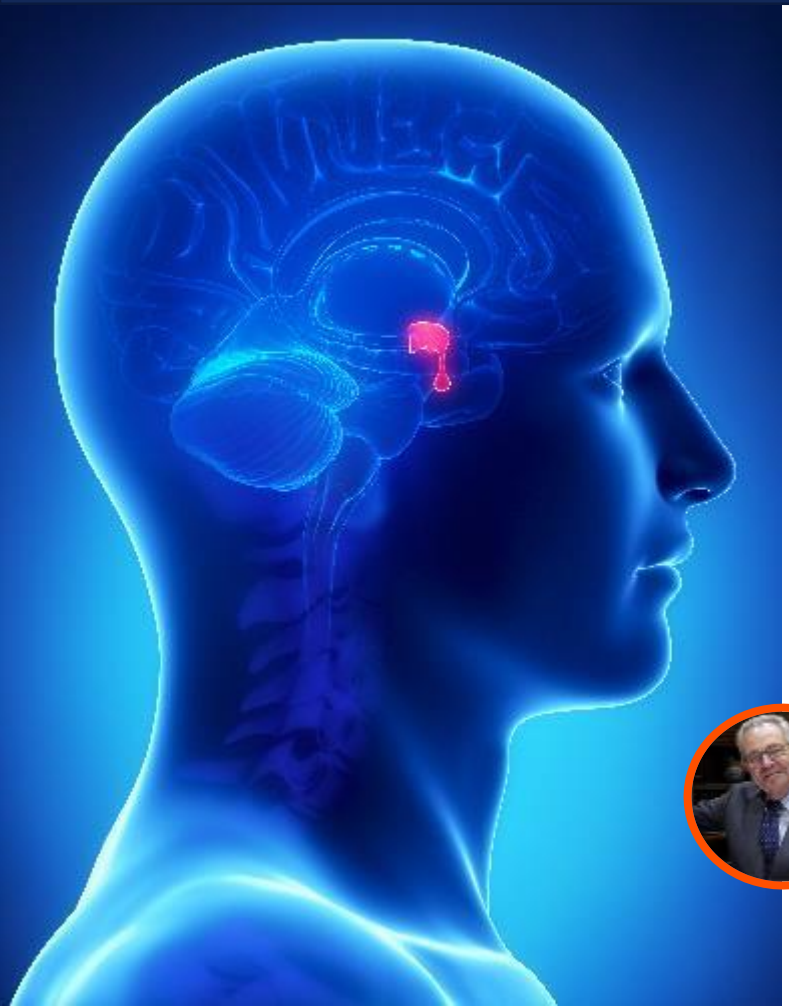

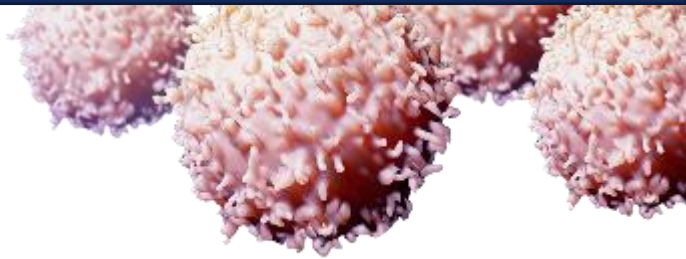

touchCONGRESS Webinar

Continuing the conversation in growth hormone disorder – how do we progress towards personalized medicine for patients with acromegaly?

Professor John Wass
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Webinar overview

Personalized medicine for acromegaly

- Part 1. European Congress of Endocrinology 2019: Latest information and guidance on the need for early diagnosis and monitoring of acromegaly?
- Part 2. European Congress of Endocrinology 2019: Most recent data on patient and disease characteristics in individuals with acromegaly, particularly in relation to comorbidities?
- Part 3. European Congress of Endocrinology 2019: Latest findings on the treatment of acromegaly?

Part 1.
European Congress of Endocrinology 2019: Latest information and guidance on the need for early diagnosis and monitoring of acromegaly

Focus on excess morbidity and mortality of delayed diagnosis

Acromegaly – an insidious hormonal disorder

Acromegaly is a slowly progressing disease caused by a pituitary tumour (adenoma) that results in chronic hypersecretion of GH and excess circulating IGF-1[1,2]

Appearance-related symptoms:

- Enlarged jaw, hands and feet
- Coarsened facial features
- Skin thickening

Symptoms due to internal growth/swelling:

- Colon polyps and fibroids
- Joint disease
- Carpal tunnel syndrome
- Organ enlargement
- Sleep apnoea

Annual incidence is between 0.2–1.1 cases/100,000 people[1,2]

Disease prevalence ranges from 2.8–13.7 cases/100,000 people[1,2]

Tumour-related symptoms:

- Vision loss
- Headaches
- Menstrual dysfunction
- Erectile dysfunction
- Loss of libido

GH, growth hormone; IGF-1, insulin-like growth factor 1.

1. Dineen R, et al. *QJM.* 2017;110:411–420. 2. Zahr R, et al. *Eur Endocrinol*. 2018;14:57–61.

Prolonged diagnostic delay in acromegaly is associated with long-term morbidity and excess mortality: data from a nationwide study

Eposito D, et al.

A Swedish investigation into diagnostic delay (DD), including its impact on morbidity and mortality

- **603 patients (n=603) identified in the Swedish National Patient Registry: 280 men and 323 women with a mean age at diagnosis of 51.8 years**
- **Mean diagnostic delay (time between first registered comorbidity and diagnosis) was 5.5 years, with a longer delay in women**

MORBIDITY

- 96% of patients had comorbidities at any time
- **Median number of comorbidities significantly higher in patients with DD (p<0.0001)**
- Most frequent comorbidities were neoplasms, cardiovascular and musculoskeletal
- The longest DD was for neurological-psychiatric symptoms

MORTALITY

- 61 deaths (vs. 42.2 expected) resulting in a standardized mortality ratio of 1.45
- **Excess mortality was only found in patients with a DD >10 years**
- In patients with a DD <10 years or no DD, mortality was similar to the general population

DD is a frequent occurrence in acromegaly, with longer delays experienced by women, and the delay is associated with excess morbidity and mortality.

DD, diagnostic delay.

Esposito D, et al. *Endocrine Abstracts* 2019:63:GP48.

A case of 'micromegaly': need for revision of oral glucose tolerance test (OGTT) cut-offs with modern growth hormone assays in acromegaly

Schilbach K, et al.

A case study highlighting the need to revise current gold standard OGTT cut-offs for the diagnosis of acromegaly[1]

2014 – presentation

- 45-year-old man with occasional elevated IGF-I concentration
- GH nadir of 0.3 µg/l measured with modern, monoclonal antibody assay (acromegaly ruled out)

Regular follow-up due to clinical presentation and comorbidities

- IGF-I persistently elevated but GH nadir remained below 0.4 µg/l in two repeated OGTTs
- Patient refused surgery on a pituitary microadenoma (size unchanged on annual MRI)

2018 – treatment

- Patient agreed to transsphenoidal tumour resection; GH-secreting pituitary adenoma confirmed
- IGF-I concentration within gender- and age-specific reference range 10 weeks after surgery, and GH suppressible to <0.05 µg/l after oral glucose load

Clinical features and comorbidities:

- Typical physiognomy
- Arterial hypertension
- Sleep apnoea
- Impaired glucose tolerance
- Hypogonadotropic hypogonadism
- Obesity

The commonly used OGTT cut-off of 0.4µg/l can miss mild/early acromegaly, particularly if modern, highly sensitive GH assays are used. The need to review OGTT cut-offs for defining acromegaly is supported by research presented at ENDO 2019.[1]

GH, growth hormone; IGF-I, Insulin-like growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test.

1. Schilbach K, et al. *Endocrine Abstracts* 2019:63:P252; 2. Micko A, et al. *J Endocr Soc.* 2019;3(Suppl 1):SAT-431.

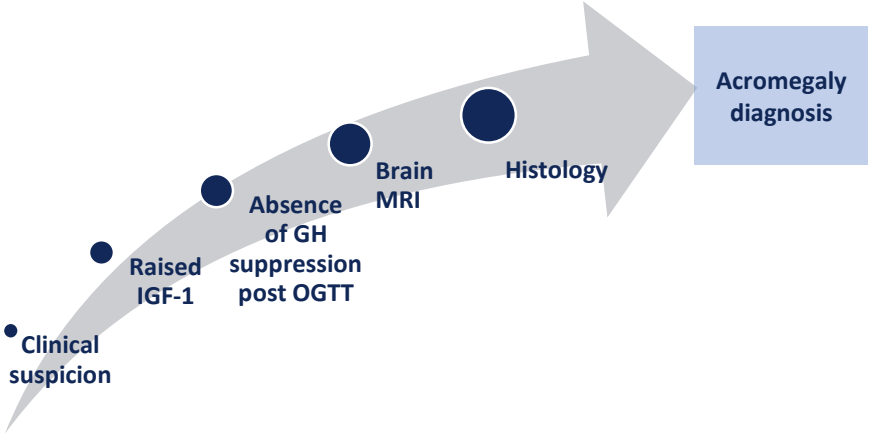
touchime

Delayed diagnosis of acromegaly: a two-year journey

Bitar AA, et al.

The case of a 69-year old female diagnosed with acromegaly two years ago following the initial onset of facial and acral symptoms and after already developing colonic hyperplastic polyps one year pre-diagnosis

- After recognition of phenotypical features of acromegaly, IGF-1 level was elevated at 624 nmol/L, OGTT failed to suppress GH nadir levels, and brain MRI showed a pituitary macroadenoma which was identified histologically as a mixed, sparsely granulated somatotroph and lactotroph adenoma
- If the hyperplastic polyps detected on the colonoscopy one year previously had been recognised as a feature of acromegaly, diagnosis may have been established sooner



- **Onset of acromegaly can be subtle yet harmful in older patients, leading to delayed diagnosis**
- **A lack of awareness of hyperplastic polyps as a potential feature of acromegaly indicates the need to raise awareness of the characteristics of the condition across specialities**

GH, growth hormone; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test.

Bitar AA, et al. *Endocrine Abstracts* 2019;63:EP121.

Patients' perspectives on acromegaly diagnostic delay: a qualitative study

Sibeoni J, et al.

The first exploratory single-centre qualitative study exploring the patient experience of the acromegaly diagnostic pathway using a thematic analysis

1. What happened for patients before diagnosis

- Misdiagnosis and uncertainty result in long DD
- State of terror due to unexplained physical changes; unable to recognize themselves
- Lack of understanding about bodily changes

2. What happened for patients after diagnosis

- Mixed responses to diagnosis – shock, worry, relief
- Obsession with being looked at by others; invading thoughts about the condition

3. Style/type of doctor involved

- Patients encounter different types of doctors on their journey to diagnosis, as well as after diagnosis

4. Patients' suggestions for limiting DD

- Increase doctor knowledge of acromegaly, including dentists and stomatologists
- Proactive patients
- Increased public awareness

Active medical involvement and awareness is critical to diagnosis and the catastrophic dimension of the patient experience should be addressed.

DD, diagnostic delay; HCP, healthcare provider.

Sibeoni J, et al. *Eur J Endocrinol*. 2019;180(6):339–352.

Summary

- ✓ Diagnostic delay is common in acromegaly, ranging from months to over 10 years, with a longer delay for women
- ✓ Diagnostic delay can be associated with excess morbidity and mortality
- ✓ The commonly used OGTT cut-off of 0.4 µg/l may be contributing to diagnostic delays as it can miss mild/early acromegaly, particularly if modern, highly sensitive GH assays are used
- ✓ Active medical involvement and awareness is critical to diagnosis and the catastrophic dimension of the patient experience should be addressed

Acromegaly is catastrophic enough without the added health and personal complications that result from delays in diagnosis.

GH, growth hormone; OGTT, oral glucose tolerance test.

What does the future hold for acromegaly diagnosis?

Part 2
European Congress of Endocrinology 2019: Most recent data on patient and disease characteristics in individuals with acromegaly

Focus on recognizing comorbidities for personalized treatment strategies

What are the patient and disease characteristics of acromegaly?

Screening is recommended for all patients presenting with the clinical characteristics of acromegaly, but an awareness of known associated comorbidities is also critical for personalized treatment strategies

Some of the many clinical features of acromegaly:[1]

- **Mass tumour effects** – headaches, visual impairment, hyperprolactinemia
- **Systemic effects of GH/IGF-1 excess** – soft tissue and skin changes, acral enlargement, increased sweating
- **Cardiovascular features** – hypertrophy, congestive heart failure, coronary disease
- **Metabolic features** – impaired glucose metabolism, insulin resistance
- **Respiratory** – macroglossia, upper airway obstruction
- **Bone/joint manifestations** – vertebral fractures, increased articular cartilage thickness
- **Other endocrine consequences –** menstrual abnormalities, hypercalciuria

Clinical features and comorbidities of acromegaly depend on:[2]

- Levels of GH and IGF-1
- Tissue and organ sensitivity
- Age
- Tumour size
- Time to diagnosis

Comorbidities associated with acromegaly:[1,3]

- Type 2 diabetes mellitus
- Carpal tunnel syndrome
- Osteoarthritis
- Hypertension
- Sleep apnoea
- Cancer
- Colon polyps
- Goitre
- Kidney stones

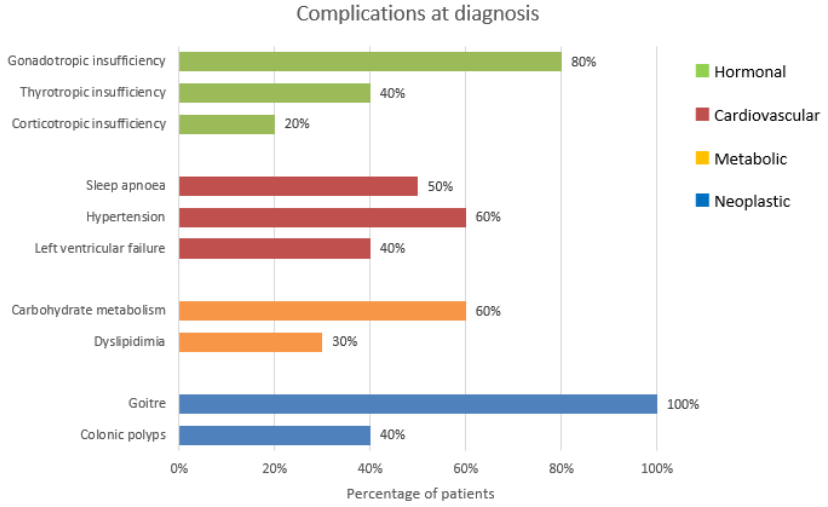
GH, growth hormone; IGF-1, insulin-like growth factor 1.

1. Abreu A, et al. *Pituitary* 2016;19:448–457; 2. AlDallal S. *Int J Gen Med*. 2018;11:337–343; 3. Dineen R, et al. *QJM.* 2017;110:411–420.

Acromegaly complications at the time of diagnosis
Elmehraoui O, et al.

A retrospective examination of complications at time of acromegaly diagnosis

- 10 patients with pituitary adenoma (mean age at diagnosis = 49 years, sex ratio of M/F = 0.66, average diagnosis delay = 8 years)
- Only one case of valvulopathy complicated by atrial fibrillation
- Osteoarticular complications:
  - Extremities hypertrophy (n=9)
  - Arthralgia (n=5)
  - Carpal tunnel syndrome (n=1)



Many complications exist at time of diagnosis, particularly hormonal, cardiovascular, metabolic and neoplastic complications. This necessitates the need to screen for comorbidities and multidisciplinary management.

Elmehraoui O, et al. *Endocrine Abstracts* 2019;63:P680.

Metabolic fingerprint of acromegaly and its potential usefulness in clinical practice

Biagetti B, et al.

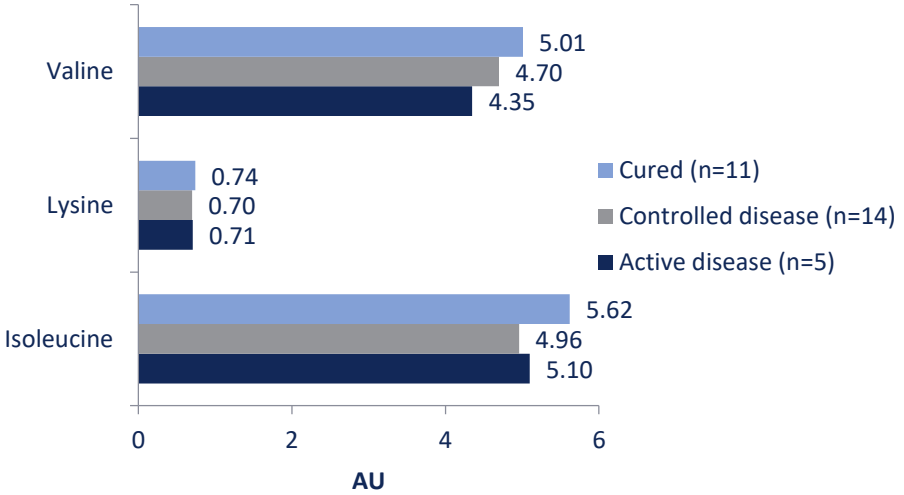
A comparison of serum metabolic fingerprints to: 1) identify metabolites and pathways that could be used as biomarkers of acromegaly, and 2) investigate whether metabolomics can differentiate active versus well-controlled acromegaly

The serum metabolic fingerprint was compared between patients with acromegaly (n=30) and controls (n=30) matched by age, gender, BMI and smoking habits.

Compared to the control group, patients with acromegaly presented with (p≤0.01):

- Lower levels of BCAAs
- Lower levels of pyruvate
- Higher levels of dimethylamine

BCAA levels were lower in patients with active disease compared to those with normal serum IGF-1 (p≤0.05).



A key metabolic fingerprint of acromegaly patients is lower BCAAs, particularly in those with active disease.

AU, arbitrary unit; BCAA, branched-chain amino acid; BMI, body mass index; IGF-1, insulin-like growth factor 1.

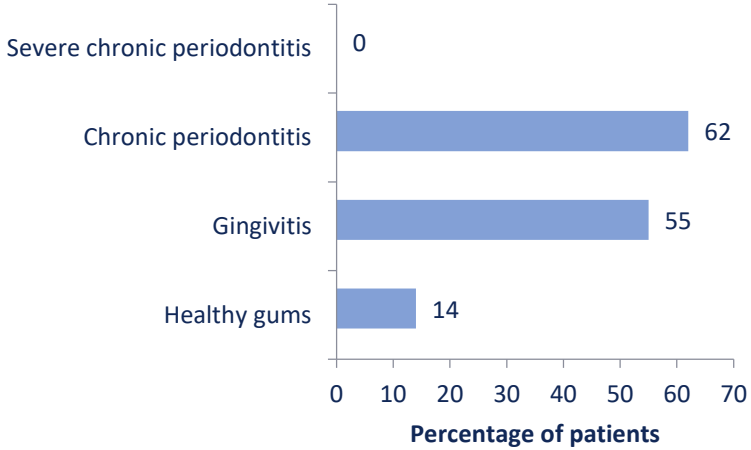
Biagetti B, et al. *Endocrine Abstracts* 2019;63:P226.

Assessment of oro-dental manifestations in a series of acromegalic patients: the AcroDent study

Roumeau S, et al.

A prospective analysis of the oro-dental state of patients with acromegaly

Variables	Value
Patients (n=29)	13 male; 16 female
Age	59.1±16.0 years
Micro adenoma	5
Macro adenoma	21
Controlled acromegaly	52%
Number of comorbidities per patient	3.7±1.7
Time from diagnosis	13.3±12.9 years



37.8% had bulky oral bony outgrowths, such as large maxillary or mandibular tori and multiple vestibular exostosis

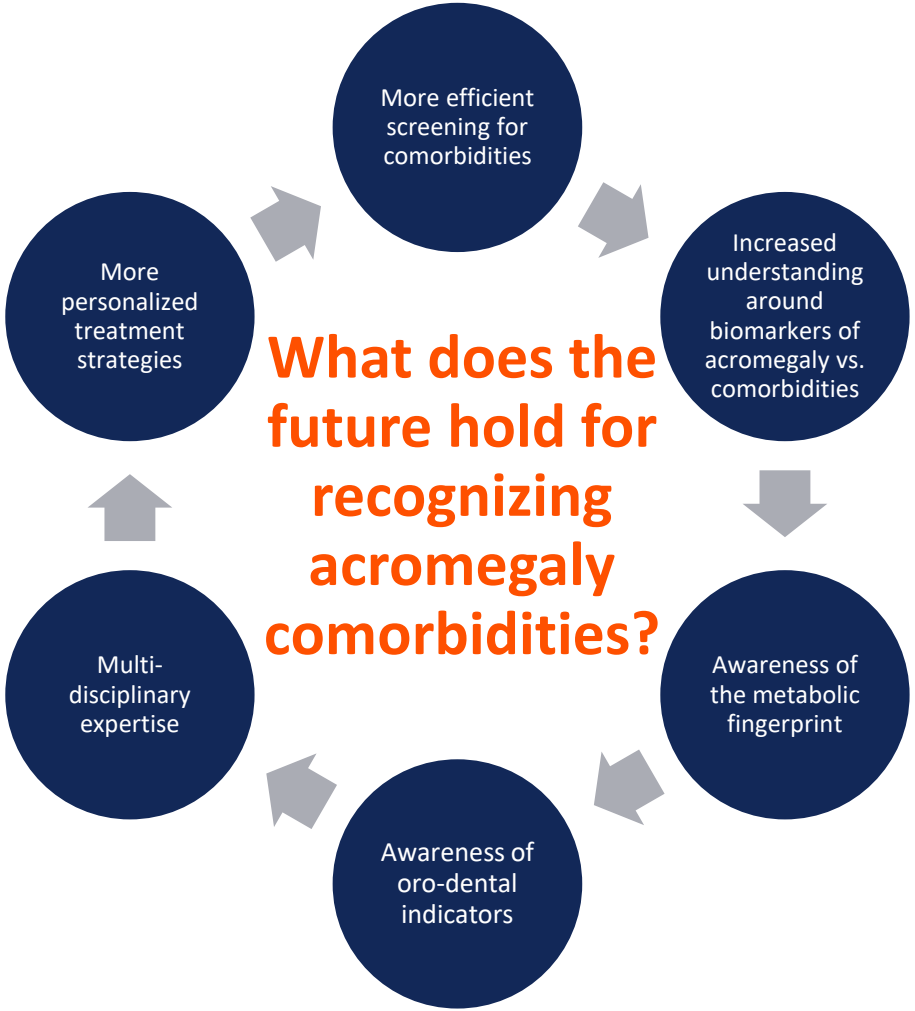
Large oral bony outgrowths, chronic periodontitis and gingivitis could indicate acromegaly, necessitating dental examinations within the diagnosis, treatment and management of acromegaly.

Roumeau S, et al. *Endocrine Abstracts* 2019;63 P682.

Summary

- ✓ Hormonal, cardiovascular, metabolic and neoplastic comorbidities are frequent in acromegaly and need to be screened for to provide personalized treatment strategies
- ✓ A key metabolic fingerprint or biomarker of acromegaly patients is lower branched-chain amino acids, particularly in those with active disease
- ✓ Large oral bony outgrowths, chronic periodontitis and gingivitis could indicate acromegaly, necessitating dental examinations within the diagnosis, treatment and management of acromegaly

Treatment and management of acromegaly requires a concerted focus on associated comorbidities, as well as an understanding of acromegaly and comorbidity biomarkers. This will help drive personalized care.

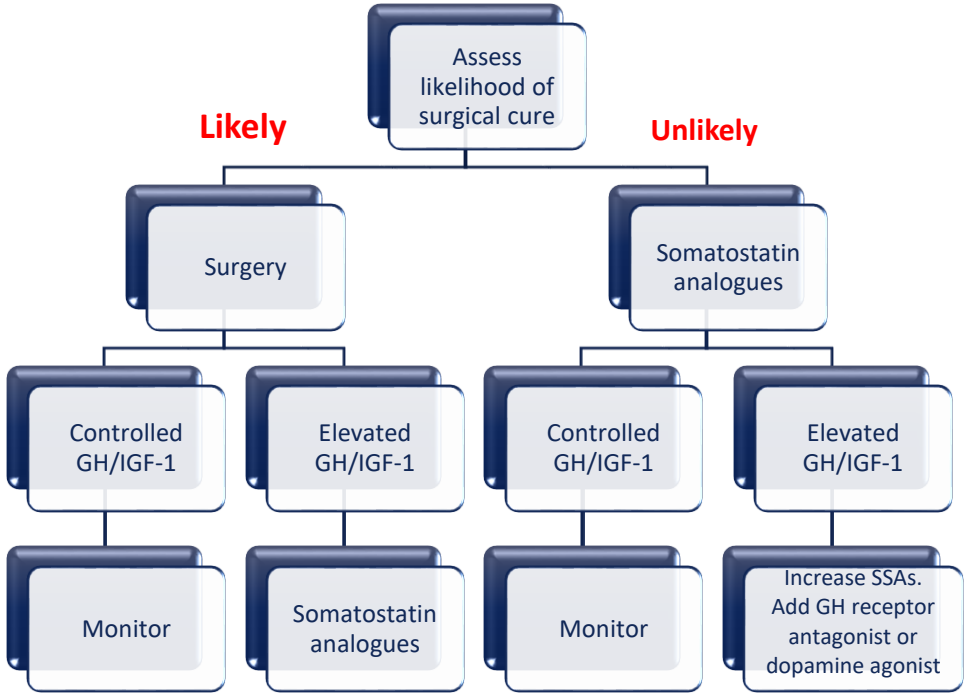

More efficient screening for comorbidities
Increased understanding around biomarkers of acromegaly vs. comorbidities
Awareness of the metabolic fingerprint
Awareness of oro-dental indicators
Multi-disciplinary expertise
More personalized treatment strategies
What does the future hold for recognizing acromegaly comorbidities?

Part 3.
European Congress of Endocrinology 2019: Latest medical treatment options for acromegaly

Focus on best practice

What is the current treatment landscape for acromegaly?

The aim of acromegaly treatment is to decrease GH and IGF-1 levels to ameliorate symptoms and decrease any local compressive effects of the pituitary adenoma



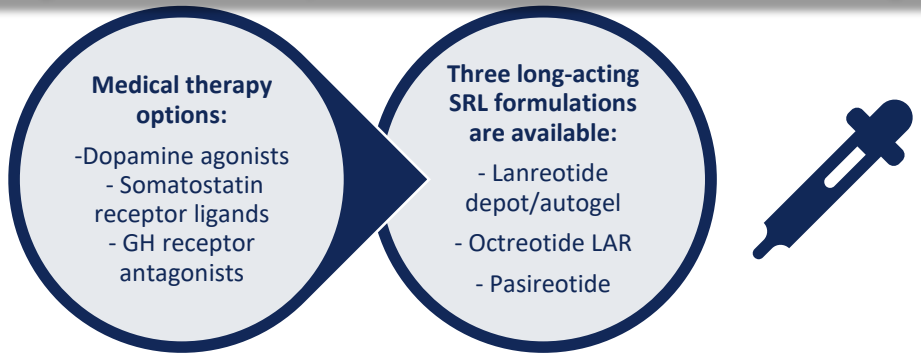
If the condition remains uncontrolled, radiation therapy or re-operation is considered

GH, growth hormone; IGF-1, insulin-like growth factor-1; SSA, somatostatin analogue.

What is the current treatment landscape for acromegaly?

The aim of acromegaly treatment is to decrease GH and IGF-1 levels to ameliorate symptoms and decrease any local compressive effects of the pituitary adenoma

- A multidisciplinary approach is recommended in the management of acromegaly, especially for the targeted treatment of associated comorbidities.
- Although the initial therapy choice will largely be driven by tumour and biochemical characteristics, **other patient-specific and disease-specific factors need to be considered in order to appropriately individualize the therapeutic approach**.
- Optimal implementation of current guidelines in routine clinical practice and appropriate use of medical therapy could improve the long-term outcomes for patients and address individualized treatment goals.



GH, growth hormone; IGF-1, insulin-like growth factor-1; LAR, long-acting release; SRL, somatostatin receptor ligands.

Effectiveness of somatostatin analogues in the treatment of acromegaly
Elmehraoui O, et al.

A retrospective, single-site analysis of the effectiveness of SSAs in the treatment of acromegaly

- 10 patients (mean age at diagnosis = 49 years; median delay to diagnosis = 8 years)
- All patients had pituitary adenoma (9 with macroadenoma and one with microadenoma)
- 8 patients received treatment with lanreotide LP 120 mg

- **Treatment with SSAs normalized IGF-1 in 62.5% of cases**
- During follow-up, the occurrence of vesicular lithiasis was complicated by cholecystitis in one patient and transit disorders in another patient

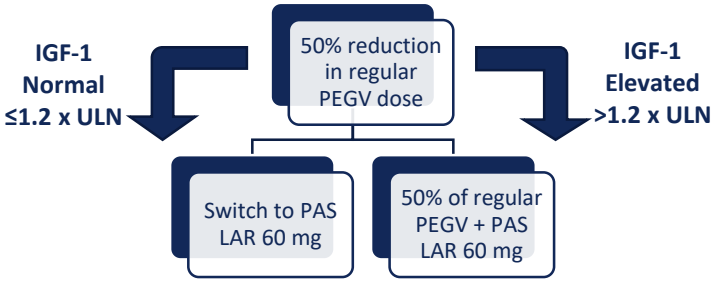
Lanreotide is effective at normalizing IGF-1, offering an alternative to somatotropic hypersecretion post-surgery or with inoperable tumours.

IGF-1, insulin-like growth factor-1; SSA, somatostatin analogue.
Elmehraoui O et al. *Endocrine Abstracts* 2019;63:EP98.

T2-signal intensity, SST receptor expression and first-generation somatostatin analogues efficacy predict hormone and tumor responses to pasireotide in acromegaly

Coopmans EC, et al.

Analysis of T2-signal intensity and SST receptor expression in relation to the hormone and tumour response during PAS-LAR treatment, and to determine to what extent this equals SRLs responsiveness



Tumour responsiveness to PAS-LAR	Hormonal responsiveness to PAS-LAR	Increased T2-signal intensity adenomas
• Hormonal unresponsiveness to SRLs • Lower SST_2 receptor expression • A trend towards higher T2-signal intensity	• Dissociation from tumour shrinkage • Higher T2 signal intensity	• Lower IGF-1 levels (PAS-LAR)

Patients not responding to somatostatin analogues with particularly large adenomas, low SST_2 receptor expression and higher T2-signal intensity are more prone to show tumour shrinkage during PAS-LAR than patients with high SST_2 receptor expression and T2-hypointense adenomas. These findings were also presented at ENDO 2019.

IGF-I, insulin-like growth factor 1; PAS-LAR, pasireotide long-acting release; PEGV, pegvisomant; SRL, somatostatin receptor ligands; SST, somatostatin; ULN, upper limit of normal.

Coopmans E, et al. *J Endocr Soc.* 2019;3(Suppl 1):SAT-LB076.

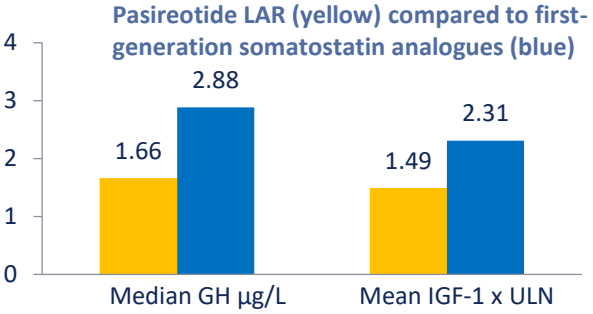
Prognostic value of short-acting pasireotide for response prediction to pasireotide LAR in patients with acromegaly resistant to first-generation analogs

Majos A, et al.

To assess whether the response to short-acting pasireotide can predict the efficacy of treatment with pasireotide LAR in patients with active acromegaly resistant to first-generation somatostatin analogues

- Following a two-month wash-out period, all patients were administered 600 µg of short-acting pasireotide and then switched to pasireotide LAR 60 mg administered intramuscularly every 28 days for three months

33% reached GH <1 µg/L	62.5% reached GH <2.5 µg/L	16.7% reached IGF-1 <1 x ULN	45.9% reached IGF-1 <1.5 x ULN



Maximal GH decrease correlated with GH and IGF-1 (r=0.72; p<0.001)

- After surgical debulking, pasireotide LAR is more effective than first-generation somatostatin analogues for decreasing GH and IGF-1 levels
- Short-acting pasireotide may predict patient response to the LAR version of the drug; better efficacy of pasireotide LAR is correlated with higher GH decrease after administration of 600 µg short-acting pasireotide

GH, growth hormone; IGF-1, insulin-like growth factor; LAR, long-acting release; ULN, upper limit of normal.

Majos A, et al. *Endocrine Abstracts* 2019;63:GP51.

ACROSTUDY – safety and efficacy in a cohort of 110 naïve patients with acromegaly treated with pegvisomant (PEGV)

Wajnrajch M, et al.

A sub-study to research presented at ENDO 2019,[1] assessing the long-term safety of PEGV in real world practice and the effect of IGF-1 normalization on treatment outcomes

110 adults with acromegaly (53.6% male), with a median age at diagnosis of 42.4 years and a median age at commencement of PEGV of 48.9 years

	IGF-1 Controlled		IGF-1 Uncontrolled	
Parameter	**Baseline**	**Year 2**	**Baseline**	**Year 2**
Mean HbA_1c (% with range)	5.8 (5.4–6.1)	5.6 (4.5–7.2)	6.1 (4.9–6.6)	6.3 (2.9–10.6)
Median AcroQoL score (with range)	54.6 (24–73)	61.4 (13–86)	59.7 (8–92)	63.6 (25–76)
Median total PAQ19 score (with range)	20 (3–38)	17.5 (1–40)	17 (0–44)	14 (3–39)

Patients were considered 'IGF-1 controlled' if the most temporally-related IGF-1 measurement was normal for that laboratory

- **Overall biochemical control was achieved with PEGV in 64.3% of patients by year 2**
- **Improved IGF-I control was associated with improved HbA_1c, quality of life and symptoms of acromegaly**

AcroQoL, acromegaly quality of life questionnaire; HbA_1c, glycated haemoglobin; IGF-1, insulin-like growth factor-1; PAQ19, patient-assisted acromegaly symptom questionnaire; PEVG, pegvisomant.

1. Wajnrajch M, et al. *Endocrine Abstracts* 2019;63:GP58.

Glucose metabolism and insulin sensitivity before and after treatment of acromegaly with either surgery or somatostatin analog: a prospective, investigator-initiated trial

Arlien-Søborg MC, et al.

To study basal and insulin-stimulated glucose metabolism during a 3-hour basal period followed by a 3-hour hyperinsulinaemic, euglycemic glucose clamp in patients (n=21) with acromegaly before and after disease control by either surgery-alone (surgery) or SSA treatment

Similarities between surgery and SSA

- IGF-I levels normalized after treatment (696±57 vs. 211±21)
- GH-dependent gene expression in muscle declined after treatment (p<0.05)
- GIR increased before compared with after treatment (3.3±0.4 vs. 4.7±0.5; p=0.001)
- Adipose tissue mass and intrahepatic lipid content increased with disease control, at the same time as lean body mass reduced

Differences between surgery and SSA

- Basal glucose levels declined after surgery but not after SSA
- SSA significantly suppressed insulin levels compared with surgery (p<0.000)
- Treatment decreased the basal state endogenous glucose production, but less so after SSA (p=0.02)
- Basal state glucose disposal was lower after SSA compared to surgery (p<0.000)
- Basal state glucose disposal after SSA was dominated by non-oxidative glucose disposal, whereas the opposite was true after surgery (p< 0.01)

- **Stimulated insulin sensitivity improves after disease control in acromegaly independent of treatment modality**
- **The paradoxical association between body composition and insulin sensitivity is unique for acromegaly and could help better understand the pathogenesis of insulin resistance**

GH, growth hormone; GIR, glucose infusion rate; IGF-1, insulin-like growth factor-1; SSA, somatostatin analogue.

Arlien-Søborg M, et al. *Endocrine Abstracts* 2019;63:OC34.

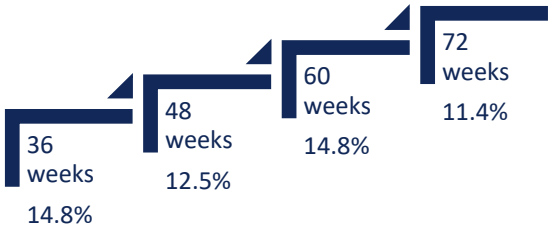
In patients with uncontrolled acromegaly, biochemical control was sustained with long-acting pasireotide over continued treatment with first-generation SSAs: results from the extension of Phase 3b, open label study

Gadelha M, et al.

Extension of a study presented at ENDO 2019, demonstrating that switching to pasireotide provided biochemical control at week 36 in 15% of patients.[1] This extension assesses the efficacy and safety of the medication in patients with uncontrolled acromegaly

- Patients (n=88) continued to receive the same does of long-acting pasireotide as in the initial 36 weeks of the study (40 mg/28 days or 60 mg/28 days)
- Dose adjusted up to 60 mg at weeks 52 and 64 depending on whether patients had achieved biochemical control at weeks 48 and 60, respectively
- Patients not achieving biochemical control during the study extension were allowed to receive concomitant treatment from week 40 with medications used to manage acromegaly

A higher proportion of patients with lower screening median GH levels achieved biochemical control at all four time points



Drug-related AEs:

Hyperglycaemia = 41.5%
Diabetes mellitus = 23.6%
Diarrhoea = 11.4%
Cholelithiasis = 8.9%
Abdominal pain = 8.1%
Alopecia = 7.3%
Sinus bradycardia = 6.5%
Blood glucose increase = 4.9%
Impaired fasting glucose = 4.9%

- **Switching to long-acting pasireotide after ≥3 months of first-generation SSAs can provide sustained biochemical control in the long-term, particularly in those patients with lower GH screening levels**

AEs, adverse events; GH, growth hormone; IGF-1, insulin-like growth factor-1; SSA, somatostatin analogue.

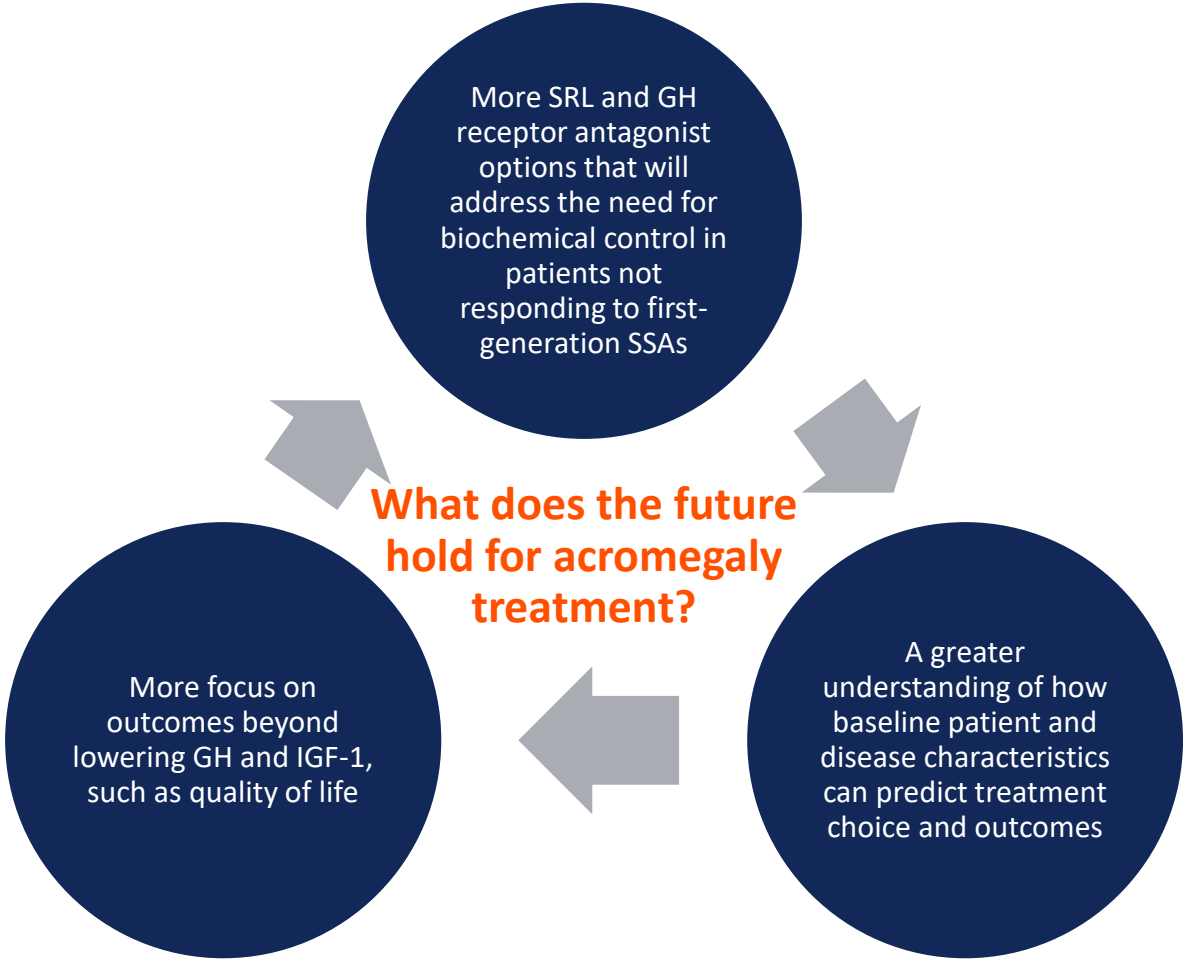
Gadelha M, et al. *Endocrine Abstracts* 2019;63:GP57.

Summary

- ✓ Lanreotide is effective at normalizing IGF-1, offering an alternative to somatotropic hypersecretion post-surgery or with inoperable tumours
- ✓ Patients not responding to first-generation somatostatin analogues now have more treatment options available to them, including second-generation SSAs
- ✓ The GH receptor antagonist, pegvisomant, has been found to achieve biochemical control by year 2
- ✓ A unique paradoxical association between body composition and insulin sensitivity could be used to help better understand the pathogenesis of insulin resistance in patients with acromegaly
- ✓ Evidence of SRL safety and efficacy continues to grow

There are an increasing number of treatment options available, which can be selected based on patient- and disease-related characteristics to facilitate treatment decision-making, multidisciplinary collaboration, and improved patient outcomes

GH, growth hormone; HbA_1c, glycated haemoglobin; IGF-1, insulin-like growth factor-1; SRL, somatostatin receptor ligand; SSA, somatostatin analogue.



GH, growth hormone; IGF-1, insulin-like growth factor-1; SRL, somatostatin receptor ligand; SSA, somatostatin analogue.

Thank you for watching