ACROMEGALY

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ABSTRACT

Acromegaly is a rare condition with an approximate incidence of 3-11 new cases per million of population per year and a prevalence of approximately 60 per million (1). There are approximately 3000 identified individuals in the UK and 15000 in the USA, although it is possible that more cases exist but do not come to clinical attention. More recent studies suggest a higher incidence of acromegaly, up to 6.9 per 100,000 according to Italian data and 7.7 patients per million per year in Iceland (2,3). The condition was named by Pierre Marie in 1886 using the Greek words akron- extremities and megas- large to describe the typical clinical appearance of the condition (4).The disease occurs as a result of excessive secretion of growth hormone. In more than 99% of cases this is due to a benign pituitary growth hormone secreting adenoma. Pituitary carcinomas are exceedingly rare. Extremely infrequently acromegaly occurs as a result of ectopic secretion of growth hormone releasing hormone (GHRH) from a peripheral neuroendocrine tumor (5,6), excessive hypothalamic GHRH secretion (7), or can result after long term exogenous GH abuse (8). Approximately 5% of cases are associated with familial syndromes, most commonly multiple endocrine neoplasia type 1 (MEN1) syndrome, but also McCune Albright syndrome, familial acromegaly, Carney syndrome, and Familial Isolated Pituitary Adenoma (FIPA). Both genders are equally affected and the diagnosis is typically made in adults aged 40-60 years of age. Younger patients often have more aggressive disease due to more rapidly growing adenomas. Acromegaly is associated with multiple systemic complications and a higher risk of mortality if untreated. Very often a multi-modal treatment approach is required to manage the condition, including surgery, radiotherapy, somatostatin analogues, GH receptor antagonist, and dopamine agonist. The management should be individualized to the patient using best practice guidelines, clinical experience, and individual patient circumstances and guided by biomarkers and clinical predictors.

PHYSIOLOGY: GROWTH HORMONE-STRUCTURE AND PHYSIOLOGY

Growth hormone is a 191 amino acid single chain protein containing two disulphide bonds. It has considerable structural homology with prolactin. Approximately 70% circulates as a 22 kD protein, 10% as a 20 kD isoform and the remainder as dimers or sulphated and glycosylated isoforms (Figure 1). Growth hormone secretion occurs in pulsatile bursts, numbering between 4 and 11 in 24 hours, especially at night, with extremely low or undetectable levels occurring in the nadir between pulses. Thus, a random single serum measurement is very limited as a means of assessing the overall level of secretion. Secretion of growth hormone is governed by both secretory and inhibitory hypothalamic factors. GHRH (growth hormone releasing hormone), ghrelin, and klotho act

to stimulate release (9), whereas hypothalamic somatostatin (a 14 amino acid peptide) exerts marked inhibitory effects on GH release. Cortistatin has been found to exert dual, stimulatory and inhibitory effects on GH secretion (10). These stimulatory and inhibitory factors are subject not only to higher influences within the brain but also to peripheral signals such that the overall secretion of growth hormone can vary widely under different physiological and pathological conditions (11) . These are summarized in Table 1.

Table 1. Factors Affecting Growth Hormone Secretion (12)

PHYSIOLOGICAL		**PATHOLOGICAL**	
Factors which increase GH secretion	**Factors which reduce GH levels**	**Factors which increase GH secretion**	**Factors which reduce GH levels**
Sleep	Overeating	Acute glucocorticoid excess	Chronic excess Cortisol/ glucocorticoids
Fasting	Obesity	Type 1 DM	Hyperthyroidism
Stress	Aging	Renal failure	Type 2 DM
Exercise	Increased IGF-1	Acute use of opiods	
Hypoglycemia		Anorexia	
Dopamine		Depression	
Increased Amino acids i.e., high protein meal		Cirrhosis	
Reduced Free Fatty acids			
Glucagon			
Testosterone and estradiol			

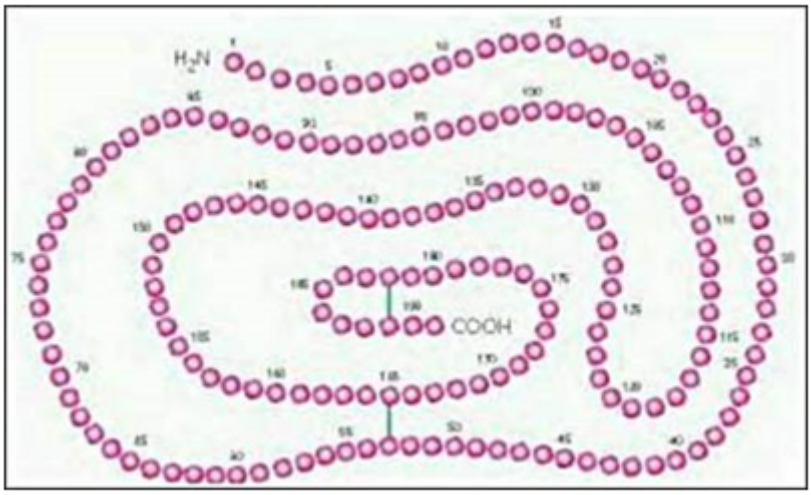

Figure 1. The 2-D structure of human growth hormone.

Growth hormone circulates in blood bound to a specific binding protein, called GH binding-protein (GHBP). This protein comprises the extracellular portion of the growth hormone receptor (GHR), which is widely distributed and present in most tissues. Activation of the growth hormone receptor occurs when the growth hormone molecule binds two adjacent receptors resulting in dimerization of the growth hormone receptors. Dimerization of the growth hormone receptor results in its activation and binding of the intracellular Janus kinase (Jak 2) tyrosine kinase. The activated JAK2-GHR complex induces multiple signaling pathways responsible for the diverse actions of GH (13,14). These include phosphorylation of a) signal transduction and activators of transcription (STAT) proteins STAT1, STAT3 and most importantly STAT 5, b) SRC family kinases which trigger the MAP kinase pathway, c) insulin receptor substrate (IRS) proteins which activate phosphatidylinositol-3-kinase (PI3K) and Akt pathway, and d) SH2B1, a scaffold protein that upregulates GH action in the actin cytoskeleton (13). Intracellular growth hormone signaling is suppressed by several proteins, especially the suppressors of cytokine signaling (SOCS) 1-3 and protein tyrosine phosphatases SHP1, SHP2 (14,15). While there have been suggestions that GHR polymorphism could play a role in variable responses to the GHR antagonist Pegvisomant therapy, so far studies have not convincingly demonstrated this relationship (16).

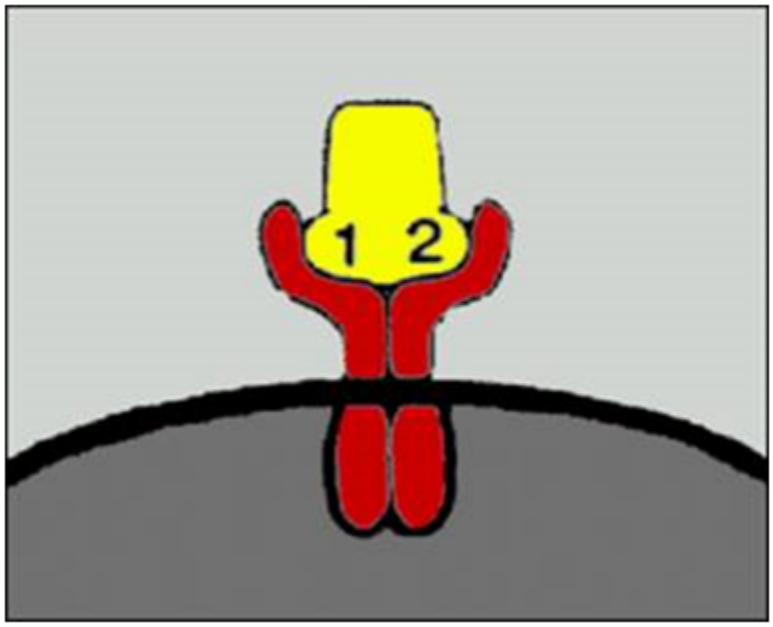

Figure 2. The growth hormone molecule binding to the membrane surface growth hormone receptor. Signaling and transduction only occur when adjacent receptors bind the two specific binding sites on the growth hormone moiety to form a dimer.

One of the major proteins induced by growth hormone is insulin-like growth factor-1 (IGF-1)——Although classical endocrinology states that it is hepatic derived IGF-1 acting in an endocrine manner that is responsible for most, if not all, of the effects of growth hormone, it is becoming increasingly clear that local production of IGF-1 acting either in a paracrine (nearby cells) or autocrine (on the same cell) manner also has important biological effects, predominant of which is stimulating cell proliferation and inhibiting apoptosis (17). Elegant gene 'knock-out' experiments have demonstrated that animals with selective hepatic IGF-1 loss have a normal phenotype and growth, despite marked reduction in serum IGF-1 levels (18). Furthermore, patients with severe GH deficiency, perhaps as a result of pituitary surgery, usually have serum IGF-1 levels just below or at the lower end of the normal range. Thus, rather than being the sole effector of growth hormone, serum IGF-1 should perhaps be more accurately regarded as a marker of serum growth hormone concentrations. Circulating IGF-1 does however have important effects in regulating pulsatile growth hormone secretion with IGF-1 acting in a negative feedback fashion suppressing growth hormone release.

Central Regulation of GH Secretion

GHRH consists of 44 amino acids, the first 27 from the N-terminus being essential for physiological activity (19). GHRH containing neurons are located in the arcuate nucleus and surrounding the venteromedial nucleus which is considered the major site of GHRH activity. Somatostatin producing neurons are predominantly present in the dorsolateral arcuate nucleus and share close synaptic connections with the GHRH neurons (20). While these two hormones form the key components of local autocrine short feedback regulation of GH secretion; it is further modulated by interactions with central neuropeptides. Dopamine,

serotonin, norepinephrine, neuropeptide Y regulate GH output through their interactions with GHRH and Somatostatin neurons (20). GH exerts its own local negative feedback along with local IGF-1 feedback. The Neuropeptide Y system contributes to the rise in circulating GH seen in the fasting state (21).

A long negative feedback also exists and growth hormone induces hepatic secretion of IGF-1, which in turn inhibits growth hormone release through various mechanisms including modulating GH gene transcription, reducing GH mRNA expression through POUF1 /CREB protein interactions and altering somatostatin release through paracrine activity (20,22,23).

Ghrelin and Growth Hormone Secretion

GH pulsatility is primarily driven by nutritional status. The potent growth hormone stimulating action of ghrelin is now well established. Ghrelin was identified as a natural ligand responsible for regulating GH secretion in the acylated form (24). It is a 28 amino acid peptide, which is modified by Ghrelin-O-Acyl-transferase (GOAT) enzyme to mediate its GH secretory action through IP3 signaling pathway (25). Expression of ghrelin is found in many tissues including both the gastrointestinal tract and the CNS, with the strongest concentrations located in the stomach. Ghrelin mediates its orexigenic actions through the vagal nerve stimulation and eventually acting on the hypothalamic appetite center though the noradrenergic pathway (26). Gastric expression of ghrelin is reduced following feeding and increased by fasting, hypoglycemia and after leptin administration. On other hand, leptin seems to variably effect GH secretion depending on the nutritional status. The exact mechanisms of leptin driven GH changes are not well understood (27).

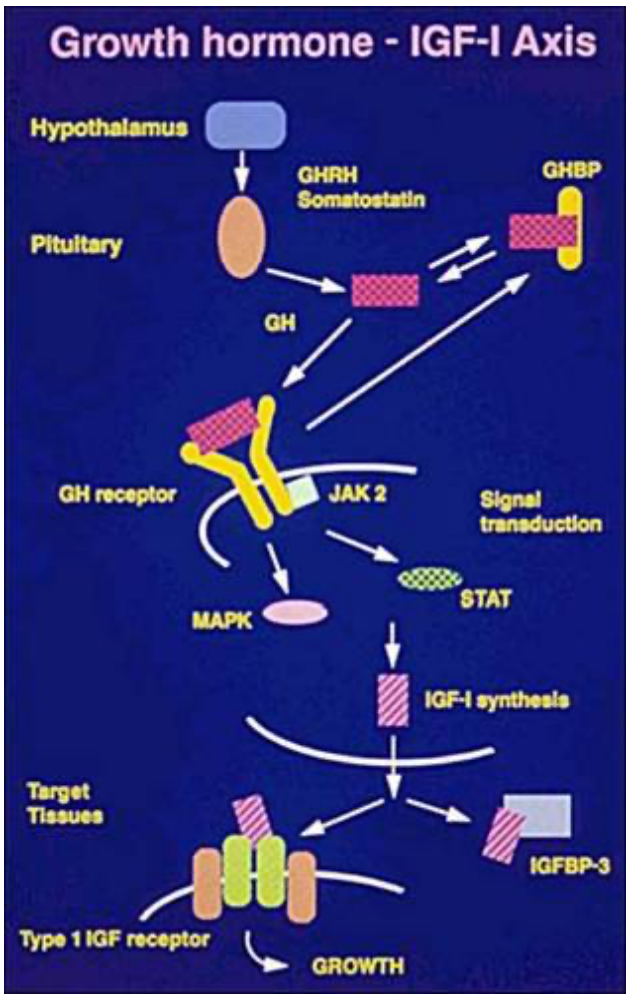

Figure 3. The growth hormone/ insulin-like growth factor-I axis.

Peripheral Regulation of GH Secretion

Systemic energy homeostasis is a potent influence on GH secretion, with interactions by glucose, free fatty acids, adipokines, leptin, ghrelin, and insulin (28-30). Several hormone systems have regulatory effects on growth hormone secretion. Hypothyroidism is associated with low levels of both growth hormone and IGF-1, and in children leads to short stature (31). Thyroxine replacement has been shown to reverse these deficits. Further evidence from studies in rodents indicates that growth hormone gene expression is regulated by thyroid hormone acting through a thyroid hormone responsive element in the promoter region of the growth hormone gene (32,33). GH replacement has been shown to reduce the Free T4 levels and increase Free T3 levels, by the effect on type 2 iodothyronine deiodinase (34). Glucocorticoids are inhibitors of somatic growth both in humans and experimental animals and individuals with either Cushing's syndrome or taking exogenous corticosteroids have been shown to have reduced growth hormone secretion.

Gonadal hormones also play a role in the neuroregulation of growth hormone secretion. In both sexes spontaneous growth hormone secretion is increased during puberty, and reduced in those with delayed puberty (35), suggesting that both estrogen and testosterone influence growth hormone secretion. The estrogen related reduction of IGF-1 seems to be responsible for relatively higher GH levels in females compared to men, with similar IGF-1 levels (36,37). Hypoglycemia is a potent inducer of growth hormone secretion, and insulin induced hypoglycemia remains the most employed provocative test of growth hormone reserve in humans. Hypoglycemia reduces hypothalamic somatostatin secretion facilitating growth hormone release. A delayed rise in GH levels is noted after acute hyperglycemia and is likely a result of GHRH rise (38) In contrast, hyperglycemia suppresses growth hormone secretion from the healthy pituitary. The availability of amino acids as in the post-prandial state stimulates growth hormone secretion whilst elevated non-esterified fatty acid levels suppress growth hormone release.

IGF-1: Structure and Function

IGF-1 is a single chain polypeptide of 70 amino acids with three intrachain disulphide bridges, coded by a gene situated on the long arm of chromosome (39). It has 48% amino acid sequence homology to pro-insulin, the A and B domains of IGF-1 have 60-70% homology but there is no homology with the C domain. IGF-1 has a specific receptor, which is structurally and functionally very similar to the insulin receptor. It consists of two extracellular α-subunits which are the hormone binding sites and two transmembrane β-subunits which are involved in initiating intracellular signaling. Post-receptor signaling mechanisms are also similar for IGF-1 and insulin receptors, both activating the tyrosine kinase and IRS-1 cascades. IGF-1 can bind to the insulin receptor but with only 1-5% affinity compared to insulin. Under normal physiological conditions it is thought that IGF-1 acts via the specific IGF-1 receptor, but in the presence of high concentrations of IGF-1 there is likely to be cross activation with the insulin receptor. IGF-1 receptors are found on most tissues with the notable exceptions of liver and adipose tissue. Hybrid IGF-1/insulin receptors have now been well documented and sequenced but their role is unclear (40).

The majority of circulating IGF-1 is produced by the liver with bone, adipose tissue, kidney, muscle and many other tissues producing a smaller quantity. Plasma concentrations of IGF-1 in the human are regulated by growth hormone, insulin, age, and nutritional state. Bioavailability of IGF-1 is determined by its binding proteins (see below). Growth hormone and insulin are the main regulators of hepatic IGF-1 production. The precise regulation of local IGF-1 synthesis is uncertain, but it is influenced by many other trophic hormones such as ACTH, fibroblast growth factor, and TSH (41).

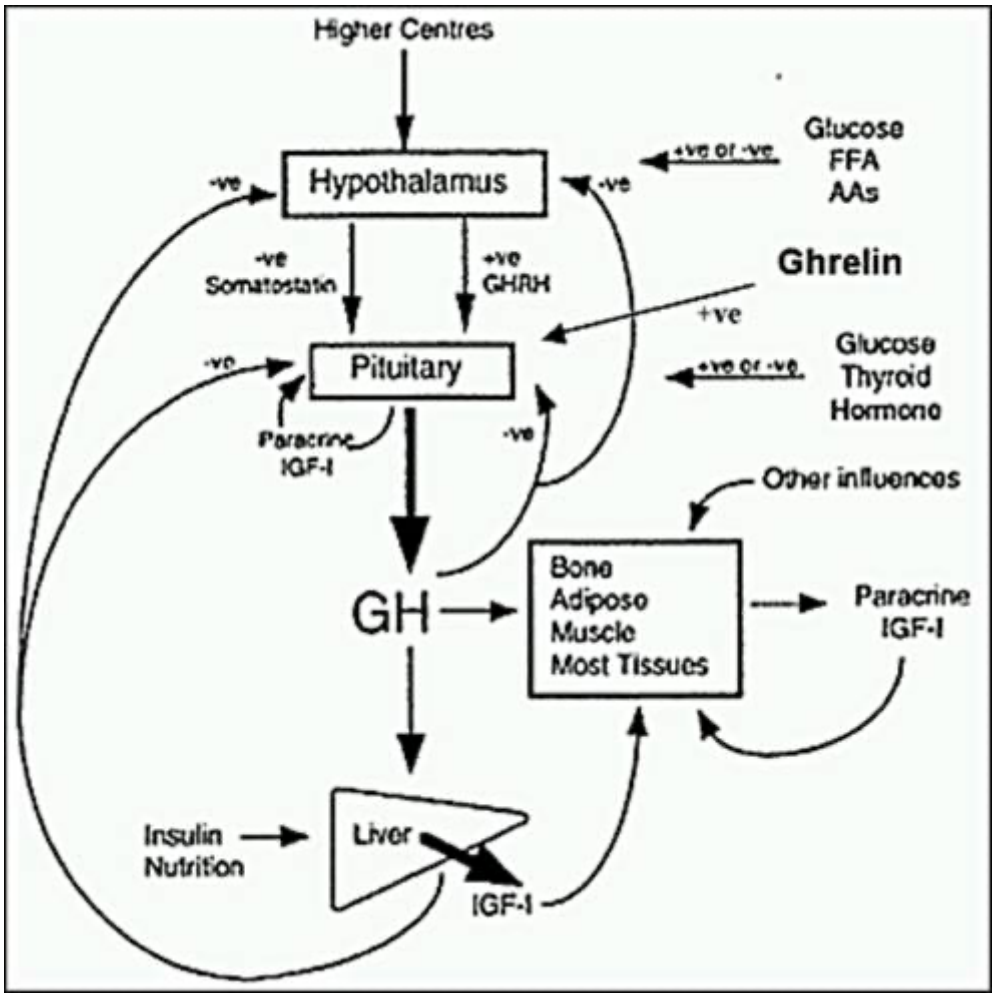

Figure 4. The regulation of growth hormone secretion.

IGF Binding Proteins (IGFBPs)

Unlike insulin the majority of IGF-1 circulates in plasma bound to a variety of binding proteins which determine its bioavailability and modulate its biological action (42). The majority of IGF-1 is bound in a 150 KDa complex with IGFBP-3 and form an acid labile subunit ALS (42). This large molecule (termed the ternary complex) is unable to pass through endothelium and acts as an intravascular reservoir of inactive IGF-1. The half-life of IGF-1 in the complex with IGFBP-3 and ALS is 12-15 hours compared with 10-12 minutes for free IGF-1. The exact mechanisms by which IGF-1 is released from the ternary complex to allow access into the tissues is not known; however, IGFBP degrading protease activity has been well documented in many biological fluids and clinical states.

Current knowledge suggests that IGFBP-1 and IGFBP-3/ALS are the binding proteins which have the major effects on the bioavailability of IGF-1(40). IGFBP-1 is inversely related to insulin levels, has a circadian variation with the highest levels being found overnight when insulin levels are lowest, and inhibits the hypoglycemic action of IGF-1 (43). Growth

hormone secretory status is the main regulator of plasma levels of ALS (42).

PATHOLOGY OF ACROMEGALY

Acromegaly is most commonly the result of pituitary adenoma and rarely due to non-pituitary neuroendocrine tumor/ neoplasia (NET/ NEN). Pituitary tumors are commonly monohormonal or plurihormonal in nature with further distinct subtypes. These subtypes of tumors are responsible for their characteristic behavior and can sometimes guide management (44). The common subtypes are discussed below.

1) Monohormonal densely granulated somatotroph adenomas are the most common type of GH-secreting pituitary tumors. They have predominance of the large, dense secretory granules which contain GH and appear deeply eosinophilic on staining. They account for 30-40% tumors and while tend to lead to higher GH levels, they are usually slow growing tumors, in older patients with mild disease, and retain a predictable response to SSA therapy. Somatic mutation in Gs-α subunit of GNAS has found to be the most common abnormality in GH secreting tumors leading to increased cAMP activity (45).

2) Sparsely granulated somatotroph adenomas form the second most common type of tumor. As the name suggests, they are lightly eosinophilic on HE staining due to the increased presence of keratin aggregates and reduced GH containing granules. While they present with lower GH levels, the tumor behavior is relatively aggressive. They tend to be larger, more invasive with higher ki67 proliferation indices and are less responsive to SSA therapy. Further studies suggest reduced expression of E cadherin and SSTR2 in sparsely granulated tumors as factors likely to be responsible for poor response to SSA ***(44)***.

3) Mammosomatotroph adenoma from a monohormonal Pit-1 lineage cells is a common pathology found in younger individuals with acromegaly. They are densely granulated and co-stain for GH and PRL. They behave in a more benign fashion with high GH and PRL levels leading to early presentation, when the tumor is smaller at diagnosis. They respond to SSA therapy similarly to densely granulated tumors ***(46)***.

4) Mixed somatotroph and lactotroph tumors are formed of bihormonal cells with variable combination of somatrotroph and lactotrophs. In variable combinations they comprise of sparsely granulated and densely granulated cells all of which express Pit 1. They tend to be less amenable to treatment and are reported to have frequent disease recurrence ***(47).***

5) Mature Plurihormomal Pit1-Lineage tumors frequently immunostain for TSH along with GH, PRL and are found to express GATA3 ***(48)***. Clinical presentation includes features of thyroid overactivity with thyrotoxicosis with non-suppressed TSH.

6) Acidophil stem cell adenomata are tumors comprising of immature GH and PRL secreting tumor cells of a single precursor. The histology shows chromophobic or slightly acidophilic cells, with abundant granular cytoplasm of oncocytic distribution (44). Patients present with hyperprolactinemia which is disproportionate to the size of the tumor. They are frequently invasive and less responsive to dopamine agonist therapy.

7) Poorly differentiated Pit-1 lineage tumors comprise of tumor cells with strong expression of Pit-1 and variable expression of estrogen and GATA3. They are polyglonal and spindle shaped poorly differentiated cells which stain variably for GH, PRL, TSH, and alpha subunit. They are usually macroadenomas, with invasion of surrounding structures and high risk of recurrence (46).

8) Pituitary carcinomas are very rare and form less than 1% of cases. They are difficult to distinguish clinically, and diagnosis is confirmed with evidence of

distant metastasis and high ki67 index (e.g., >10%) on histology. These tumors frequently require multi-modal therapy, including chemotherapy, temozolamide and radiation (44).

9) Pituitary hyperplasia is suspected radiologically when there is a uniformly enlarged pituitary gland with no distinct focus of gadolinium enhancement. Hyperplasia is confirmed on histology when the pathology shows expanded pituitary acini containing all of the adenohypophysial cell types, but with increased numbers of somatotrophs and/or mammosomatotrophs (46). The histological diagnosis should prompt the clinician to explore for a GHRH secreting tumor elsewhere or consider investigations for specific genetic conditions associated with acromegaly (highlighted in table 4) such as MEN1, Carney Complex, and McCune Albright Syndrome (49).

Non-pituitary sources of disease include GHRH or GH secreting central and peripheral tumors. Hypothalamic tumors such as hamartomas, choristomas, gliomas, and gangliocytomas producing GHRH result in pituitary hyperplasia and very often the diagnosis remains elusive until patient has undergone pituitary surgery. Carcinoid tumors secreting GHRH are recognized as rare peripheral cause of acromegaly and usually are bronchial in origin (50). An ectopic location of pituitary adenomas has been reported in the tract of dorsal migration of the adenohypophysial cells. While a significant number of peripheral tissues have been found to secrete GH (51), reports of GH secreting peripheral tumors include lung, pancreatic and adrenal tumors.

Table 2. Pathology Associated with Acromegaly (44,52-54)	
Pituitary adenoma	Densely granulated somatotroph adenoma Sparsely granulated somatotroph adenoma Mixed cell somatotroph and lactrotroph adenoma Mammosomatrotroph (monohormonal Pit-1 lineage) adenoma Acidophil stem cell adenoma Plurihormonal adenoma Poorly differentiated Pit-1lineage tumor Pituitary hyperplasia Pituitary carcinoma Rare: ectopic pituitary adenomas identified in sphenoid sinus or parapharyngeal tissue
Ectopic hormone secretion	Central: Hypothalamic tumors Ganglioneuroma

	Peripheral: Bronchial carcinoid, small cell lung cancer, adrenal tumor, pancreatic neuroendocrine tumor
Exogenous GH replacement or abuse	
Pseudoacromegaly	Pachydermoperiostosis IGF signaling pathway diseases Severe insulin resistance

CLINICAL FEATURES OF ACROMEGALY

The clinical manifestations of acromegaly evolve gradually over a long time and as a consequence there is a lag time of about 5-10 years, from symptom onset to diagnosis (55,56). In the recent decades, there seems to be some early recognition of the condition, particular in individuals investigated for pituitary 'incidentaloma', for example with hypogonadism as a presenting feature (57). One third of the cases, have co-existent symptoms of hyperprolactinemia, which aids in early diagnosis (58).

Tumor Related

Growth hormone secreting pituitary adenomas are frequently (more than 70%) large tumors (macroadenoma, ≥ 10 mm in diameter) which may present with local mass effects such as headache (often severe and out of proportion to the size of the pituitary tumor), hydrocephalus, visual field defects, ophthalmoplegia, or other cranial nerve palsies (59). As the lesion increases in size deficiencies of other anterior pituitary hormones may also occur. Microadenomas (< 10 mm in diameter) are conventionally thought to be less common, but tend to represent one third of the cases (60,61). However patients presenting with pituitary tumors, without clear features of acromegaly may have elevated IGF-1, and GH positive immunohistochemistry on the resected tumor specimen (62) and such silent growth hormone tumors seem to be more common in females with a higher risk of recurrence (63). The term micromegaly is used to describe such clinical presentations (64,65). Recognition of such presentations should prompt the endocrine specialist to consider GH secreting tumors in all presentations, but especially in the younger patient with pituitary tumor.

Hypopituitarism has been found to occur in about 40% cases with variable frequency of hypogonadism, adrenal insufficiency, and secondary hypothyroidism (66,67). Hypogonadism, presenting as decreased libido, infertility or oligo/amenorrhea is a common finding at presentation; it may be due to both gonadotrophin deficiency as well as hyperprolactinemia, either from coexistent excessive secretion of prolactin or from stalk compression. Hypogonadism has been reported even in patients with microadenomas with normal prolactin, thereby suggesting an independent effect of GH hypersecretion (68). Menstrual irregularities, PCOS, subfertility and erectile dysfunction can occur as a consequence of GH excess (69,70). The occurrence of diabetes insipidus in relation to a pituitary adenoma is extremely rare and should raise the possibility of an invasive pathology (71,72).

Soft Tissue and Skeletal Changes

The most characteristic feature and one that usually precipitates the diagnosis is a change in appearance as a consequence of soft tissue and bony changes.

The common changes include coarsening of the facial features, broadening of the nose, thickening of the lips, macroglossia, and prominence of the supraorbital ridges. There is enlargement of the hands resulting in their characteristic 'spade-like' appearance and soft dough-like consistency of the palms. Ring size increases; a sensitive objective assessment of disease activity and response to treatment. Similar changes occur in the feet which become wider with increase in shoe size. Elongation of the jaw results in prognathism which contributes to dental malocclusion, interdental separation, and temporomandibular joint pain (73,74).

Greasiness of the skin is a frequent finding with excessive sweating, one of the most sensitive signs of growth hormone excess. Skin tags are a frequent finding, likely related to epithelial cell hyperproliferation in response to IGF-1 (74). Additional dermatological manifestations include hypertrichosis, psoriasis, acanthosis nigricans, and cutis verticis gyrata, with the latter two seen more commonly in severe cases (75). Skin changes are a result of deposition of glycosaminoglycans in the subcutaneous tissue, along with increased proliferation of dermal fibroblasts as a consequence of GH and IGF-1 action (74). These changes tend to reverse after treatment, at least partially if not completely. The lean body mass is higher in individuals with acromegaly, while there is increase in adipose tissue post therapeutic intervention (76). This reversal of body composition tends to stabilize by three months of the surgery (77). In addition to the negative impact on body fat, reversal of GH excess has been found to increase intrahepatic lipid accumulation (78).

Generalized organomegaly is not well reported with acromegaly, in contrast some earlier assumptions of the disease process but enlargement of thyroid, prostate, salivary glands, heart, liver and spleen has been recognized (79). Macroglossia, increased thickness of laryngeal structures and vocal cord enlargement increases the risk of anesthesia and makes intubation difficult (80). Ultrasound evidence suggests the presence of increased organ stiffness and commonly reported features include renal cysts, thyroid nodules, multinodular goiter, gallbladder polyps, and polycystic ovaries (79). Mucosal edema and hypertrophy of vocal cord can result in voice changes, but true existence of voice abnormalities is debated (81,82). Patient reported questionnaire and evaluation of voice parameters seem to demonstrate presence of micro perturbations, lower amplitude and poor quality of voice in individuals with active disease (82,83).

The skeletal manifestations of acromegaly result from multiple factors which include direct effect of GH, IGF-1, altered calcium phosphate metabolism, hypogonadism, diabetes, and over replacement of steroids (84,85). Acromegaly results in increased bone resorption and altered bone formation according to various cross-sectional studies, but the effect of GH, IGF-1 on bone health is complex. GH mediates its effect on bone through systemic IGF-1 with action on cortical bone, whereas bone IGF-1 seems to be responsible for cancellous bone health. There is emerging evidence of correlation of sclerostin levels with acromegaly related bone disease (86). The high prevalence of vertebral fractures (VF) in active acromegaly has been known for a long time with some studies reporting incidence as high as 60%, and dependent on the duration of disease and gender (males>females) (84,87). In a French study, authors have suggested that the skeletal abnormalities are more likely vertebral deformities than true fractures (88). Screening for VF is recommended in all patients with active acromegaly as it has a significant impact on quality of life, morbidity, and development of cardiac and pulmonary complications (85,89). Standard DXA seems to be less reliable in predicting

the risk and Volumetric DXA with quantitative assessment of the trabecular bone density seems to provide more reliable information of acromegaly related bone disease (87,90). Unfortunately it is difficult to undertake this test routinely and therefore alternative use of newer methods such as non-invasive 3D-SHAPER and TBS Trabecular bone score assessments may be considered (90). While vertebral changes are most discussed, consequences of acromegaly include development degenerative diseases in all weight bearing and non- weight bearing joints, predominantly shoulder, hip and knees (84,91). The prevalence of radiographic evidence of at least one joint involvement has been found to be as high as 99% (92). Patients with active disease seem to be have higher prevalence of reduced cortical density at hip compared to patients with non-functioning pituitary adenomas (93). Degenerative joint changes in early acromegaly related arthropathy appear different from usual osteoarthritis, and are noted as widened joint spaces contributed by cartilage hypertrophy and marked osteophytosis, in contrast to standard OA (94). Acromegaly related arthropathy is associated with a significant impact on quality of life and tends to progress despite improvement in disease status (89). Routine use of anti-resorptive therapy is currently not well established, but considering the wider implications of the disease on bone health in active disease, it seems reasonable to consider offering bone protective therapy in patients with early evidence of bone disease (90).

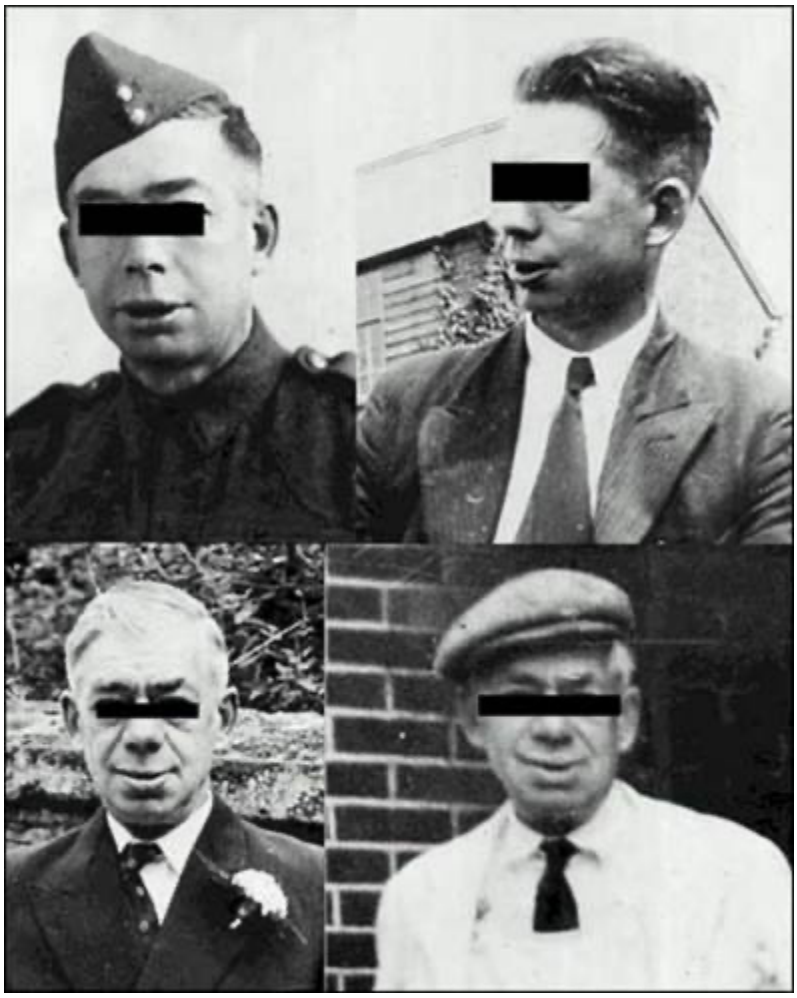

Figure 5. The typical facial appearance of acromegaly. Evolution of the appearances over 2 decades

Sleep Disordered Breathing

Sleep apnea syndrome (SAS) is a well-recognized manifestation of GH excess and seems to have been variably reported with incidences of 40-80% and about 11.7-20 times higher prevalence than in general population (55,95). Evaluation of the bony changes in the facial skeleton showed significant differences in patients with acromegaly and SAS, compared to patients without SAS. But soft tissue enlargement of upper airways contribute more to the narrowing of the pharyngeal airway space than the craniofacial skeleton changes (95). CT and MRI assessment of upper airways demonstrate pharyngeal hypertrophy and upper airway stenosis correlating with the severity of obstructive sleep apnea (96). Patients with SAS have been found to have more features consistent with metabolic syndrome, such as hypertension and DM compared to patients without SAS (97). Improvement in SAS noted after intervention seems to correlate with positive changes in tongue volume and pharyngeal soft tissue (98). Unfortunately, complete reversal of SAS does not occur and persistent SAS is seen in about 40% of treated cases. It is likely due to effect of additional factors on SAS such as age, male gender, smoking, and obesity (84). A direct inhibitory effect of GH on central respiratory center can result in

a non-obstructive central pattern of sleep apnea (99). This phenomenon seems to be much less prevalent than obstructive disease, while a mixed pattern has also been reported (100).

Muscular Changes

Musculoskeletal pain is typically progressively evident during the disease course, with close to 90% patients reporting pain as a dominant symptom (101). Irrespective of the severity of the acromegaly, pain contributes significantly to reduced quality of life (101). Studies demonstrate that GH excess leads to hypertrophy of the type 1 muscle fibers with variable findings for type 2 fibers (102-104). The predominant abnormality of type 1 muscle fibers strength seems to be responsible for evident muscle weakness noted in high velocity activities (105). While earlier studies consistently reported muscle weakness in acromegaly, a recent study used quantitative measures suggest patients with active acromegaly may have higher proximal muscle strength, but reduced hand grip which normalizes after treatment (103). It is postulated that the difference in findings could be related to pain interfering with true assessment of muscle function (103). Ultrasound evidence showed increased tendon thickness, enthesisitis, soft tissue enlargement but reduced muscle volume in some lower limb muscles in a cohort of thirty nine patients (106). There is emerging evidence that acromegaly has a complex effect on muscle strength and volume (107). Differential interactions of GH, Muscle Ring Factor -1 (MuRF-1), and myostatin seem to be responsible for chronic effects of GH excess on skeletal muscles (108).

Neurological Abnormalities

Carpal tunnel syndrome is present in approximately 60% of patients at diagnosis but about 80% will have electrophysiological evidence of median nerve neuropathy (109). The pathophysiology is due to swelling of the median nerve itself within the carpal tunnel rather than extrinsic compression from increased volume of the carpal tunnel contents (110). This is well evident on MRI and Ultrasound studies of the median nerve, and seems to correlate with the abnormal nerve conduction studies (110-112). Similar peripheral nerve abnormalities and abnormal nerve conduction studies have been noted in other peripheral nerves including peroneal, tibial, ulnar, sural nerves (112,113) and polyneuropathy is more common in uncontrolled disease (114). Unfortunately it seems some of the changes are not completely reversible, despite normalization of disease markers (115). Patients with active acromegaly have altered cardiac autonomic function, which contributes to the cardiovascular risk (116,117). This seems to respond to active intervention (118). There is not much evidence of central nervous involvement related to the disease (113), with some report of delayed brainstem auditory evoked potentials (119). Restless leg syndrome has been reported to be present in 20% of cases and negatively impacts the quality of life (120).

Cardiac Complications

Cardiovascular diseases continue to remain one of the most common causes of morbidity in patients with acromegaly and account for 60% of the mortality with this condition (121,122). The range of abnormalities detected at the time of diagnosis have been reported to be hypertension, cardiac hypertrophy, arrhythmias, coronary artery disease, and systolic heart failure, in the order of prevalence (123,124). Hypertension presents with higher diastolic readings than systolic BP measurements (125). Based on ambulatory BP monitoring readings, it seems that the prevalence of hypertension is about 22% at diagnosis, much lower than earlier studies with single office measurements (126). Anti-natriuretic effect of GH is a direct consequence of GH action on the epithelial sodium

channel ENaC in cortical collecting ducts of the kidney (127). This sodium retention leads to volume expansion and further compounded by GH effects on cardiac output, impaired endothelial function, increased peripheral resistance and co-existent sleep apnea are some factors that lead to development of hypertension (128).

Acromegaly related cardiomyopathy is a consequence of GH and IGF-1 effect on cardiac myocytes, regulation of cardiac muscle specific gene transcription, and increased fibrosis (129). It has been described to undergo three stages of disease progression (130). In the first phase biventricular concentric hypertrophy is described related to muscle hypertrophy and increased contractility and leads to a hyperkinetic syndrome. As the disease progresses, patients tend to develop diastolic dysfunction with more prominent ventricular hypertrophy. Patients report reduced exercise tolerance and it is common for disease to be diagnosed in this phase. If untreated patients may progress to develop overt diastolic and systolic dysfunction presenting as congestive heart failure in about 3-4% cases and is a poor prognostic marker (123). The presence of left ventricular hypertrophy correlates with disease duration and various studies report prevalence from 11-78% (84,131). Cardiac Magnetic Resonance (CMR) studies have demonstrated variable prevalence of left ventricular hypertrophy compared to echocardiographic studies (132,133). CMR is more reliable in identifying myocardial fibrosis and RV systolic dysfunction then echocardiography (133). Despite the presence of cardiovascular abnormalities associated with ischemic heart disease, recent studies report no increase in prevalence of Ischemic heart disease, in comparison to normal population (55,134).

Cardiac arrhythmias have been reported to occur in about 7-40% cases of acromegaly. A wide range of rhythm disturbances described in patients with acromegaly include paroxysmal atrial tachycardia, supraventricular tachycardia, sick sinus syndrome, ventricular ectopic, and ventricular tachycardia (130). A typical acromegaly related left ventricular rhythm disturbance, results from abnormal and dyssynchronous loss of peak contraction of corresponding cardiac segments (135). Mitral and aortic regurgitation have been commonly associated with acromegaly and seem to correlate with the duration of the disease (136). Unlike cardiomyopathy and arrhythmias which improve or even completely reverse with disease control, valvular disease is irreversible and only tends to stabilize with intervention (130).

Metabolic Complications

Growth hormone is a potent insulin antagonist and acromegaly results in abnormal glucose tolerance in many patients with frank diabetes mellitus in up to 50% cases at diagnosis. Lipid abnormalities, in particular elevation of serum triglycerides, reduced HDL levels, increased small dense LDL particles, and increased lipoprotein-a (Lp(a)) may be an accompanying feature of insulin resistance and is noted in one third of the cases (137,138). Chronic GH excess results development of insulin resistance by several mechanisms. Reduced glucose uptake occurs by increased levels of free fatty acids and reduced expression of GLUT1 and GLUT 4 receptors (139). GH also results in development of a pro inflammatory state in the adipose tissues with alterations of the genes coding visfatin and IL6 (140). The degree of insulin resistance correlates with IGF-1 levels (141) and improves with management of the disease. Development of IGF receptor resistance beyond a threshold for IGF-1 has been reported in states of chronic GH excess leading to further insulin resistance (142). Visfatin and irisin levels have been suggested to correlate with metabolic abnormalities and cardiovascular risk factors (143,144). When choosing

treatment, octreotide, and lanreotide have less impact on the glycemic variations, while pasireotide can aggravate hyperglycemia. Pegvisomant has a favorable on the metabolic parameters (145).

Table 3. Clinical Manifestations and Complications Reported with Acromegaly			
Tumor related local effects	Headache Visual field defects Cranial nerve abnormalities Hydrocephalus Temporal lobe epilepsy Hyperprolactinemia Hypopituitarism		
Systemic effects			
Skin changes	Hyperhidrosis Oily skin Skin tags Hypertrichosis Acanthosis Cutis verticis gyrata	**Cardiac**	HT Cardiomyopathy Valvular heart disease Arrhythmia Heart failure
Soft tissues changes	Acral enlargement Change in voice quality Visceromegaly (thyroid, prostate, liver, salivary glands)	**Neurological**	Peripheral nerve abnormalities Autonomic dysregulation Lumbar canal stenosis Narcolepsy Restless leg syndrome
Orofacial changes	Prognathism Frontal prominence Dental malocclusion TMJ pain Gingival enlargement Macroglossia	**Pulmonary**	Sleep apnea Restrictive lung disease Subclinical hypoxemia
Musculoskeletal	Vertebral deformities Kyphosis Arthralgia and arthritis Myopathy Degenerative arthropathy	**Neoplastic**	Colon polyps Thyroid cancer Breast cancer

	Calcific discopathy Hypermobility		
Endocrine and Metabolic	Hypogonadism PCOS DM, insulin resistance Hypertriglyceridemia Erectile dysfunction	**Renal**	Increased GFR Hypercalciuria Glomerulosclerosis
Hematological	Increased thrombosis risk	**Psychiatric**	Depression
Ocular	Increased risk of diabetic retinopathy Extraocular myopathy Glaucoma Epiphora		

Thyroid Abnormalities

Patients with GH excess have been demonstrated to have a rise in TSH and T3 levels with no significant relation with the FT4 levels (146). There is a direct correlation of IGF-1, GH levels with thyroid volume. Multinodular goiter is one of the most common thyroid abnormality in patients with acromegaly with frequencies of 69.5 to 79.1% being reported by some authors (147). Patients in remission after surgery have been shown to have change in the consistency of the thyroid nodules, reduced vascularity, and volume (148). Over the course of follow up of patients with active acromegaly, thyroid nodule enlargement seemed to correlate with IGF-1 levels with increased prevalence of differentiated thyroid cancer (papillary thyroid carcinoma) in this subgroup (149,150). Despite the increasing understanding, routine screening for thyroid nodules is not yet recommended but assessment should certainly be considered in patients with a palpable nodule (151).

Neoplasia

The true risk of cancer continues to remain debated with concerns of heterogeneity in the study population, selection biases, variable screening strategies, and limitations of using standardized incidence ratios as the reporting indices (84). In the recent years, some large cohort population studies suggest higher cancer risk than general population. Acromegaly has been associated increased risk of cancers, particularly colon, kidney, and thyroid cancer in a large Italian survey (152). A similarly large Danish cohort has reported increased incidence of colon, thyroid, breast, gastric, and urinary bladder cancers (153).

Animal models and *in vitro* studies suggest anti-apoptotic and tissue proliferative role of GH and IGF-1. IGF-1 deficiency has been found to result in protection from tumor development. GH signaling pathways and autocrine GH action contribute to tumorigenesis and in colonic tissue this mechanism results in reduced action of tumor suppressor proteins

(84,154). Colon cancer has been studied in detail in patients with acromegaly. Patients have a higher prevalence of adenomatous and non-adenomatous polyps than general population (155) with reported trend varying between 6-30% (156). Colonic pathology is related to disease activity with patients with elevated serum growth hormone and IGF-1 levels being particularly prone to developing colonic adenomas (157). Although the exact pathogenesis of these tumors remains uncertain it is likely to involve altered homeostasis of cell numbers within the colonic epithelial crypts; increased proliferation and decreased apoptosis within the crypts of patients with acromegaly have both been documented (158). Colorectal neoplasia in acromegaly has different characteristics compared to the general population, in that the adenomas are more likely to be located in the right side of the colon, tend to be bigger and are more often multiple as well as demonstrating increased dysplasia (159).

It is now generally accepted that patients with acromegaly should be regarded as a high-risk group for colorectal cancer and regular colonoscopy screening should be offered to all patients. Current evidence suggests that this should begin at the age of 40 years with the subsequent interval depending both on disease activity and the findings at the original colonoscopy screening (160). In the presence of a polyp (hyperplastic or adenoma) or elevated serum IGF-1 levels screening should be repeated after five years, whilst a normal colonoscopy screening, or serum IGF-1 level within the normal range suggests screening every 10 years may be appropriate. As approximately 30% of lesions occur at the cecum or in the ascending colon, total full-length colonoscopy is required. This should be performed by an experienced colonoscopist, as the cecum is reached in only about 70% of patients in inexperienced hands. Due to their slow bowel transit time and elongated colon, patients with acromegaly require rigorous bowel preparation, often twice that necessary for the patient without acromegaly. Failure to visualize the cecum necessities a repeat colonoscopy or failing this examination using CT virtual colonoscopy (156).

Lung Complications

Pulmonary complications are common in acromegaly. Total lung volume and residual volume are increased, along with narrowing of both large upper airways and more commonly small airways (161,162). In a large study Storrmann *et al* reported higher prevalence of small airway obstruction in females. They also highlighted presence of subclinical hypoxemia in patients with acromegaly. The findings did not correlate with levels of IGF-1 of duration of disease (163). Tracheal structural abnormalities have been found to be responsible for large airway disease (164).

Ocular and Auditory Complications

A wide variety of ocular complications have been reported in patients with acromegaly, apart from visual field defects. The prevalence of proliferative diabetic retinopathy has been variably reported to be higher in patients with acromegaly (165) in some studies, while others suggest it is likely that there is increased retinal vessel branching, and noted no difference in retinopathy rates (166). Extraocular muscle enlargement has been reported by few authors and rarely has resulted in presentation of diplopia (167-169). Studies have highlighted increased intraocular pressure, increased corneal thickness and increased retinal thickness in patients with acromegaly, with rare reports of epiphora (170-172). The association of acromegaly with hearing disturbances has not been well reported. There have suggestions of abnormal bony changes, changes in middle ear pressures and internal acoustic meatus contributing to variable hearing abnormalities (173,174). But findings have not

been widely validated and association of acromegaly with hearing loss is not well established (175).

Other Systemic Complications

Hematological abnormalities are not common with acromegaly. Recent evidence suggests patients with active acromegaly may be at a higher thrombotic risk and this could contribute to cardiovascular risk (176,177). Higher levels of fibrinogen, factor VIII and thrombin tend to result in hypercoagulable state in active untreated disease (178). Rare case reports of polycythemia, myeloma, and Waldenstrom's macroglobulinemia have been reported (179,180).

GH and IGF-1 receptors have been found in kidneys and suggest local autocrine and endocrine activity of GH at the level of nephrons (51). The effect of GH excess on kidneys has not been well described. Chronic GH exposure leads to renal hypertrophy and structural changes to include glomerulosclerosis (181) . Patients with acromegaly have been reported to have increased GFR, reduced renal excretion of sodium, potassium, hypercalciuria, hyperphosphaturia, greater prevalence of microalbuminuria and micro-nephrolithiasis, irrespective of comorbidities (182-185).

Morbidity and Mortality in Acromegaly

It is established that uncontrolled acromegaly results in a considerable increase in morbidity with an overall mortality at least two-fold that of the general population (186). In early epidemiological reviews more than 50% of patients had died by the age of 60 years, usually as a result of diabetes, cardiovascular, respiratory or cerebrovascular disease (187). With improved treatment of both the underlying disease and these complications, patients are now surviving longer although may then be susceptible to other complications such as malignancy (188). The determinants of mortality included older age and IGF-1 levels at diagnosis, treatment modality, and malignancy (121). Prolonged diagnostic delay has been found to positively correlate with morbidity and mortality (189). Longitudinal population cohorts indicate a negative impact of female gender on the presence of comorbidities and mortality (37,190).

DIAGNOSIS OF ACROMEGALY

The diagnosis is made using a combination of clinical examination and biochemical assessment. Serum growth hormone concentrations are typically elevated, and although pulsatility may be reduced, levels may fluctuate widely in acromegaly. Due to the pulsatile nature of growth hormone secretion, a single growth hormone measurement is of little use in either monitoring or confirming the diagnosis of acromegaly. GH levels are affected by age, gender, and comorbid disease states and these factors need to be taken into account when interpreting results. These factors have been outlined in table 1. Due to variations between assays, it is recommended that a standardized and similar performing assay is used for monitoring of the disease activity. Most modern assays detect the highly prevalent GH 22kDa isoform and the most common preparation used to calibrate GH assays is the latest recombinant IRP 98/574 (197). It is useful to be aware of the interferences of the local assay with biotin and Pegvisomant. Various tests used in screening, diagnosis, and management of acromegaly are discussed below.

Biochemical Tests at Diagnosis

a) IGF-1 levels: A single serum IGF-1 level has been advocated as being a useful first line test for the diagnosis of acromegaly as it is elevated in the majority of subjects. It is an indirect assessment of

growth hormone secretion with approximately 25% of patients having a discrepancy between the mean value of a growth hormone day curve and an IGF-1 level. IGF-1 secretion is subject to several influences including liver and renal dysfunction, nutrition, diabetes mellitus, physiological factors such as age, gender, and the presence of a statistical correlation between its levels and those of growth hormone should not be used as proof that they are interchangeable (198). However, despite these limitations, from a practical point of view, an elevated serum IGF-1 measurement may be useful as confirmatory evidence, assuming that age and sex matched normal ranges are used, and for monitoring treatment (199). Standardized IGF-1 (IS 02/254) is recommended for manufacturers of IGF-1 assays (52,200).

b) GH day curve: The assessment of growth hormone hypersecretion requires the mean value of serial samples taken throughout the day (e.g., 5 samples over a 12-hour period). The samples should be taken through an indwelling venous cannula to avoid the stress effects of repeated venipuncture. In normal subjects, the majority of values throughout the day are undetectable, but in acromegaly typically each value is measurable, often with a fixed rate of secretion (201).
c) Oral glucose tolerance test: Failure of normal suppression of serum growth hormone following administration of oral glucose remains the 'gold-standard' biochemical test (202). 75 g of oral glucose is given at 9 am to the fasting patient and plasma glucose and serum growth hormone levels are measured at baseline, 30, 60, 90, 120 (and 150) minutes thereafter. In normal subjects, growth hormone levels suppress to undetectable values (typically <0.1 ng/ml) when ultrasensitive assays are used, whilst in acromegaly serum growth hormone remains detectable, and in approximately 30% of cases there is a paradoxical increase (199). In conventional practice failure to suppress serum growth hormone to a level < 0.4 ng/ml following ingestion of glucose supports the diagnosis of acromegaly. The use of this test also detects those patients with impaired glucose tolerance or diabetes mellitus other than individuals with poor diabetes control (203). False-positive results can be seen in conditions where GH levels are elevated such as stress, type 1 diabetes mellitus, cirrhosis, chronic renal failure, during adolescence, and by drug use (L -dopa, heroin, estrogen 201,204).
d) TRH test: In cases of remaining doubt about the diagnosis of acromegaly, a TRH test can be used (200 mg of thyrotrophin releasing hormone given intravenously with serum measurement at 0, 20 and 60 minutes). In normal subjects TRH inhibits growth hormone secretion with a fall in serum concentration, whilst approximately 60% of patients with acromegaly demonstrate a paradoxical rise in growth hormone levels (205). In mild disease with relatively low GH levels, TRH stimulation has been suggested to confirm early diagnosis (206).
e) Others: IGFBP3 levels correlate with mean 24 hour GH levels and IGF-1 levels, but due to the wide overlap with normal and diseased individuals, is a poor parameter for measuring disease activity (207). In the rare patient in whom a non-pituitary etiology is suspected, measurement of serum GHRH may be performed, typically with very elevated levels occurring in ectopic GHRH syndromes such as neuroendocrine tumors. Basal serum prolactin should also be measured as prolactin may be co-secreted with growth hormone in up to a third of patients with acromegaly, which often indicates therapeutic responsiveness to the use of dopamine agonists. In those with hyperprolactinemia the presence of macroprolactin should be excluded (208).

In patients with atypical clinical symptoms such as GI symptoms, hypoglycemia, renal stones, clinicians should consider exploring possibility of coexisting genetic tumors or extra pituitary source of GH abnormality, such as carcinoid tumors.

Biochemical Tests Used to Define Disease Activity to Guide Outcomes

a) Octreotide test: Acute challenge with octreotide 100mcg sc dose can help predict response to SSA when hourly values are measured over 6 hours (209,210). Not all clinicians perform this test and many treat with a long-acting SSA independent of a challenge test (211).
b) IGF-1 levels: IGF-1 levels can take over three months to normalize in the post-operative period and until then cannot be reliably used to guide management. In longer term the aim of treatment is to keep levels within the normal ranges (52). In patients with Pegvisomant therapy, IGF-1 is the variable that guides response to treatment (212).
c) Random GH levels: Random levels can be used to define surgical cure and values as early as day 1 can be undertaken if no pre-operative GH suppressing therapy was used, bearing in mind the effect of post-operative stress. A serum GH <0.4 µg/L favors disease remission and a level <1 µg/L indicates good control and normalization of the mortality risk (151).
d) OGTT: OGTT can be undertaken to evaluate post-operative outcome if random GH values >1µg/L. A nadir GH cut off of <1µg/L is associated with better long-term outcomes and would be considered as good control. Endocrine Society guidelines suggest GH nadir of less than 0.4mcg/ L could be used to define disease remission (151) It has been suggested that post-operative OGTT at 3 months is more appropriate than an early test in 3 weeks and is likely to help avoid false positives (213).
e) Other tests: The GH day curve test is rarely required for long term monitoring. The mean GH value of <2.5µg/L correlates better with disease control but it is unreliable in patients who have undergone radiotherapy due to alterations of GH pulsatility pattern (214). Post-operative TRH test has been suggested to predict long term disease remission, but again is rarely required (211).

Radiological Assessment

Historically the diagnosis of pituitary tumors causing acromegaly was made on the basis of changes to skull bones with demonstration of enlargement of the fossa. With advances in radiology, pituitary MRI with gadolinium enhancement is considered the optimal modality and should be undertaken to determine size of the tumor, define tumor characteristics and assess threat to surrounding structures. At diagnosis, more than 70% of patients with acromegaly have a macroadenoma (≥10 mm in diameter) which often extends laterally to the cavernous sinus or superiorly to the supra-sellar region. Younger patients often present with more aggressive disease, with more invasive tumors which often extend inferiorly. On T1 weighted images the pituitary adenoma tends to be of lower signal intensity than the surrounding normal gland and enhances less briskly than the normal gland after injection with intravenous gadolinium contrast. Tumors >15mm, supra-sellar extension, and cavernous sinus extension of the tumor has been associated with lower rate of surgical cure (215). Radiologic grading of pituitary tumors using KNOSP classification is widely used in predict disease invasiveness and tumor response. Some studies report cavernous sinus invasion as the strongest factor predicting surgical outcome (216,217).

In the last decade there is substantial evidence to suggest that hypointensity on T2 weighted MRI is suggestive of good response to somatostatin

analogue SSA therapy (218,219). Based on histological characteristics, hypointense T2 weighted tumors correlate with a densely granulated histological subtype and tend to be less aggressive in behavior (220,221). In the post-operative phase, MRI should be considered approximately 3 months after surgery to allow post-operative changes to settle. Subsequent surveillance scans should be guided by biochemical markers as they guide correlation with tumor recurrence. Unless concerned, unenhanced imaging may be preferred for patients expected to require long term surveillance to reduce exposure to gadolinium (222). There are limitations of MRI when it comes to evaluation of persistent or residual disease. In these cases, use of C11 Methionine Positron Emission technology MET-PET with co-registration of volumetric MRI has been found to provide valuable information to guide repeat surgery or targeted gamma knife surgery (223,224). In patients with previously reported empty sella or residual parasellar tissue where surgeons would struggle to consider intervention, the information provided by MET-PET has been found to be useful with positive outcomes. Other tracers that have been studied and reported to guide management include N13 ammonia PET, DOTATATE PET (225,226).

In rare cases of ectopic GHRH secretion, a pituitary MRI can sometimes help differentiate between a pituitary adenoma and hyperplastic pituitary tissue (53). The use of somatostatin receptor scintigraphy (particularly Gallium Dotatate) is useful to correlate the source of ectopic hormone production to an unexpected finding on a conventional body imaging.

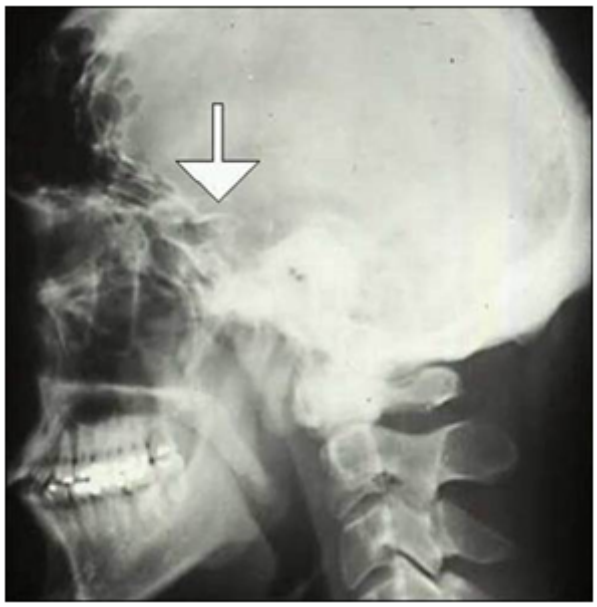

Figure 6. Enlargement of pituitary fossae on lateral skull x-ray.

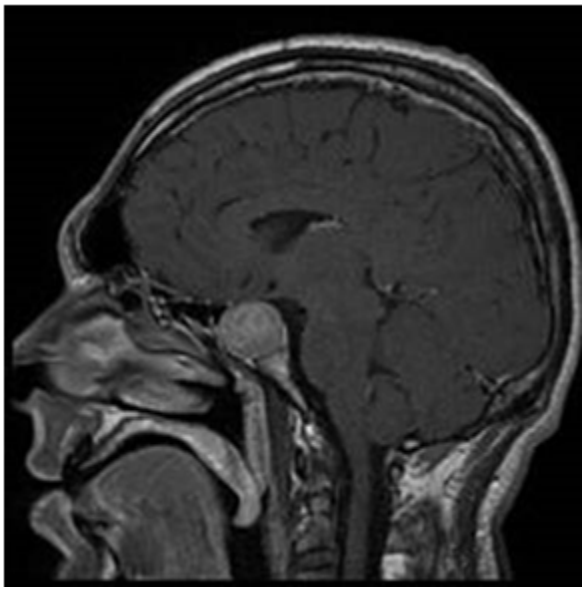

Figure 7. MRI demonstrating a somatotroph macroadenoma of the pituitary gland.

Neuro-Ophthalmological Testing

Neuro-ophthalmological assessment should be undertaken in all patients with macroadenomas, especially where tumor is visibly contacting the optic chiasm. At the initial consultation visual acuity should be assessed with the use of Snellen charts and fundoscopy performed to exclude optic atrophy, retinal vein engorgement, or papilledema from pressure on the visual pathways. Visual fields may be assessed by confrontation using a red pin. Patients with any clinical symptoms or evidence of optic chiasmal compression from imaging studies require formal assessment of visual fields with formal perimetry or visual evoked responses, stimulating each half field in turn. Optical coherence tomography should be used to assess retinal nerve fiber layer as a marker of chiasmal damage.

Although permanent loss of vision and/or visual field defects usually result from long standing optic chiasmal compression, the shorter the time of compression the easier and more complete is the reversal of any visual field deficit. Surgical decompression may result in rapid improvement in visual fields within hours or days, although the presence of optic atrophy reduces the likelihood of this occurring. Because onset is often insidious, patients may be unaware of any alteration in their vision, although once documented its presence requires them to inform the vehicle licensing authority as driving ability may be impaired. An exception to this usual gradual deterioration is pituitary hemorrhage when visual loss may be sudden with a loss of central vision and development of bitemporal field defects and possible ophthalmoplegia often accompanied by changes in higher mental function.

Assessment of Pituitary Function

Assessment of the integrity of the other pituitary hormones needs to be performed by a combination of the appropriate basal and dynamic tests. These are mentioned in other Endotext chapters. Prior to and following pituitary surgery, both residual pituitary function and the growth hormone secretory status

should be evaluated. Basal endocrine testing for early morning cortisol, thyroxine, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, testosterone/estrogen, prolactin, and serum & urinary osmolality, should be performed. Where there is doubt, a provocative test should be made of ACTH reserve.

Histological Assessment

Histology provides valuable information to determine tumor characteristics. Keratin staining is essential to distinguish between densely granulated and sparsely granulated tumors. Further use of immunohistochemical IHC staining modalities is increasing found to help understand tumor behavior. Details of various histological subtypes are highlighted in table 2. IHC staining for different transcription factors Pit-1, SF-1, or Tpit along with hormonal staining is used to understand the tissue of origin. Ki67 labelling index is widely used to determine proliferation rates, though it does not always predict tumor behavior. Evaluation of somatostatin receptor SSTR expression is used to guide response to SSA therapy. Additional immunostaining modalities used in recognition of familial tumors are menin, p27, AIP and SDH expression (227).

Genetic Testing

Over the last decade, we have seen an increasing understanding of the role of specific genes and mechanisms responsible for development of pituitary tumors. The genetic disorders associated with acromegaly are summarized in table 4.

The most exciting developments relate to recognition that aryl hydrocarbon receptor interacting protein (AIP) mutations can account for familial pituitary adenomas. Such cases may present in younger patients with more aggressive tumors, including somatotroph adenomas. Testing for AIP mutations (FIPA) should be considered for any patient with a family history of pituitary tumor, especially GH and/or prolactin secreting tumors (228). This is particularly so, in those presenting at younger age (<30 years) with aggressive pituitary adenoma. There is some evidence that the response to somatostatin analogue treatment is reduced in acromegaly associated with AIP mutation (229). Data from the German Pituitary Registry suggest that even in younger patients with acromegaly that the prevalence of AIP mutations is low (<5%) (230). X-LAG X-linked acrogigantism mutation is reported to lead to about 80% cases of pre-pubertal acromegaly (231). GH secreting adenoma is reported to occur in approximately 6% of patients with MEN1 (232). In practice patients presenting at a young age with acromegaly, co-existent hypercalcemia, and certainly those with a family history of pituitary tumors should be considered for MEN1 and AIP gene sequencing, respectively.

Table 4. Genetic Disorders Associated with Acromegaly (233,234)			
Genetic condition	**Gene implicated**	**Inheritance**	**Clinical features**
X-LAG	GPR101	X-linked dominant or sporadic	Mostly females Age <5 years Hyperprolactinemia at diagnosis Can be de-novo and family history may be absent
Familial isolated pituitary adenoma	AIP	Autosomal dominant or sporadic	Younger males Higher GH levels Poor response to SSA therapy
MEN1	MEN1	Autosomal dominant or sporadic	Presence of primary hyperparathyroidism, pancreatic disease along with pituitary adenoma
MEN4	CDKN1B	Autosomal dominant	Presence of pituitary and parathyroid neoplasms with pheochromocytomas, thyroid and other tumors
Carney complex	PRKAR1A	Autosomal dominant	Skin pigmentation, Atrial myxoma, GH or PRL excess, Cushing's due to primary pigmented nodular adrenocortical disease Somatrotroph hyperplasia or multifocal adenoma
Mc Cune Albright	GNAS	Autosomal dominant or sporadic	Average age of diagnosis 23 years Acromegaly seen in 20-30% cases Hyperprolactinemia present at diagnosis Café-au-lait spots Peripheral Precocious puberty Somatrotroph hyperplasia
SDH mutation	SDHx	Autosomal dominant or sporadic	Phaeochromocytoma, paraganglioma and primary hyperparathyroidism present
Neurofibromatosis	NF1	Autosomal dominant	Few case reports of children and adolescents with optic glioma, rarely adenoma reported Mechanisms unclear

Investigations for Complication Screening

Acromegaly is associated with a significant number of co-morbidities most of which are present at time of diagnosis. Once the diagnosis is established it is essential to evaluate for complications such as DM, hypertension, dyslipidemia, osteoporosis, sleep apnea, carpal tunnel syndrome, quality of life, and neoplasia. A suggested screening approach is outlined in table 5.

Table 5. Suggested Strategy for Screening for Complications (52,145,222)

Co-morbidity to evaluate	Screening test	Frequency
Hypertension	Measurement of BP Ambulatory BP monitoring in selected cases	6 monthly
DM	Hba1c, FBG OGTT in selected cases	At diagnosis and 6 monthly if normal
OSA	Clinical evaluation and Epworth scale Polysomnography for confirmation	At diagnosis and annually
Cardiomyopathy	ECG Echocardiography	At diagnosis and 3-5 yearly if normal
Dyslipidemia	Lipid profile	At diagnosis and 6 monthly
Colon polyps	Colonoscopy	At diagnosis in patients >40 years age, and 10 yearly if normal, 3-5 yearly if polyp noted and IGF-1 elevated
Thyroid nodules	Clinical evaluation Thyroid US guided by examination	Annually
Vertebral disease	Bone morphometric study using thoracic x-ray, thoracic and lumbar spine x-ray DEXA	At Diagnosis and yearly, guided by symptoms
Cerebral aneurysm	Cerebral MR angiography	Infrequently
QOL	ACROQOL	Annually

DIFFERENTIAL DIAGNOSIS

Patients with tall stature are frequently suspected to have acromegaly, but absence of soft tissue changes and normal biochemistry should prompt investigations for alternative causes such as Marfans syndrome, homocystinuria, or a familial trait. Pseudoacromegaly or acromegaly mimics are rare disorders with clinical manifestations strongly suggestive of GH excess, but without any biochemical evidence favoring the diagnosis. Pachydermoperiostosis is reported more commonly in males and has an autosomal recessive inheritance. It has been reported secondary to *HPGD* mutations or *SLCO2A1* mutation, which lead to an increase in prostaglandin E2 (235).

MANAGEMENT OF ACROMEGALY

Given the chronic nature and associated significant increased morbidity and mortality of acromegaly, treatment is required for almost all patients. Three modalities of treatment are available: surgery, pituitary irradiation, and medical therapy. All of these have advantages and disadvantages and more than one modality is frequently needed, sometimes all three. The decision as to whether to treat and the modality employed must be based on a number of factors, including patient age and general health, wish for fertility, severity of disease and any associated complications, and the risk/benefit ratio of the proposed treatment modality. The goals of treatment are summarized in Table 6.

Consensus guidelines define goals for treatment of acromegaly. These include achieving an age-matched normal range IGF-1 and GH <0.4 mcg/L (236).

Table 6. Acromegaly- Aims of Treatment
1. Removal of the pituitary tumor and resolution of mass effects
2. Relief of the symptoms and signs of acromegaly
3. Restoration of normal rates of secretion of growth hormone and IGF-1
4. Maintenance of normal anterior pituitary function
5. Prevention of recurrence
6. Assessment and treatment of chronic complications

Whilst the general principles of these aims are accepted by all endocrinologists, there remains considerable controversy as to the degree of growth hormone reduction that should be the target and what level should be regarded as normal. The use of sensitive growth hormone assays has demonstrated that abnormal patterns of growth hormone secretion can remain despite reduction in mean circulating concentrations to extremely low levels, and thus complete restoration to normality is often not achieved. Early epidemiological reviews, particularly those documenting the results of surgery, tended to regard a mean level of less than 5 ng/ml as being satisfactory. It has become clear in recent years that the excess mortality associated with acromegaly can be significantly reduced and indeed restored to that of the normal population by aggressive treatment and reduction of serum growth hormone concentrations to a mean level of less than 1 ng/ml and/or a serum IGF-1 within the aged-matched reference range. Thus, rather than using the word cure, it is may be more appropriate to consider an average growth hormone

concentration of ≤ 1 ng/ml as representing a "safe" level, whereas current consensus is to aim for <0.4 ng/ml (236).

Surgery for Acromegaly

Trans-sphenoidal surgery is the initial treatment of choice for most patients. Originally performed by Harvey Cushing in 1910, the lack of adequate visualization prevented its reintroduction for routine use until the mid-1970's. With modern equipment and in experienced hands, it is a safe procedure with a low complication rate and mortality of less than 0.5%. The most commonly used approach is with the patient in a semi-reclining position via a mid-line nasal route. Using a sub-labial or direct nasal approach, the mucosa is cleaved off the nasal septum providing access to the sphenoid sinus and subsequent removal of the fossa floor. A less satisfactory alternative approach is via the ethmoidal sinus. Pituitary adenomas are usually soft and easily removed with curettes although firmer and larger tumors may require piecemeal removal. Using this technique, even tumors with a significant suprasellar extension can be removed via the trans-sphenoidal route, although massive tumors may require a craniotomy. Such transcranial surgery is however associated with increased morbidity and mortality and is rarely required. More recent surgical techniques include the use of intra-operative MRI (237) and intra-operative growth hormone measurement (238). The development of endoscopic trans-sphenoidal surgery offers several advantages over the conventional technique, and is the now the method of choice. Reported advantages over the microscopic technique include superior tumor clearance, especially suprasellar extension, less surgical morbidity, fewer complications, and reduced post-operative discomfort (239), though evidence suggests endoscopic surgery and microsurgery yield similar outcomes in the most experienced hands (240). Endonasal endoscopic surgery, with ability to resect cavernous sinus located adenoma will increasingly be standard of care in pituitary surgery.

A key recent development in the management of acromegaly internationally is the formalization of a team approach, with endocrinologist, neurosurgeon, specialist nurses, oncologists, radiologists, and histopathologists increasingly working as a single-team, making consensus decisions in a timely and coordinated fashion. There is general acknowledgement that functioning pituitary tumors are best managed in centers with larger volume and experience of rarer conditions (236). Certainly, this practice is increasingly the case in Europe and the USA.

The success rate of trans-sphenoidal surgery depends on several factors: (i) the size of the tumor, (ii) pre-operative growth hormone values and (iii) the skill and experience of the surgeon and (iv) most importantly cavernous sinus invasion. A predictive model using age, KNOSP classification, and pre-operative GH levels has been proposed to predict surgical remission and guide pre-operative medical management and long term management (241). Although different series have often used different criteria to determine success rates, in experienced hands post-operative mean growth hormone levels of less than 1 ng/ml should be achieved in 70%-90% of microadenomas and 30%-50% of macroadenomas (52). Pre-treatment of patients with somatostatin analogues before trans-sphenoidal surgery is increasingly becoming standard practice, even if early surgery is being planned, as it results in significant shrinkage (approximately 50%) of the adenoma and may improve the subsequent surgical cure rates (242).

Complications of trans-sphenoidal surgery include diabetes insipidus, CSF rhinorrhea, meningitis, and hypopituitarism. Diabetes Insipidus is usually transient

but may be permanent in approximately 5% of cases depending on the criteria for its diagnosis. A serum osmolality of greater than 295 mosmols/l with a simultaneous urine osmolality of less than 150 mosm/l is confirmatory. It responds well to desmopressin (DDAVP, subcutaneous, oral, or intranasal).

Radiotherapy in Acromegaly

Radiotherapy in the management of pituitary disorders including acromegaly is discussed in detail in another Endotext chapter. Pituitary irradiation is usually used as an adjunct to pituitary surgery when growth hormone levels remain elevated. In elderly patients or those unfit for surgery, it may rarely be used as first-line therapy (243). There are several techniques that have been used: conventional mega-voltage external irradiation, stereotactic single high dose irradiation, interstitial implantation of yttrium ^{90} seeds, and whole particle proton beam therapy. Only the first two will be discussed here.

Conventional mega-voltage irradiation has been in routine use for over 40 years and consequently there is a wealth of experience principally relating to it being both a safe and effective technique. A linear accelerator is used as the source; less satisfactory is a cobalt source. Irradiation is focused onto the pituitary fossa using modern CT/MRI imaging and planning, which allows for accurate dosimetry and minimal variation in the daily dosage to surrounding structures, using IMRT. This is particularly so for the optic chiasm, damage to which is avoided by the use of daily fractions of less than 200 cGy. The majority of centers advocate a total dose of 4500 cGy given in 25 fractions of 180 cGy over 5-6 weeks via a minimum of three fields (one frontal and two temporal). Numerous studies have confirmed the efficacy of such mega-voltage irradiation with a 50% fall in growth hormone values occurring in the first two years, regardless of basal levels, followed by a continuing exponential decline thereafter (244). The majority of patients therefore do eventually achieve a level of less than 2 ng/ml, although the interval to reach this depends on the baseline levels. A similar response is seen with IGF-1 with approximately 60% of patients eventually achieving a normal serum level after 10 years. Although it is recognized that pituitary irradiation is associated with several potential adverse consequences, these are rare when irradiation is delivered properly, other than an increased prevalence of hypopituitarism. At ten years after irradiation, approximately 60% of patients are hypogonadal, 50% ACTH deficient, and 40% requiring thyroxine replacement. However, the prevalence prior to irradiation, either due to the pituitary tumor itself or previous surgery should be taken into account, with baseline figures being 40% hypogonadal, 35% ACTH, and 15% TSH deficient (244). Other concerns include development of secondary tumors in up to 2% of cases, radiation induced optic neuropathy in up to 5% cases, cerebrovascular events in up to 20% of cases over 20 years duration, brain necrosis, and psychocognitive impairment (245-247).

Stereotactic single high dose pituitary irradiation using either the gamma knife (radiosurgery) or stereotactic multiple arc radiotherapy (SMART) has received increasing attention in recent years as an alternative to conventional irradiation. These techniques permit the delivery of a single high dose of irradiation to a previously mapped area whilst also ensuring a rapid reduction in radiation exposure to surrounding structures. Median dose delivered is 15-35Gy and invariably achieves good tumor control at 5 years follow up and about 50% biochemical remission at 5 years (247) Care needs to be taken with tumors close to the optic chiasm. Initial impressions suggest that growth hormone levels fall to normal earlier than after conventional radiotherapy, but that hypopituitarism occurs just as often (248). Side effects of secondary brain tumors and cerebral vasculopathy seem to be

lower but long term studies are awaited (247). Although the stereotactic technique has clear advantages over conventional external irradiation in terms of precise mapping to a specified tumor volume, it may not encompass tumor tissue that is not visualized radiologically. This is in contrast to conventional irradiation which is usually configured to encompass the whole of the pre-operative tumor volume, and thus will treat tumor beyond the resolution of imaging techniques. It is for this reason that stereotactic irradiation should be seen as complementary to conventional irradiation.

Medical Therapy of Acromegaly

Three different types of medical therapy are currently used in the treatment of acromegaly, dopamine agonists, somatostatin analogs and growth hormone antagonists.

DOPAMINE AGONISTS IN THE TREATMENT OF ACROMEGALY

From their discovery and synthesis in 1971 until the introduction of somatostatin analogs in the mid-1980's, dopamine agonists, such as bromocriptine, were the sole medical therapy for acromegaly. However, they are relatively ineffective and whilst approximately 80% of patients will show a reduction in growth hormone levels, only about 10-15% achieved a mean level of less than 2 ng/ml (249). Furthermore, the doses required, often 20 - 30 mg of bromocriptine per day, are much higher than those needed for prolactin-secreting pituitary adenoma. Consequently, the side effects of nausea, headache, dizziness, postural hypotension, and nasal stuffiness tend to be worse, although can be minimized by taking the drug in the middle of a main meal to slow absorption and most patients will demonstrate tachyphylaxis. Unlike in patients with prolactinomas (where an excellent treatment response is expected), there may be only a modest reduction in tumor size but this is usually insignificant. Cessation of treatment results in rebound growth hormone hypersecretion. The use of bromocriptine in acromegaly is limited. The development of the long-acting dopamine agonists such as cabergoline offered greater convenience and reduced side effects, although again high doses of up to 4 mg per day may be needed (250). A meta-analysis has demonstrated that its use can achieve normalization of IGF-1 levels in 34% of patients (251). There are no accurate predictive tests as to which patients will respond to dopamine agonists, but it has a place in the management of mixed growth hormone and prolactin secreting tumors and patients with mild IGF-1 elevation. Combination therapy with SSA is frequently used in patients with co-secreting tumors with good effect (252).

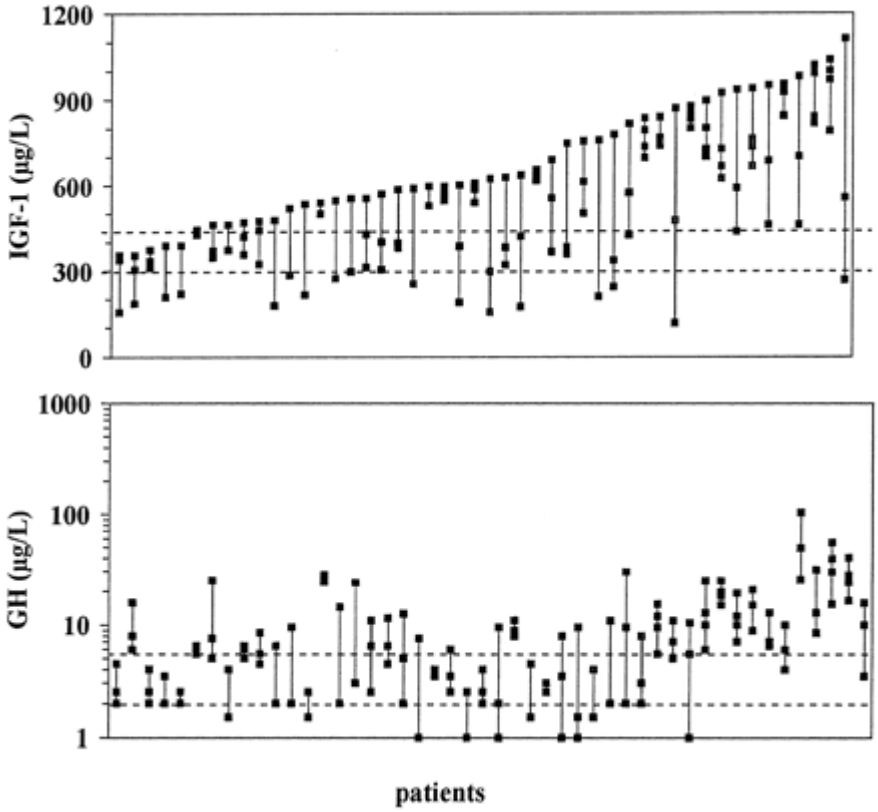

Fig 8. Plasma IGF-1 and GH responses to dopamine agonist suppressive therapy in patients with pure GH secreting tumors. The upper squares indicate the pretreatment levels and lower squares correspond to the concentrations obtained by progressively increasing the weekly dose of cabergoline i.e., 1.0, 1.75, and 3.5 mg, respectively. Note the log scale for GH.

SOMATOSTATIN ANALOG TREATMENT OF ACROMEGALY

The development of octreotide (Sandostatin, Novartis, Basel, Switzerland) a synthetic somatostatin analog, represented a major advance in the treatment of acromegaly. In contrast to the short half-life of native somatostatin (approximately 90-seconds), the 8 amino acid octreotide has a half-life of about two hours. Following a single 100 mcg dose, there is prolonged suppression of growth hormone which lasts for several hours, and indeed this response to a single dose can be used to predict the long-term efficacy of octreotide. It is administered by subcutaneous injection and thus a thrice-daily regimen results in stable drug concentrations and maximal effect. More than 90% of patients show a reduction in growth hormone levels, with approximately 50-60% achieving levels of less than 2 ng/ml and a normal serum IGF-1 level. The usual doses are between 100-200 mg three times daily although occasional patients may require higher doses. This biochemical improvement is matched by rapid clinical improvement. The efficiency of octreotide and other somatostatin analogs (SSAs) such as lanreotide is linked to their preferential binding of the human somatostatin receptor type 2 (SSTR2) with reduced or absent binding of SSTR1, SSTR3, SSTR4 or SSTR5. Somatostatin analogs also have additional

and independent, but poorly understood, analgesic properties on the headache associated with acromegaly.

Since the introduction of short-acting octreotide, depot formulations of somatostatin analogs have become available. These consist of the active drug incorporated with microspheres of biodegradable polylactide and polyglycolide polymers which allow the slow release of analog after intramuscular injection. There are currently three such preparations available, octreotide LAR (Sandostatin LAR, Novartis) which is given at a variable dose of 10 mg, 20 mg or 30 mg at recommended four weekly intervals, lanreotide (Somatuline Autogel, Ipsen Biotech, Paris, France), which is given as a single dose of 60-120 mg every 28 days as a sub-cutaneous depot formulation, and the more recently licensed Pasireotide LAR. Pasireotide has increased affinity for SSTR5, and this has led to a license for the treatment of Cushing's disease in addition to acromegaly. The SSA medications are also used in the treatment of neuroendocrine tumors arising outside the pituitary gland, in particular small bowel carcinoid tumors and pancreatic neuroendocrine tumors. Sandostatin and Lanreotide Autogel are of similar efficacy in suppression of growth hormone and IGF-1 with safe growth hormone levels (<2 ng/ml) occurring in approximately 60-70% of patients (253), although a meta-analysis of patients unselected for somatostatin responsiveness indicated that normalized IGF-1 levels and safe growth hormone levels occurred in a higher proportion of LAR treated than lanreotide treated patients (254).

Regardless, of the comparative effects, there is variability in individual patient's sensitivity to these analogs and more than 90% of patients who achieve adequate control with 4 weekly octreotide LAR injections will also do so with 6 weekly injections (255). Consequently, careful dose titration needs to be performed on each patient. This is particularly important given the cost of these depot formulations; in the UK, the approximate annual cost of octreotide LAR given 4-weekly is £8000 for 10 mg injections, £11000 for 20 mg and £14000 for 30 mg, whilst the cost for lanreotide Autogel 90 mg is approximately £10000 per annum. Biosimilar agents will increasingly become available perhaps with reduced cost.

Pasireotide is a novel cyclohexapeptide somatostatin analogue which is selective for SSTR2, 3 and 5, but also shows increased binding to SSTR1 compared to octreotide (256). The extended receptor affinity of pasireotide has led to it being referred to as a "second generation somatostatin analogue" with the original depot formulations being termed "first generation" analogues. More recent clinical trial data relating to Pasireotide in acromegaly indicates that this agent is modestly more potent than Sandostatin LAR in achieving control of GH and IGF-1, has long term safety, and also has a place in the management of seemingly octreotide resistant disease (257). A Phase III study showed that in new presentations of acromegaly achievement of control of GH and IGF-1 is superior with pasreotide (over octreotide) with about 20% patients achieving complete remission at 6 months, in a group resistant to first generation SSA therapy, suggesting that pasireotide may replace the earlier SSAs in treatment strategies in the future (258). Recent data from the PAOLA extension study showed that of the patients who achieved biochemical control at some point, 65.6% cases did so after 6 months of treatment. Increasing dose from 40-60mg allowed better remission rates (additional 28%) with reasonable safety profile (257). The drug seems to be particularly useful in the management of severe headaches in patient with acromegaly.

Oral octreotide as an agent coupled to a transient gut absorption enhancer and has been very recently approved by the FDA. Phase 3 studies have shown that it helps achieve about 65% control of IGF-1 and

GH when switched from injectable SSA and sustains the benefit in about 90% individuals for at least 13 months of follow up (259). It is prescribed in the dose of 40-80mg per day and studies have demonstrated better absorption in a fasting state (260). The most commonly reported adverse effects include headache, nausea, and arthralgia.

The side effects of somatostatin analogs are related to the widespread distribution of somatostatin and include effects on the gastrointestinal system, comprising colic type abdominal pain, diarrhea, flatulence, and nausea, although these tend to resolve with time. In the long-term gastritis occurs in a significant proportion of patients and perhaps most significantly gallstones form in approximately 50% of patients after two years of use. This is due to both an inhibition of gall bladder contraction and alterations in the composition of bile with cholesterol supersaturation. However, perhaps due to the gall bladder paresis, the majority of these remain asymptomatic. The effects of SSAs on glucose metabolism are multifactorial. While they improve insulin sensitivity by reducing growth hormone levels, they also exert direct inhibitory actions on insulin secretion by the pancreatic cells. The net result is normal glucose tolerance in the majority of patients. With their improved patient convenience, there have been suggestions that these depot formulations should be used as first-line treatment for acromegaly. However, their increased cost and the need for continuing treatment should be borne in mind. At present, there remains general consensus that whilst they may have a role prior to surgery to try and decrease tumor size, their major place is post-operatively as an adjunct to irradiation whilst waiting for growth hormone levels to fall. Provisional evidence suggests that treatment of acromegaly with somatostatin analogs prior to surgery improves the cardiovascular risk and respiratory status and may therefore have a place in larger and invasive tumors (261,262). Patients who remain uncontrolled despite the use of these somatostatin analogs may gain additional benefit with the addition of a dopamine agonist, but this is the exception rather than the rule. The incidence of hyperglycemia or diabetes is higher when patients are treated with pasireotide. This and the cost of the drug have thus far limited its use in the UK, though other health care economies have more readily incorporated pasireotide into the acromegaly treatment algorithm.

GROWTH HORMONE ANTAGONISTS IN ACROMEGALY

The development of Pegvisomant, the novel growth hormone receptor antagonist, is a major advance in the treatment of acromegaly. The development of this molecule utilizes the knowledge that the growth hormone molecule contains two distinct sites which bind to two corresponding unique sites on the respective growth hormone receptor dimer. Pegvisomant is a modified recombinant growth hormone molecule which has increased affinity to the first growth hormone receptor binding site but with decreased affinity to the second binding site. Thus, receptor dimerization and subsequent signal transduction is prevented. Its conjugation with polyethylene glycol (PEG) increases its molecular size, prolongs its half-life and reduces its antigenicity. Based on long term experience, some authors propose Pegvisomant to be most effective medical therapy to date and suitable as first line intervention in selected cases (263). In a study of 152 patients treated for up to 18 months, normalization of IGF-1 occurred in 90% of patients, although doses of up to 40 mg a day were required (264). Growth hormone levels cannot be measured in routine assays as the drug itself interferes with growth hormone assays and pituitary-derived growth hormone increases modestly. Pegvisomant is currently administered as a daily subcutaneous injection of approximately 1 ml in

volume. Theoretical concerns exist regarding the increase in circulating growth hormone levels due to the loss of any negative feedback effects on the tumor, but although experience is still limited there is no evidence to date of risk of pituitary tumor growth (263).

Pegvisomant is generally well tolerated although abnormalities of liver function occur in some patients. Its major use is for patients who are resistant to SSAs, either as a sole agent or as an additive agent. A study observed that the combination of 4-weekly octreotide LAR and weekly Pegvisomant normalized IGF-1 in more than 90% of patients with active disease who were not controlled with octreotide alone (265). Other suggestions for its use have been in patients with diabetes or impaired glucose tolerance, in whom SSAs might worsen glycemic control. Higher doses may be required in patients with severe disease, DM, and obesity. However, the change in dosing frequency and additional cost needs to be weighed against the use, if required, of simple oral hypoglycemic agents. The major drawback of Pegvisomant other than its usual requirement for daily injection, as opposed to the 4-6 weekly administration of SSAs, is its cost of approximately £3000 per per month, which can amount to £36000 per annum for patients resistant to SSAs (266).

A combination study demonstrated improved IGF-1 control with Pegvisomant and cabergoline, an approach which might enable a lower dose of the Pegvisomant to be used with reduced costs (267). Emerging data suggest that Pegvisomant may be an effective long-term treatment for acromegaly (263,268). Several European countries have registries providing regular outcome data related to Pegvisomant treatment in acromegaly. However, cost and approval restrictions mean that Pegvisomant is not yet universally available. Combination treated with SSA and Pegvisomant is likely the most effective medical strategy. Table 7 contains a summary of reported studies assessing effectiveness and safety of this treatment approach.

Table 7. Pegvisomant (PEG)-Somatostatin Receptor Ligand (SRL) Combination Studies

Study	Design	Prior SRL treatment at time of enrollment	Study treatments		IGF-1 normalization[d] (%)	Median weekly effective PEG dose (mg)	Tumor size	Glycemic control	QoL/ symptom improvement	>3-fold elevation in hepatic enzymes (%)
			SRL	PEG						
Feenstra [64] (n = 26)	Prospective, OL Duration: 42 weeks Objective: Dose-finding, efficacy	≥6 months inadequate control	LAN 120 mg/mo or OCT 30 mg/mo	Starting dose: 25 mg/week (adjusted q6 weeks until IGF-1 normal) Max dose: 80 mg/week	At any time: 95	60 (40–80)	No tumor growth seen in all 19 patients with available MRIs	NA	NA	19.2
Neggers [65]	Prospective, OL	≥6 months	LAN 120 mg/	Starting dose: 40 mg/week	At any time: 100	60 (40–160)	>25 % decrease	9/10 patients	Yes	15.6

(n = 32)	Duration: Median 138 weeks (35–149) Objective: efficacy and safety	inadequate control	mo or OCT 30 mg/mo	(adjusted q6 weeks until IGF-1 normal) *Dose reduced if IGF-1 level fell in the lowest quartile* Max dose: 160 mg /week			in 13 %[e] No change in size in the remaining	with DM had significant HbA1c decrease that continued after IGF-1 stabilized		
Neggers [70] (n = 86)	Prospective, OL Duration: up to 4.5 years Objective: safety 1 group (n = 63) followed for IGF-1 normalization 1 group (n = 23) controlled on SRL alone, followed for QoL improvement and safety	≥6 months inadequate control	LAN 120 mg/mo or OCT 30 mg/mo	Uncontrolled group: Starting dose: 25 mg/wk (n = 19) 40 mg/wk (n = 13) Variable starting dose guided by baseline IGF-1 (n = 26) QoL group: 20 mg/week Median dose (n = 23): 60 mg/week (20–200)	NA	NA	≥20 % decrease in 19%[f] No increase in any patients	NA	NA	15.1
Trainer [68] (n = 84)	Prospective, OL, randomized Duration: up to 40 weeks Objective: efficacy and safety	≥6 months inadequate control	OCT varying doses (median 30 mg/mo)	Starting dose: 10 mg/day (adjusted in 5 mg increments q8 weeks until IGF-1 normal) Max dose: 30 mg/day Min dose: 5 mg/day	End-of study: Combo versus PEG monotherapy: 62 versus 58 (ns)[g]	NA	≥20 % increase in 1 patient on PEG monotherapy	Mean fasting and post-OGTT glucose and HbA1c significantly lower only in monotherapy group, no change	Yes, in both groups	Combo = 13.8[h] PEG monotherapy = 3.7 OCT monotherapy = 3.5

	1 group (n = 29): PEG added to current OCT 1 group (n = 27): PEG monotherapy 1 group (n = 28): IGF-controlled on OCT monotherapy (control group)							in combo group		
van der Lely [67] (n = 57)	Prospective, OL Duration: up to 28 weeks Objective: efficacy and QoL improvement	≥6 months inadequate control[a] (confirmed on a 4-month run-in period)	LAN 120 mg/mo	Starting dose: 60 mg/week (adjusted q8 weeks until IGF-1 normal) Max dose: 120 mg/week	End of study: 57.9 At any time: 78.9	60[b]	>20 % decrease in 13.2 % >20 % increase in 24.5 %	Decrease in mean fasting insulin in non-diabetic patients after combination	Yes	11[c]
Bianchi [69] (n = 62)	Retrospective, observational Duration: 6-year study period Objective: efficacy and safety 1 group: PEG added	≥12 months inadequate control	LAN 120 mg/mo or OCT 30 mg/mo	Starting dose: 10 mg/day (adjusted according to IGF-1 by individual managing physicians)	End of study: 55.5 versus 80 ($p < 0.05$) At any time: 66.7 versus 82.8	Final weekly dose: 140 versus 105 (ns)	Decrease: 3.7 % versus 0 (ns)	NA	NA	11.1 versus 14.3 (ns)

	to current SRL (n = 27) 1 group: PEG monotherapy (n = 35)									
Neggers [66] (n = 141)	Prospective, OL Duration: median 4.9 years (0.5–9.2 years) Objective: long-term efficacy and safety 1 group (n = 112) followed for IGF-1 normalization 1 group (n = 29) controlled on SRL alone, followed for QoL improvement and safety	≥6 months inadequate control	LAN 120 mg/mo or OCT 30 mg/mo	Starting dose: 25 mg/week (n = 27) 40 mg/week (n = 18) Variable starting dose guided by baseline IGF-1 (n = 67) (adjusted q6-8 weeks until IGF-1 normal)	At any time: 97.3	80 (60–120)	≥20 % decrease in 16.9 %[i] Significant tumor growth in one patient who required TSS, followed by RT	NA	NA	15.6

PEG pegvisomant, *SRL* long-acting somatostatin receptor ligand, *QoL* Quality of life, *OL* open-label, *LAN* Lanreotide, *OCT* Octreotide LAR, *OGTT* 75 g oral glucose tolerance test, *NA* not available

[a]Inclusion criteria: responders to daily PEG monotherapy (presumed previously uncontrolled on SRL therapy), or partial responders to the highest marketed doses of either PEG at 3 months or SRL at 6 months

[b]Post hoc analysis: eight patients whose mean IGF-1 levels were similar while on pegvisomant monotherapy and during the co-administration period were able to reduce their weekly pegvisomant dose by 50 %

[c]Defined as > 2 × ULN in this study

[d]Different study criteria for IGF-1 normalization: defined by either end-of–study IGF-1, or lowest IGF-1 achieved

[e]Previous pituitary surgery: 1/4; Primary medical therapy: 3/4; none had radiotherapy

[f]Previous pituitary surgery: 2/14; Primary medical therapy: 11/14; one patient had radiotherapy

[g]12/21 patients who did not achieve normal IGF-1 received PEG < 20 mg/day

[h]2/3 patients with elevations >10 × ULN received OCT 60 mg/28 days

[i]None had radiotherapy

Table 8. Medical Agents for Acromegaly Including Drugs Under Trial (Most Relevant Targets in Bold). (269-272)

Agent	Route of administration	Molecule	Target	Dose	Side effects
Cabergoline	Oral	Dopamine agonist	DR2	1-4mg /day	Nausea, headache, dizziness, postural hypotension, and nasal stuffiness. Rare concerns of mood disorders and valvular fibrosis
Octreotide LAR	IM	Somatostatin analog	SSTR2 - SSTR5	10-40mg 4 weekly	Gastrointestinal side effects, GB sludge, reduced GB contractility, cholelithiasis, hypothyroidism. Variable effect on glucose. Rare sinus bradycardia, alopecia
Lanreotide ATG	Deep SC	Somatostatin analog	SSTR2 - SSTR5	60-120mg 4 weekly	
Pasireotide LAR	IM	Somatostatin analog	SSTR1, SS TR2,	40-60mg 4 weekly	Same as above. Also, Hyperglycemia

			SSTR3, SS TR5		
Pegvisomant	SC	GH receptor antagonist	GH receptor	10-40mg / day	Injection site reactions, abnormal liver enzymes, increase tumor size?
Tamoxifen	Oral	Selective estrogen receptor modulator		20-40mg / day	Bone marrow suppression, gynecologic malignancies, hepatotoxicity, ocular effects, thromboembolic events (271)
Octreolin®	Oral	Somatostatin analog	SSTR2 - SSTR5	40-80mg/day	Nausea, bloating, diarrhea, GB stones, dysglycemia
THERAPIES UNDER TRIAL					
Glide Octreotide Acetate (GP02)	Needle-free version of regular octreotide acetate	Somatostatin analog	SSTR2 - SSTR5	Immediate release drug, details unclear	Trial data not available
IF-2984®	SC	Somatostatin analog	SSTR1, SS TR2, SSTR3, SS TR5	Immediate release drug, details unclear	Trial data not available
CAM2029	SC	Somatostatin analog		20mg monthly depot	Similar to Other SSA
DG3173 (Somatoprim , now called as Veldoreotide)	SC	Somatostatin analog	SSTR2, SSTR4, SSTR5	100-1800µG TDS	Injection site reactions, GI side effects
ATL1103	SC	Antisense molecule	GH receptor (mRNA)	200mg twice weekly	Injection site reaction
Q-chip Octreotide	SC	Somatostatin analog	SSTR2 - SSTR5	10-30mg weekly	Diarrhea, DM
Botulinum neurotoxin SXN101959	–	Engineered neurotoxin	GHRH receptor	1mg/kg	

Intravail Octreotide ProTek ®	Oral/nasal	Somatostatin analog	SSTR2 - SSTR5		
VP-003 hydrogel formulation	SC implant	Somatostatin analog		84mg 6 monthly	Similar to SSA

PERSONALISED MANAGEMENT OF THE PATIENT WITH ACROMEGALY

Acromegaly is a rare condition and is best managed by expert teams with a personalized approach. Patient factors, the presence of co-morbidity, quality of life, and resource availability each influence the approach to management. The Endocrine Society guidance is commonly considered and increasingly biomarkers of disease status and activity are used to guide decision making.

Surgery with an intention of cure, or debulking remains the first line of management in most cases. Current evidence suggests that in cases of growth hormone secreting microadenoma, surgery alone will result in achievement of 'safe' growth hormone levels in approximately 70-90% of patients. As per the Knosp criteria tumors that cross the lateral tangent of the intracavernous and supracavernous internal carotid arteries are classified as grades 3A, 3B or 4 and are considered invasive (273,274). Surgical remission rate falls when an invasive macroadenoma (<50%) or a giant adenoma (<20%) is present, in contrast to non-invasive tumors (76%). Those with the highest pre-operative growth hormone concentrations, large tumors, or ones with invasion of cavernous sinus are least likely to be 'cured' by surgery alone (275). Older age and lower GH levels are associated with likelihood of cure (276). There may circumstances where consideration could be given for the use of cabergoline for IGF-1 values below twice the upper limit of normal. Use of SSA could be considered pre-operatively in patients with an intention to reduce disease burden or tumor volume prior to surgery to facilitate intervention.

Several biomarkers have been suggested to help guide response to first generation SSA. In a pre-operative patient T2 hypointense lesion is more likely to respond to SSA. Most of the other biomarkers are guided by histology outcome such as presence of densely granulated tumor, anti-Cam5.2 staining pattern, SSTR2a expression, and Ki-67 are well-established IHC biomarkers for response to first-generation SSA therapy (277). SSTR2a expression is also as useful marker for Pasireotide response (278). Other markers suggested to predict poor SSA response include low AIP expression, low zinc finger protein ZAC1 (a zinc finger protein expression), poor response during acute octreotide test, the presence of a gsp mutation, low expression of E-cadherin, the expression of sst5 and its truncated isoform (sst5TMD4), higher expression of miR-34a, the expression of β-arrestin, and Raf kinase expression, but these are not well validated (274). While presence of AIP expression is useful to guide use of first generation SSA, it does not seem to correlate with effectiveness of use of Pasireotide (279). There are no IHC markers to guide use of Pegvisomant, but patients with lower IGF-1 respond better (280).

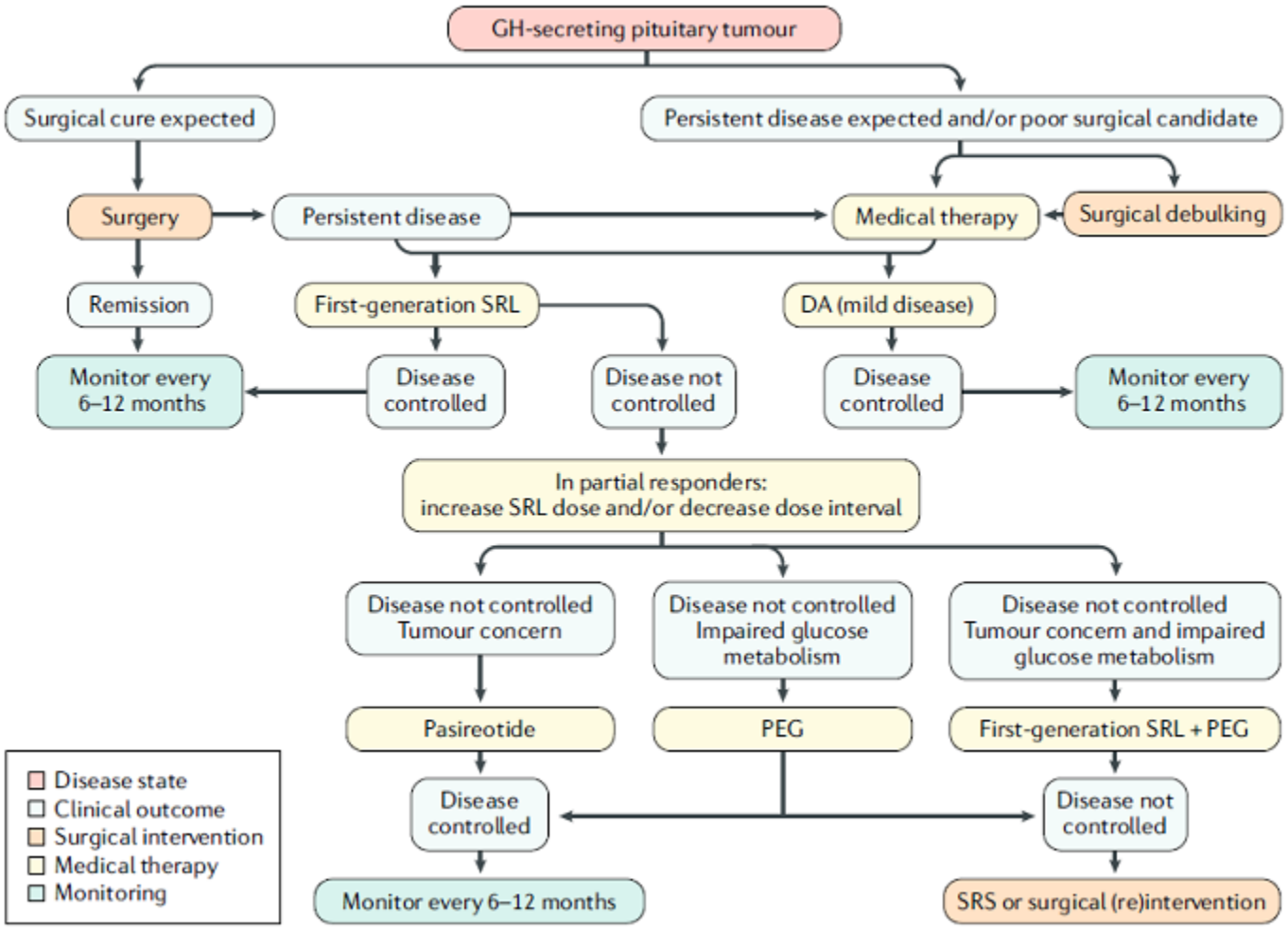

Figure 9. Algorithm for management of acromegaly: *Colao 2019*.

TREATMENT STRATEGY IN ACROMEGALY

Figure 9 summarizes the initial and subsequent strategies and options used at each stage of patient management. Practical issues including medication and treatment availability, patient factors, and surgical expertise will each have an influence on treatment. Following confirmation of the diagnosis of acromegaly surgical treatment should be considered for all patients with a confirmed somatotroph adenoma (80). Current evidence suggests that in cases of growth hormone secreting microadenoma, surgery alone will result in achievement of 'safe' growth hormone levels in approximately 70-90% of patients. This figure falls when a macroadenoma (<50%) or a giant adenoma (<20%) is present. Those with the highest pre-operative growth hormone concentrations are least likely to be 'cured' by surgery alone. In those post-operative patients with continuing growth hormone excess, further treatment is indicated, and this can be medical or radiotherapy treatment. A second surgical procedure will result in 'safe' growth hormone levels in only 20% of patients. Recognizing that radiotherapy does not result in an instant lowering of growth hormone levels, medical treatment is commonly required, especially in the short-term. On average, two

years following external beam irradiation growth hormone levels have decreased by approximately 50% with a further fall resulting in 75% reduction at 5 years. Newer stereotactic radiotherapy techniques, when used appropriately, may affect a more rapid reduction in growth hormone levels. However, since the tumor in such cases is usually a macroadenoma, we would only use radiosurgery as “salvage therapy” in the face of poor control of tumor secretion or regrowth following conventional radiotherapy. Available adjunctive medical options include the use of dopamine agonists, somatostatin analogs (first and second generation), and Pegvisomant. Bromocriptine will normalize growth hormone levels in only 10% of patients, although this may rise to 30% with cabergoline. Octreotide and lanreotide, particularly in their depot formulations which last 4-6 weeks, will normalize mean growth hormone levels in 70-80% of patients, and are therefore highly effective, albeit expensive. Pasireotide results in more potent GH lowering, and in many countries is becoming a key part of the treatment algorithm. The growth hormone receptor antagonist, Pegvisomant, is now well established and may be used in patients resistant to these agents. Periodic assessment with IGF-1 measurement and growth hormone profile testing should be performed at regular intervals to facilitate titration of doses and determine response to radiotherapy. Following irradiation it is reasonable to assess growth hormone status after appropriate discontinuation of medical therapies at 6-monthly intervals for 2 years and thereafter yearly. In all patients with acromegaly efforts should be made to optimize lung and cardiac function and particular attention be made to the management of cardiovascular risk factors including smoking, dyslipidemia, and abnormalities of carbohydrate metabolism. ‘Extra-hepatic acromegaly’ describes the concept that elevated GH concentration results in tissue specific pathological effects despite normalization of serum levels of IGF-1 (295). It has been postulated that combined use of SSA (to lower GH) and pegvisomant (to control IGF-1) may be the most appropriate strategy for patients who fall into this category.

Treatment of Refractory Disease

Acromegaly with invasive non-responsive adenoma, with either persistent GH excess or invasive adenoma is a rare and difficult management problem often needing multi-modal therapy. Table 7 summarizes data from studies reporting use of combination medical therapy in cases resistant to first line SSA therapy. Few studies have reported using higher dose Pegvisomant or Combination of Pegvisomant and Pasireotide in these refractory cases with good effect (281,282). Use of radiotherapy has been utilized for control of the tumor volume in aggressive disease, while others have considered using the alkylating agent temozolamide or even cytotoxic therapy (222,283).

Management of Acromegaly in Pregnancy

Pregnancy in a healthy non-pregnant female is associated with gradual decline in pituitary derived GH levels, as the placental GH levels rise throughout the pregnancy. IGF-1 levels initially tend to decrease due to enhanced estrogen effect on liver, but eventually the levels rise as an action of placental GH. These physiological changes seem to explain the relatively less aggressive or rather benign course of acromegaly in pregnancy (284).

Infertility is more common in active disease, and patients often patients require treatment to achieve pregnancy. Evaluation of baseline tumor volume in a planned pregnancy is useful to safely plan monitoring during pregnancy. GH and IGF-1 levels are unreliable due to assay interference and are not routinely used to guide decision making (212). As a consequence of

physiological changes, prevalence of gestational diabetes and hypertension is higher in women with acromegaly, but this seems to correlate with the pre-pregnancy control and not the degree of rise of IGF-1 (285). For patients with macroadenoma, serial visual field testing is required during pregnancy. Patients with intractable headaches, cranial nerve deficits or visual manifestations are likely to require intervention. If MRI is required it is best undertaken as unenhanced study (212). As GH does not cross the placenta, no direct effect on the disease on fetus have been reported. Studies have shown that the tumor size does not usually increase during pregnancy (286). The current recommendations suggest all medical therapy should be ceased at diagnosis of pregnancy. If pregnancy is pre-planned it is recommended that long acting SSA are discontinued about two months prior to pregnancy and patient switched to short acting octreotide injections (151,287). Safety data for the use of SSA and Pegvisomant is not substantial, but the available evidence has not shown any significant impact on maternal or fetal outcomes. There are reports of SSA use being associated with small for gestation babies, without malformations and similar concerns with use of dopamine agonists (285,288). While there are concerns for premature delivery the data for use of Pegvisomant in pregnancy is more encouraging (289).

NOVEL AGENTS IN THE TREATMENT OF ACROMEGALY

A number of novel agents are in advanced stages of development for the medical treatment of acromegaly. These include agents that continue to work by the somatostatin mechanism as well as new mechanisms of action. Developments in the understanding of the molecular pathogenesis of growth hormone excess and pituitary tumor development have led to the identification of novel targets for drug development. New treatments need to be safe and well tolerated, as well as effective and importantly cost effective.

An anti-sense oligonucleotide has been developed directed against the growth hormone receptor. Early clinical trial data suggests that this strategy may prove effective in reducing growth hormone signaling and IGF-1 generation in patients with acromegaly (290). The drug was well tolerated in an early clinical trial with injection site reactions the most common adverse event reported.

Novel compounds with combined affinity for SSTR2, SSTR5 and the dopamine D2 receptor are also being developed and *in vitro* show enhanced inhibition of growth hormone release (291). The ongoing development of these chimeric analogs may increase the efficiency of currently available analogs (292).

Somatoprim or Veldoreotide is a novel somatostatin analogue. This agent has affinity for the SST2, 4 and 5 receptors. A phase II study to investigate the efficacy of this agent in acromegaly is underway. STAT3 signaling is an important mechanism in the regulation of growth on dependent gene expression. GH-secreting adenomas overexpress STAT3. Recently a STAT3 inhibitor has been shown to suppress growth action. Thus, there is early evidence that this novel strategy may have a role in the treatment of acromegaly in the future (293). In addition, a new formulation of subcutaneous octreotide depot has been trialed in phase II studies, demonstrating superior efficacy to intramuscular octreotide (294).

In summary, continuing advances in the understanding of the mechanisms responsible for pituitary tumor development and the regulation of GH secretion, are aiding the further development of existing therapeutic agents and enabling the creation

of new promising treatment for patients with acromegaly.

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