# Acromegaly Protocol

## A note on growth hormone assays

Measurement of growth hormone has been technically difficult. A variety of different assays have been used around the world over the years, and it was rare that results reported in one centre would be directly comparable with results reported in another centre. However, generally accepted GH targets at one time were <5mU/litre for adequate control and <2mU/litre for optimal control into the biochemically "cured" range..

Recently attempts to standardize GH measurement have included a change to mass units and calibration against internationally available standards. The conversion factor from mU/litre to μg/litre was initially set at 2, and so in much of the literature the accepted targets are given as 2.5 μg/litre and 1.0 μg/litre.

For the assays now in use in Edinburgh, a conversion factor of 3 applies. Thus, the equivalent targets are 1.67 μg/litre and 0.67 μg/litre. However, a decision has been made to round these down, partly for simplicity, and partly in recognition that GH levels should be well below these thresholds in truly normal (i.e. non-acromegalic) people. Thus, our targets are 1.5 μg/litre and 0.5 μg/litre.

The table summarises these changes, which should be borne in mind when reviewing the literature. For example, our measurement of 1.5 μg/litre will often be equivalent to literature reports of 2.5 μg/litre, or older reports of 5mU/litre. It is prudent to look for details of the assay used in any reports. However, this comes with the caveat that equivalence is no more than approximate, as measurements were unstandardized for so long. Furthermore, in many of the clinical series that form the evidence base for GH targets, the assay in use changed one or more times, so that the results may not have been comparable even in patients attending the same centre.

| | **Old** | **New (x2)** | **New (x3)** | **Edinburgh** |
|---|---|---|---|---|
| **Random GH (threshold for "control")** | 5mU/l | 2.5 μg/l | 1.67 μg/l | 1.5 μg/l |
| **OGTT nadir GH (threshold for diagnosis or "cure")** | 2mU/l | 1.0 μg/l | 0.67 μg/l | 0.5 μg/l |
| **IGF-1** | Age/sex matched | Age/sex matched | Age/sex matched | Age/sex matched |

Differences in GH levels by gender and age have been repeatedly reported (both for random and GTT samples(Markkanen 2006, Arafat 2008, Rosario 2008+2010) such that young women(under 40)>older women>men seemingly in some reports in a ratio as great as 3:2:1 close to 0.5 μg/l levels(Rosario 2008+2010). Thus whilst there is little appetite currently for using gender-specific ranges and single adult thresholds are retained it may be useful to remember that close to threshold levels these matters may inform clinical judgement often making a GH just >threshold more significant in an older man than younger woman.

# Diagnosis

## Roles of Acromegaly GTT and IGF1.

***When pituitary disease is present/suspected but there is no specific clinical suspicion of Acromegaly:-*** then an IGF1 should be a routine inclusion in pituitary screening tests with an IGF1 normal for age and sex being regarded as reasuring the GH axis is normal. An elevated IGF1 level or separate reason to specifically suspect acromegaly would warrant an acromegaly GTT.

***When there is suspicion of Acromegaly***:- the acromegaly GTT remains a key test with a GH nadir <0.5 μg/L excluding acromegaly whilst ≥0.5 is diagnostic of acromegaly.

Thus a diagnosis of acromegaly is established by:-

- IGF-1> age- and sex-matched normal range and.
- Failure of GH to suppress (to <0.5μg/litre) during a 75g GTT

***Random GH is not used in diagnosis of acromegaly***. GH is normally released in pulses and random levels vary widely.

## Acromegaly Glucose Tolerance Test

*Indication*: diagnosis of acromegaly, and monitoring treatment success in confirmed cases.
*Contraindications*: none.
*Precautions*: if patient is on insulin, this should be omitted.

### Procedure:

*Preparation:*

- unrestricted carbohydrate diet for 3 days prior to the test;
- fast from 22:00 hours the previous night – water is allowed (fast > 10 hours);
- morning medication is omitted, and taken when test completed.

*Patient aspects of test:*

- patient should attend at 08.30, and procedure is explained;
- patient should be seated throughout test – smoking is not permitted;
- discontinue test if any glucose is lost by vomiting;
- breakfast is given when test has been completed;
- patient should be reminded to take medication if applicable.

*Technical details of test (75g GTT);*

- give laboratory prior warning of test;
- place IV cannula for sample collection >10 mins prior to commencing test
- time 0 - take blood for growth hormone, IGF-1, glucose and any other bloods;
- patient then consumes 410 ml Lucozade from standard bottle (if unable to tolerate, give Polycal 120 ml as an alternative - this should be recorded);
- times +30 +60 +90 +120 min – take blood for growth hormone and glucose;
- specimens: brown top gel for GH and IGF-1, yellow top flox for glucose;
- samples including baseline bloods are sent to lab on completion of test.

### Interpretation:

Growth hormone should suppress to <0.5 μg/litre in normal people (though a truly normal response is probably well below this level – some suggest <0.2 μg/litre). In acromegaly failure of suppression occurs, and there may be a paradoxical rise in GH in response to the glucose challenge.

Growth hormone may be elevated in the following conditions, so interpret with caution: stress, high catabolic states (renal and hepatic failure), pregnancy, diabetes, use of oestrogen-containing drugs, tall adolescents. If taking oestrogens and GH nadir close to 0.5 μg/L consider stopping oestrogens and repeating.

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# Primary Management of Acromegaly

## Pituitary surgery

For acromegaly due to pituitary adenoma, pituitary surgery is the preferred option. This includes pituitary microadenomas, macroadenomas and tumours with extrasellar extension. Clearly each case will need to be considered on its merits, including the patient's preference and the technical difficulty of surgery.

This is somewhat different from recent international guidelines, which have suggested that primary medical therapy may be preferred for tumours that are not likely to be cured surgically (e.g. Melmed 2009). It is acknowledged that surgical cure rates are lower for larger or invasive tumours. UK data indicate cure rates of 100% for tumours too small to detect on MRI, 67% for microadenomas, 56% for intrasellar macroadenomas and 36% for extrasellar macroadenomas (see Bates 2008).

Surgery is preferred based on two principles. Firstly surgery offers the possibility of cure even in cases when this seems not a probability. Secondly surgical debulking reduces tumour mass improving the likelihood of subsequently achieving biochemical cure with medical therapy. Medical therapy is evolving and improving and long acting somatostatin analogs reduce tumour mass >20% (average 50%) in 75% of patients (Melmed 2009). Despite this current medical therapy in acromegaly is unable to deliver the degree of tumour involution commonly seen in prolactinomas. The only randomized trial to date comparing primary surgery with primary medical therapy appears to favour surgical treatment (81 patients, predominantly macroadenomas – Colao 2009).

### Medical therapy prior to surgery

There is some evidence that pre-treatment with somatostatin analogues improves the outcome of surgical resection, presumably by inducing tumour shrinkage. The evidence is not conclusive, with two RCT and one retrospective series suggesting a benefit (Mao 2010, Carlsen 2008, Colao 1997) and two retrospective series suggesting slight (Abe 2001) or no benefit (Losa 2006).

In Edinburgh, the recommendation is for medical pre-treatment for macroadenomas with extrasellar extension. Treatment is with long acting somatostatin analogues as described in the later section on adjuvant therapy. Reports of pre-operative somatostatin

therapy have been for 3-6mths (Abe, Mao, Carlsen and Colao et al) and exceptions to the **presumption that surgery for macroadenomas should not be delayed** will be on a case by case basis. There is insufficient evidence to confidently identify which patients will benefit most from such pre-operative somatostatin analogue treatment. It is acknowledged in those on somatostatin analogue therapy "There is, in general, a concordance between biochemical and anatomical response" and "Increased tumor size has not been reported in patients achieving biochemical control"(Melmed 2009). Accordingly monitoring the medical response may be of assistance in identifying those where moving quickly to early surgery seems paramount. Growth hormone receptor antagonist treatment should not be used preoperatively.

### Peri-operative management

See the separate protocol for management of pituitary patients on the neurosurgical ward.

## Primary medical therapy

Where a decision is made not to proceed with pituitary surgery, primary medical therapy should be offered.

### Dopamine agonist therapy

Cabergoline is the dopamine agonist with most evidence of efficacy. Cabergoline may be effective in lowering growth hormone levels, but significant success is seen in fewer than a third of patients and bromocriptine is reported less effective. Dopamine agonist use cannot be recommended in all cases, but should be considered on an individual patient basis particularly in patients reluctant to take injected treatment.

Intuitively, cabergoline ought to be more effective at lowering GH in patients who have tumours which co-secrete prolactin and GH, though evidence suggests that in fact this is not the case (Sherlock 2009).

### Somatostatin analogue therapy

Somatostatin analogues are the principal medical therapy for acromegaly. Retrospective studies have reported biochemical control rates of ~70% in selected populations, and ~30-40% in unselected populations, of acromegalic patients. Mean tumour volume reduction is ~50%, with ~75% of patients showing at least 20% volume reduction (Melmed 2009).

SA treatment is as described in the later section on adjuvant therapy.

### Growth Hormone Receptor Antagonists (Pegvisomant)

This newer therapeutic option holds promise of powerful symptomatic and IGF-1 suppression. However it is very expensive and has a restricted role only in severe acromegaly where other treatment options have left inadequate symptomatic and biochemical control (high IGF-1). Monitoring is by IGF-1 levels as GH level (but not action) is elevated on this treatment). Pegvisomant alone does not drive tumour shrinkage and rarely (<2%) continued expansion occurs. Whilst shrinkage from

concurrent somatostatin analogues will often occur – it is not recommended to use pegvisomant as part of medical therapy specifically used pre-surgery.

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# Monitoring After Primary Therapy

The key monitoring after primary surgical (±medical) treatment involves:-

(1)monitoring of the GH axis (IGF1+GH assessment – see below),

- IGF1 on any (thus random) blood sample,
- GH assessment involves establishing GH is suppressible below thresholds defined by a nadir on a 75g oral glucose tolerance test (acromegaly GTT) or being persistently below an "optimal control" threshold on random GH measurements. The relative merits of testing GH with or without an acromegaly GTT are debated but GTT traditionally has been used in the initial (6 weeks) post-op assessment and may be less appropriate when there is concurrent somatostatin analog treatment and when clinically stable (see further under "Interpretation of Results" below).

(2)other pituitary function tests (PFTs)

- PFTs will include Short synacthen test, prolactin, fT4 (±TSH), testosterone in men (±LH, FSH, at times oestriadiol in amenorrhoeic women) and U+Es if diabetes insipidus has been an issue. If PFTs are abnormal the clinical judgement is used regarding the need for hormone replacement and repeat PFT monitoring

(3)monitoring pituitary appearance/tumour bulk – preferentially by MRI scan. .

The key initial assessments are at 6 weeks and 3 months – usually allowing a multidisciplinary team (MDT) assessment using IGF1+GH, PFTs and post-op MRI imaging to establish a management plan.

Whilst a summary of common elements in management and interpretation of monitoring is given below it is paramount that individual cases have **appropriate MDT assessment** initially after 3 months post-op and subsequently if management becomes problematic or radiotherapy is considered.

## Common Elements in Monitoring Acromegaly and Efficacy of Treatment

*After primary surgical (±medical) treatment:*

- standard PFTs+IGF-1, acromegaly GTT 6 weeks after surgery.
- at ~3mths after surgery - post-op MRI pituitary, also if IGF-1/GH/PFT assessments were abnormal at 6 wks often repeated especially IGF-1
- ➔Thus at ~3 mths after primary Rx able to "triage" into groups (i)-(iii):-

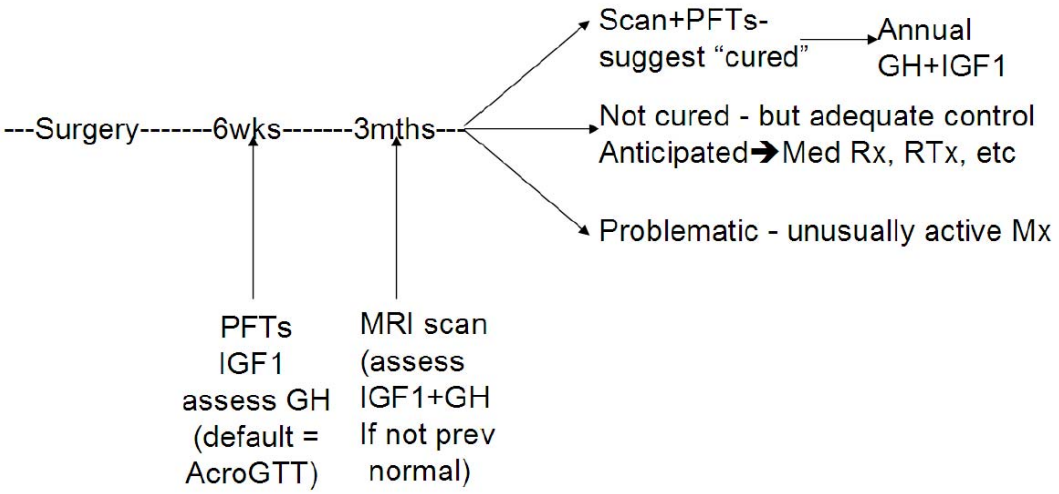
**(i)Putatively cured**: "biochemically cured", normal PFTs and post-op scan consistent with this. It is often then appropriate to monitor only annual IGF1 + GH

**(ii)Not cured but eventual adequate control anticipated**:-

The majority of such patients will receive adjuvant treatment (medical therapy +/or radiotherapy). Some common management consequences are:-

- *Radiotherapy* – patients should have monitoring PFTs usually annually when IGF1+GH show no progression. Routine MRI imaging is usually not required.
- *On Medical Treatment*- biochemical control does not exclude tumour expansion – thus require initially annual MRI imaging reducing in frequency if good control and good biochemical-radiological correlation apparent. Arguably if no radiotherapy, monitoring PFTs can reduce to just IGF1+GH if biochemically + radiologically stable but this may be unclear for >1year and PFTs should be rechecked if concern re-emerges of tumour progression (eg by worsening of GH/IGF1 control or tumour bulk on re-imaging).
- Occasional patients with good control especially women of reproductive age although not "cured" by IGF1+GH levels, are observed usually via annual PFTs, without Radiotherapy or Medical Treatment.

**(iii)Problematic** – signs of uncommon problems in control evident. Often young patients with large macroadenomas and particulatly high IGF1 + GH post-op.
Such patients have individualised management, typically with frequent monitoring and usually have aggressive treatment contemplated at an early stage -with multi-agent medical therapy, specialised radiotherapy (eg γ-knife) or reoperation.




***Common early Post-op Acromegaly Assessment***

## Interpretation of results

In acromegaly as a whole, the mortality rate is approximately double that of the general population. Retrospective studies have shown that mortality rates are normalized in patients who achieve random/fasting GH <2.5µg/litre (1.5µg/litre in Edinburgh – see page 1), and also normal age- and sex-matched IGF-1 levels (Holdaway 2008). These criteria are thus deemed to indicate acceptable "Control" is present whilst a superior level of control consistent with an optimal/"biochemically cured" outcome is also defined.

***"Control" of acromegaly is defined by:***

- GH <1.5µg/litre across GTT;
- normal age- and sex-matched IGF-1.

**Biochemically "cured" ("Optimal control" into the "cured range")**

- normal age- and sex-matched IGF-1.

- and either ➔Nadir during GTT of GH <0.5μg/litre;
  or ➔ random GH levels persistently<1μg/litre (based on a recent consensus statement: Giustina 2010)

Traditionally the post-operative GH status has been established at 6 weeks post-op (with GTT nadir <0.5μg/litre establishing biochemical "cure"). Alternatively assessing random GH on several occasions (perhaps minimum 3 randomly or if preferred could be across 2 hours without GTT) and showing persistently <1μg/litre fits with recent consensus for establishing "optimal control" into the "cured range" (Giustina 2010). Both these initial approaches avoid being easily misled by a single "rogue" GH result, without the difficulties of a GH day curve.

Once biochemically "cured" status is established – either GTT nadir or random GH may be used at subsequent assessment for demonstrating maintenance of optimal control and typically with increasing time if all GH measurement have been <1μg/litre (including on basal samples on any GTTs) monitoring reverts to checking a single random IGF1 and GH at clinics. The role of ongoing acromegaly GTT monitoring is clearest when there is no concurrent somatostatin analog treatment perhaps especially if basal GH>1μg/litre.

### Discordant GH and IGF-1 results

It is not uncommon for IGF-1 to suggest good control but GH to be elevated (or vice-versa). The problem of interpreting such results is widely acknowledged. There is no strong evidence that one test should be favoured over the other, nor that patients with discordant results with only very borderline elevation of a result require adjuvant therapy. The following can be useful to consider:-

- Usually when discordant, repeating the IGF1+GH assessments regularly is wise
- Do changes in the level of symptoms fit with active or controlled acromegaly?
- IGF-1 levels may take 3-6 months longer to complete post-operative decline than GH
- Post-radiotherapy GH can show flatter secretory patterns, discordantly lower than IGF-1
- GH levels are somewhat higher in women, especially <40 years old (see also bottom page1).
- IGF-1 proportionately lower and GH higher has also been reported in hypothyroidism, anorexia, inflammatory bowel disease (and disorders causing nutritional problems), hepatic or renal failure, poor diabetic control, oral estrogen use and pregnancy.

Management decisions for such patients will need to be case-by-case decisions.

## Monitoring tumour size

*After primary surgical or medical treatment:*

- MRI scanning 3 months post-op, 3-6 months after initiating medical treatment.

*Follow-up in patients achieving biochemical control:*

- no scanning routinely if surgery and/or radiotherapy were only treatments;
- periodic scanning required if on medical therapy (biochemical control does not exclude tumour expansion);

*Follow-up in patients without biochemical control:*

- annual scanning by default if receiving medical therapy;
- no scanning required if not on medical therapy and biochemistry stable.

# Adjuvant Therapy

Adjuvant therapy should be considered whenever the primary treatment (usually surgery) has failed to achieve biochemical control.

## Radiotherapy

The decision to offer radiotherapy must be made at a multidisciplinary meeting in conjunction with the oncologist. Broadly, the default position in Edinburgh is that patients who do not achieve targets for GH and IGF-1 should be recommended to have radiotherapy.

This is different from some recent guidelines, which positioned radiotherapy as third- or fourth-line (e.g. Melmed 2009). However, extensive experience in the UK has shown that radiotherapy is highly effective for the treatment of acromegaly (Jenkins 2006). Typically, radiotherapy takes around 2 years to show substantial effect, with further declines in GH and IGF-1 over as long as 20 years. Adjuvant medical therapy may be required for biochemical control in the interim.

There are a number of side effects of radiotherapy, of which the most clearly defined is hypothalamic-pituitary dysfunction. In the UK series, impaired function of the gonadal axis increased from ~40% at baseline (presumably due to surgical damage) to ~60% 10 years after radiotherapy. The desire to remain fertile, especially in younger patients, is the clearest relative contraindication to radiotherapy. Dysfunction of the thyroid and adrenal axes are slightly less common. Increased cardiovascular risk is associated with hypopituitarism, although the extent to which this is a function of measurable (and treatable) factors such as glucose intolerance, lipidaemia and blood pressure is uncertain. There are concerns about possible cognitive dysfunction due to cerebral radiation damage, though the risk and magnitude of any effect is impossible to quantify at present.

## Medical therapy

### Dopamine agonist therapy

See earlier section on primary medical therapy. Cabergoline should be considered in all cases, but is considered to show significant effectiveness in fewer than a third of patients.

### Somatostatin analogue therapy

Somatostatin analogues are the principal adjuvant medical therapy for acromegaly. Biochemical control rates of 50-70% may be expected (Murray 2008). Long-acting depots have replaced thrice-daily subcutaneous injections as the standard formulation, and are prescribed under the Lothian Joint Formulary shared care protocols (see http://www.ljf.scot.nhs.uk).

*Initiation:*

- Somatuline Autogel or Sandostatin LAR may be used – there is no clear evidence that one is better than the other;
- begin at the lowest dose (60mg Somatuline Autogel or 10mg Sandostatin LAR);

- depot injections are administered every 28 days. [This is carried out in accordance with the Shared Care protocol. Typically nursing staff (Metabolic Unit, WGH) or, by arrangement, the Community Ibsen/Novartis Reps administer the first injection and instruct the patient (especially re avoiding lumps in Somatuline Autogel). Thereafter administration should transfer under the care of the GP.]

*Dose titration:*

- acromegaly GTT and measurement of IGF-1 should be performed 3-4 months after starting therapy;
- most reduction in GH and IGF-1 is seen within 3 months – minor reductions may be seen with continued SA therapy at the same dose;
- if biochemical targets are not reached, increase to the next prescribable dose (Somatuline Autogel 60→ 90→ 120mg, Sandostatin LAR 10→ 20→ 30mg);
- acromegaly GTT and IGF-1 measurement should be performed 3-4 months after each dose adjustment;
- if biochemical control is achieved, consideration should be given to increasing the interval between injections, e.g. to 6-weekly, to save costs.

*Side effects and precautions:*

- SAs are not generally used in pregnant or breast-feeding women;
- steatorrhoea (may require pancreatic enzyme supplements);
- gallstones (it is not Edinburgh policy to routinely image the gallbladder or measure LFTs, but do so if symptomatic);
- impaired glucose tolerance or diabetes (above that associated with acromegaly);
- nausea, vomiting, bloating, abdominal cramps, flatulence, anorexia, weight loss;
- may reduce absorption of ciclosporin or cimetidine.

*Subcutaneous octreotide:*

- anecdote suggests that short-acting octreotide may be effective for symptoms such as headache that are not relieved by long-acting formulations;
- a test dose of octreotide 50μg should be administered in the department, with observation for at least 4 hours after;
- patient should be taught injection technique, and dispensed a week's supply of 50μg 3x daily (check pharmacy have this before bringing the patient in).

## Growth hormone receptor antagonist therapy

Pegvisomant is the only licensed GHRA, and may be considered for individual patients who are not controlled with SA therapy by special agreement with the Health Board. Its use is very uncommon at present, so no detailed protocol is provided.

A few general points:

- GH levels are high, because negative feedback is lost, and because pegvisomant is a minimally-altered GH molecule and so is detected by the GH assay;
- IGF-1 only is used to monitor treatment success;
- very high rates of biochemical control have been reported in clinical trials;
- periodic MRI scanning is recommended because of theoretical risk of tumour expansion akin to Nelson's syndrome (though in fact this has not been seen);
- LFT abnormalities are common, and so should be monitored frequently.

# Other Follow-up

## Annual screening

The following tests should be performed or considered annually:

- acromegaly GTT with IGF-1 (see section on monitoring, above);
- pituitary function testing (see section on monitoring, above);
- glucose tolerance (measured as part of acromegaly GTT, but do not forget to look at the glucose results!);
- lipid profile;
- blood pressure.

## Cardiovascular

*Echocardiography* is recommended once at baseline, looking for acromegaly-associated cardiomyopathy. Where the results is normal, require further routine examinations are not required.

*Cardiovascular risk* should be considered in all, taking into account hypertension or glucose intolerance that may be secondary to acromegaly. It is recommended that patients should be considered "high risk" if they have sustained uncontrolled acromegaly, or hypopituitarism. Ideally BP to 130/80, Total and Total/HDL Cholesterol to <4mmol/L.

## Colonoscopy

The rate of bowel cancer is increased in patients with acromegaly, but there is insufficient evidence to determine the ideal screening schedule, and so various guidelines exist.

Edinburgh endocrinology recommends:

- colonoscopy at baseline in all patients aged over 40;
- no further colonoscopies if biochemically "cured"
- colonoscopies every 5 years if acromegaly not "cured"/optimally controlled;
- plus follow-up as indicated if any abnormalities are seen, e.g. adenomas.

The British Society of Gastroenterology guidelines recommend colonoscopy every 5 years in all aged over 40, or every 3 years if there is active acromegaly (Jenkins 2002). As it is the gastroenterologists who arrange and perform the scopes, it must be accepted that they may follow the more intensive BSG guidelines.

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