higher** GH nadir **vs men**.

➤ OC-using females:

More than **3 fold** of premenopausal not using OC.

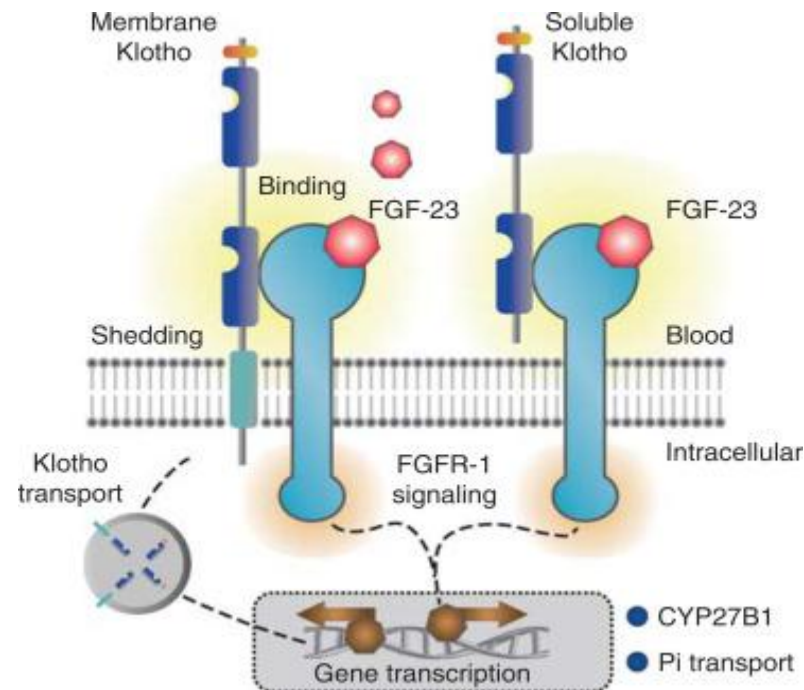
Reference GH nadir levels after OGTT accounting for **BMI, sex, and estradiol-containing OCP** use confirm the importance of these factors as **confounders in GH measurements**.

Other markers of GH action such as **IGF BP3** have been suggested to assess **discrepant** GH and IGF-I results.

- **Soluble Klotho**, predominantly expressed in the **kidney**, **correlates with GH** levels over a wide concentration range, and has been suggested to **correlate with QOL** improvements.

α -Klotho

The Klotho gene was originally identified as an **ageing suppressor** gene of restricted expression (predominantly in the kidney, brain, and parathyroid and pituitary glands), encoding a transmembrane protein, mKlotho.



soluble α -Klotho

The extracellular domain of **m Klotho** is found as a circulating **soluble α -Klotho** (sKlotho) in to blood, CSF, and urine.

Soluble α -Klotho

- Normalization of GH and IGF-1 levels has been associated with **normalization in mortality** rates, while **not** necessarily reflecting **QoL** in acromegalic patients.

Concomitant and **parallel changes** in serum **sKlotho** and **IGF-1** were observed over time in each patient, and levels of **s Klotho** and **IGF-1** appeared to be similarly **dependent on GH**.

Extra-hepatic acromegaly

Normalized GH and IGF-1 levels do **not** always coincide with symptom **Relief**, which may be explained by '**extra-hepatic acromegaly**'.

In addition to suppression of **GH secretion** from the pituitary tumor, **SRLs** also suppress **insulin secretion** in the portal vein, which by itself **downregulates hepatic IGF-1** production via GH receptors.

Extra-hepatic acromegaly

- The GH action in the **peripheral** tissues remains unaltered and might still have acromegaly-inducing effects.
- Integrated extra-hepatic GH activity may remain elevated **despite normalized serum IGF-1** levels in these patients.

❖ **Extra-hepatic GH actions** could be antagonized by the **addition of PEGV** in patients using **first or second-generation SRLs**, one might observe an **improvement of QoL** in comparison with **SRL monotherapy**.

❖ In fact, it has been shown previously that the **addition of PEGV to first-generation long-acting SRL** therapy can **improve** GH-dependent parameters of QoL.

Assays

What's new?

- Defining postoperative remission:

Using IGF-I is a well-recognized challenge, as it may require **3 months** to achieve a **steady plateau**.

Assays

What's new?

IGF-I measured **6 weeks postoperatively** may be an **early** indicator of **disease activity** in most patients.

Repeat assessment is warranted **at 3–6 months** for those with:

- IGF-I levels **mildly elevated** above the age-related normal range
- **no** cavernous sinus invasion
- postoperative **GH < 1** ng/mL

as IGF-I may yet normalize.

❖ IGF-I levels measured **6 weeks postoperatively** can be used in most patients to **assess remission**, although patients with **mildly elevated** IGF-I may yet normalize **by 3–6 months**.

Acromegaly: Therapy

What's new?

Surgical

Medical

Radiation

Sex, age, and surgical outcomes

What's new?!

- Recent studies suggest that female sex, may impact surgical outcomes.

- Premenopausal women tended to have larger, more aggressive tumor types and lower remission rates than men suggesting a more aggressive natural history and hence more adverse treatment outcomes in this subset of women.

Age- and Sex-Specific Differences as Predictors of Surgical Remission Among Patients With Acromegaly

Se Hee Park,^{1,2} Cheol Ryong Ku,^{1,3,4} Ju Hyung Moon,^{3,4,5} Eui Hyun Kim,^{3,4,5} Sun Ho Kim,^{3,4,5} and Eun Jig Lee^{1,3,4}

Results: Sex differences existed in the baseline insulinlike growth factor-1 levels and the mean tumor size. Overall, surgical remission rates were 89.7% and 76.5% in male and female patients, respectively ($P < 0.001$). Total tumor tissue resection was performed in 92.6% and 85.8% of male and female participants, respectively ($P = 0.021$). Premenopausal women had a higher proportion of pituitary adenoma with cavernous sinus invasion than did men aged <50 years (35.3% vs 21.7%, $P = 0.007$). In immediate postoperative, 75-g oral glucose tolerance tests, fewer premenopausal women reached <1 ng/dL nadir GH levels than did men aged <50 years (59.9% vs 87.7%, $P < 0.001$). Surgical results were similar in both sexes among older patients (≥ 50 years). However, premenopausal women had significantly lower long-term remission rates than did men aged <50 years (69.3% vs 88.0%, $P < 0.001$).

Conclusion: Premenopausal women with acromegaly tend to have larger tumors, more aggressive tumor types, and lower remission rates than do men. However, further studies on the clinical implications are needed. (*J Clin Endocrinol Metab* 103: 909–916, 2018)

Acromegaly in the elderly (≥ 65 years)

- Surgical remission of 73.7%
- Patients tend to have **smaller** adenomas with **lower invasion** rates.
- No significant differences in **perioperative complications** comparing those younger and older than 65 years.
- Incidence of new postoperative **pituitary deficiency** was also **similar**.
- **1/3** of patients > 65 years **stop** medication for HTN and DM.

Acromegaly: Therapy

What's new?

Surgical

Medical

Radiation

Medical Therapy Targets of the GH/IGF-I Pathway

Options for Medical Therapy

SRLs

Somatostatin receptor ligands(octreotide, lanreotid, Pasireotide)

- Directly inhibit GH secretion
- Indirectly inhibit IGF-I secretion

Dopamine Agonists

D2 receptor(Bromocriptine, cabergoline)

- Directly inhibit GH secretion
- Indirectly inhibit IGF-I secretion

GHR Antagonist (pegvisomant)

- Does not suppress GH secretion
 - Directly inhibits IGF-I secretion
-

- The somatostatin receptor ligands octreotide and lanreotide bind SST2 (somatostatin receptor subtype 2), inhibiting growth hormone secretion.
- Efficacy may be enhanced by **increasing the dose** and **injection frequency**.
- Soft-tissue **swelling** and **headache** usually resolve, **sleep apnea** abates, and **left ventricular function improves**

but hypertension may persist.

Injectable SRL

What's new?

Identifying populations most likely to **benefit from LA injectable** SRLs is important.

- ❖ Increased probability of achieving **long-term biochemical control**
- ✓ Older age
- ✓ female sex
- ✓ lower IGF-I levels at baseline
- ✓ Hypointense tumor on T2 MRI (greater reductions in IGF-I and more tumor shrinkage)
- ✓ Tumor SST2 expression, densely granulated tumor

Tumor volume response **at 12 weeks** is **not** an accurate predictor of subsequent tumor volume control.

Pituitary-Tumor Endocrinopathies, Review Article New england journal medicine

- **Patient- and tumor-specific factors at baseline** may predict **long-term** biochemical response to primary SRL treatment, while **early tumor response may not** ($\geq 20\%$ tumor volume reduction was achieved in 54% at 12 weeks and in 63% at 48 weeks).

622 patients from two European cohorts.

❖ **Biochemical response**

✓ **Lower IGF-1 at baseline** (OR = 0.82, 95% CI: 0.72-0.95)

✓ **lower body weight** (OR = 0.99, 95% CI: 0.98-0.99 , P = .038)

❖ **Partial response :**

- ✓ Presence of **type 2 diabetes** (oral medication OR = 2.48, (1.43-4.29), P = .0013; insulin therapy OR = 2.65, (1.02-6.70), P = .045)
- ✓ **Higher body weight** (OR = 1.02, (1.01-1.04) kg, P = .0023)

❖ **Nonresponse:**

- ✓ **Younger** patients at diagnosis (OR = 0.96, (0.94-0.99) year, P = .0070).

younger patients were more likely to be nonresponsive

- Octreotide and lanreotide do not generally disrupt glucose homeostasis, but pasireotide, a long-acting hexapeptide somatostatin multireceptor ligand, results in **hyperglycemia** and **new-onset diabetes** in **about 60%** of patients.

Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA) Phase 3 PAOLA study

- Randomized 198 acromegaly patients
 - Uncontrolled on octreotide LAR or lanreotide to continued treatment or pasireotide.
 - Found that **15%** and **20%** of patients treated with pasireotide **40 mg** and **60 mg**, respectively, achieved **biochemical control** after 24 weeks.
 - **0% in the octreotide/lanreotide group.**
-

123 patients Switched **uncontrolled patients** from octreotide/lanreotide to pasireotide.

At baseline, **42% were diabetic** and **49% pre-diabetic**; during the study, **42%** reported **new-onset** hyperglycemia and **24% DM**.

❖ The **risk** of drug-induced hyperglycemia and DM with pasireotide:

✓ Impaired insulin and incretin secretion

✓ **Minor effect on glucagon production.**

▪ Generally, the degree of hyperglycemia associated with pasireotide is largely **dependent on glycemic control at baseline.**

Oral octreotide capsules

What's new?!

An Evolution in treatment for patients with acromegaly



Oral octreotide capsules (OOC):

MYCAPSSA

What's new?

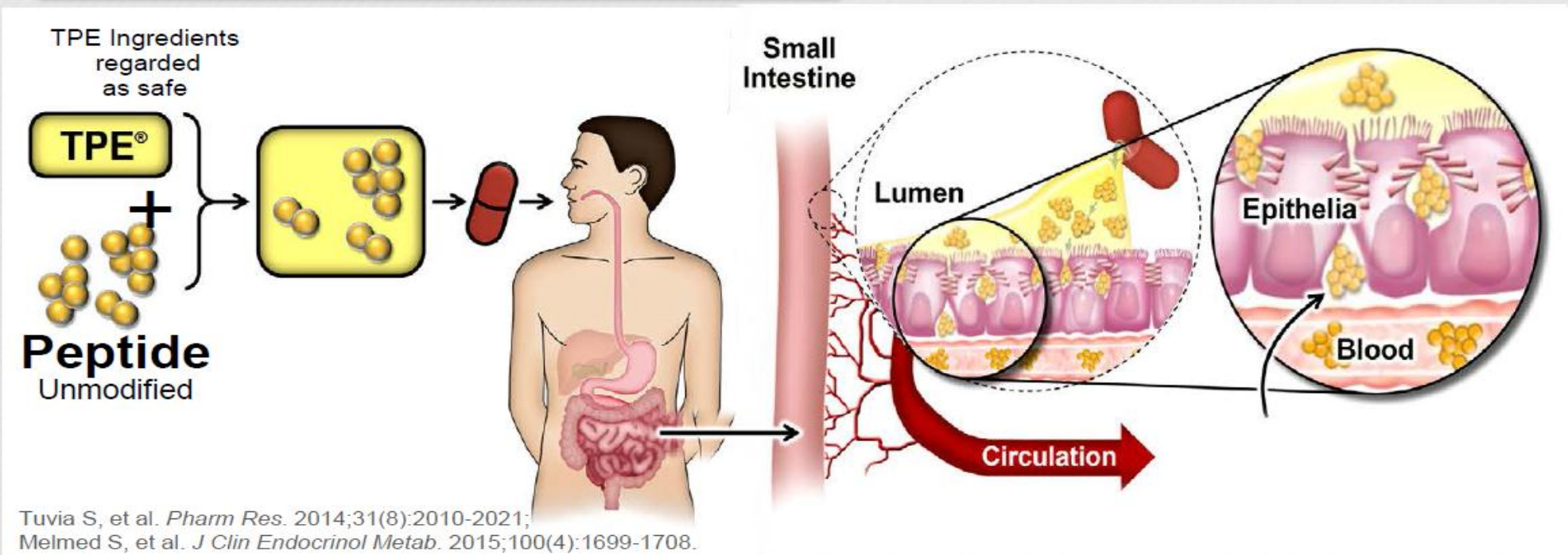
- Received approval from the FDA in June 2020.
 - For **long-term** maintenance treatment in acromegaly patients.
 - Who have **responded** to and **tolerated** treatment with **octreotide** or **lanreotide**.
 - MYCAPSSA (octreotide) **delayed-release capsules**.
 - Enteric-coated capsules.
 - Each capsule contains **20 mg** of octreotide.
-

TPE[®] is an oily suspension of octreotide that includes a number of excipients that can transiently alter epithelial barrier integrity by opening of intestinal epithelial tight junctions, arising from transcellular perturbation.

• Oral Octreotide

Peptide protected by TPE from degradation...

...then absorbed intact at therapeutic levels.



Transient Permeability Enhancer (TPE): Technology for Physiologic Opening of Tight Junctions with Peptide Absorption

Studies in healthy volunteers established that:

20 mg OOC has similar pharmacokinetics to **SC injection of 0.1 mg** of SC octreotide.

After a standardized **meal**, octreotide from OOC **lost 90% of bioavailability**.

Thus, careful administration of the capsules timed to meals is essential.

Phase 3, Randomized, Double-blind, Placebo-controlled **OPTIMAL** Study:
Methods

Inclusion criteria:

average IGF-1 \leq ULN on a stable dose of SSA (octreotide or lanreotide injections)

N=56: 28 randomized to **octreotide capsule** & **28** to **placebo**.

Duration: 36 weeks plus optional open-label oral octreotide extension

The primary endpoint: proportion maintaining biochemical response, defined as IGF-1 \leq ULN (average of values at week 34 and 36)

Secondary endpoints: Need for rescue with injectable SSAs

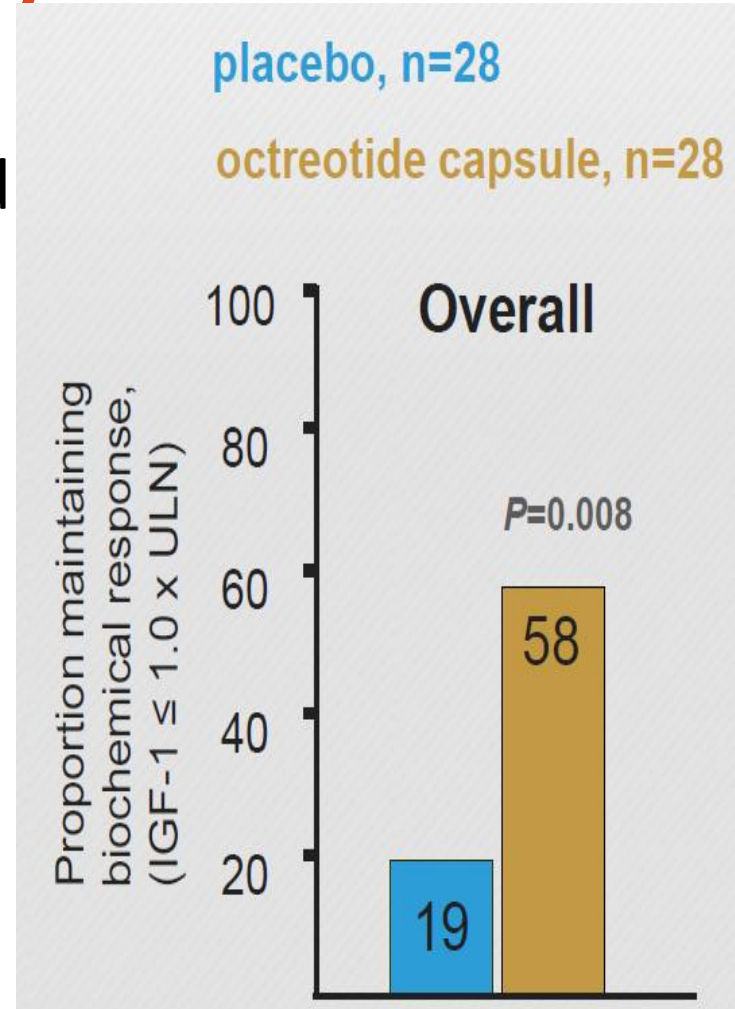
GH response (GH < 2.5 ng/mL)

Results from Phase 3, Randomized, Double-blind, Placebo-controlled OPTIMAL Study

58% of patients receiving octreotide capsules maintained normal IGF-1 vs 19% receiving placebo ($P=.008$)

Octreotide capsules were safe and well tolerated.

Conclusion: *Octreotide capsules were safe and effective for the treatment of adults with acromegaly*



Initiation and Titration MYCAPSSA:

- Initiate: a dosage of 40 mg /d, (20 mg orally twice/d).
 - Titrate : based on IGF-1 levels and patients signs and symptoms.
 - Increase the dosage in increments of 20 mg /d.
 - For 60 mg daily, 40 mg in the morning and 20 mg in the evening.
 - For 80 mg daily, 40 mg twice daily.
 - The maximum dosage: 80 mg daily.
-

- OOC can be **up-titrated** by an increment of **20 mg every 2–4 weeks** based on IGF-I and clinical symptoms.
- This is a **more rapid escalation** than is used with **injectable SRLs**, which often are up-titrated **every 3 months**.

Dopamine agonists

Dopamine agonists have been proposed for patients with **mild disease**, and the addition of cabergoline may normalize IGF-1 levels in some patients with disease that is **resistant** to somatostatin therapy.

Pegvisomant

What's new?

- useful for patients are **resistant to SRL**, as well as patients with **hyperglycemia**, since the drug **enhances insulin sensitivity**.

ACROSTUDY

ACROSTUDY is **an international**, non-interventional study of acromegaly patients treated with pegvisomant .

- Since **2004** in 15 countries.
- To study the **long-term safety** and **efficacy** of PEGV.
- This report comprises the second interim analysis of 2090 patients as of May 12, **2016**.

Prior to starting, **96%** of patients had reported surgery, radiation, medical therapy or any combinations of those.

- At start of PEGV, **89%** of patients had **IGFI levels above the ULN**.
- The percentage of patients with **normal IGFI** levels increased **from 53%** at year 1 to **73% at year 10**.

Tumor size

72.2% had no change in tumor size relative to the prior scan.

16.8% had a decrease.

6.8% an increase .

DM at baseline Pegvisomant use:

- In patients with DM improves glucose metabolism independent of IGF-I control, but does not affect glycemic endpoints in patients without DM.
- Patients with DM and those with a higher BMI require higher doses of pegvisomant and more rapid up-titration to achieve IGF-I normalization.

Combination therapy with SRL + pegvisomant What's new!

Combination therapy with pegvisomant plus SRL is increasingly being used in real-world settings.

- **Low-dose** octreotide LAR or lanreotide **plus weekly pegvisomant** is a **cost-effective** and **efficacious option for patients requiring combination therapy.**

- Combination of **pasireotide plus pegvisomant** can yield **biochemical control** rates exceeding **70%** even when pegvisomant doses are kept low.
 - However, the addition of pegvisomant does **not ameliorate** the high rates of pasireotide - induced hyperglycemia.
-

- ❖ That improved glycemia seen with pegvisomant likely due to:
Increased **insulin sensitivity** does **not ameliorate** suppression of insulin secretion driving pasireotide induced hyperglycemia.
 - ❖ **Careful patient selection** for this combination is recommended.
-

Take Home Message:

- Clinical, radiological, and histopathological characteristics are used to classify three acromegaly types.
 - Risks of complications and comorbidities associated with acromegaly are lower in patients who are biochemically controlled.
 - VFs can be assessed on thoracic–lumbar spine or lateral chest X rays, or on DXA with a morphometric approach.
 - Screening colonoscopy should be performed at diagnosis in all patients, screening should follow established guidelines.
 - Soluble Klotho, correlates with GH levels and has been suggested to correlate with QOL improvements.
 - IGF-I levels measured 6 weeks postoperatively can be used in most patients to assess remission.
-

Take Home Message:

- Women, especially when premenopausal, may exhibit lower surgical remission rates from TSS, as they tend to have larger and more invasive tumors that are less amenable to total resection.
- Studies confirm efficacy of pasireotide LAR for some patients uncontrolled on lanreotide or octreotide LAR. Treatment-induced hyperglycemia and DM are high, requiring careful monitoring for glycemic side effects.
- OOC are suitable for patients who have demonstrated complete or partial biochemical response on injectable SRL.
- Pegvisomant use in patients with DM improves glucose metabolism independent of IGF-I.
- Low-dose octreotide LAR or lanreotide plus weekly pegvisomant is a cost-effective .
- Combination of pasireotide plus pegvisomant can yield biochemical control rates exceeding 70%.

Thank you

