Acromegaly pathogenesis and treatment

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Dysregulated growth hormone (GH) hypersecretion is usually caused by a GH-secreting pituitary adenoma and leads to acromegaly — a disorder of disproportionate skeletal, tissue, and organ growth. High GH and IGF1 levels lead to comorbidities including arthritis, facial changes, prognathism, and glucose intolerance. If the condition is untreated, enhanced mortality due to cardiovascular, cerebrovascular, and pulmonary dysfunction is associated with a 30% decrease in life span. This Review discusses acromegaly pathogenesis and management options. The latter include surgery, radiation, and use of novel medications. Somatostatin receptor (SSTR) ligands inhibit GH release, control tumor growth, and attenuate peripheral GH action, while GH receptor antagonists block GH action and effectively lower IGF1 levels. Novel peptides, including SSTR ligands, exhibiting polyreceptor subtype affinities and chimeric dopaminergic-somatostatinergic properties are currently in clinical trials. Effective control of GH and IGF1 hypersecretion and ablation or stabilization of the pituitary tumor mass lead to improved comorbidities and lowering of mortality rates for this hormonal disorder.

This article reviews recent scientific discoveries that have had an impact on our understanding of acromegaly pathogenesis and clinical features. Novel approved and experimental therapies have evolved from these fundamental insights and are discussed in the context of providing added benefit to patient care and disease control.

Diagnosis

The diagnosis of acromegaly requires demonstration of dysregulated and enhanced GH secretion as well as elevated IGF1 levels, reflective of peripheral tissue exposure to tonically elevated GH concentrations (6). In acromegaly, basal GH secretion is tonically elevated with relatively blunted bursts (Figure 2). Accordingly, a random GH value of less than 0.04 μg/l effectively excludes the diagnosis of acromegaly. Importantly, an elevated randomly obtained GH measurement may not necessarily imply excessive integrated GH secretion. Net GH secretion is attenuated after age 60 (when 24-hour GH secretion is less than 50% of that in younger subjects) and by elevated BMI.

Older GH radioimmunoassays were relatively insensitive and poorly reproducible. Newer immunoradiometric assays and immunoluminometric assays are based on the use of two-site monoclonal antibodies, and although they detect GH concentrations of less than 0.05 μg/l, these assays are beset by challenges of reproducibility. Lack of universal standards, nonuniform antibody recognition of GH isoforms, and the presence of circulating GH-binding proteins contribute to method-dependent and patient-specific variability of GH measurements. In a multicenter study of GH nadir after an oral glucose tolerance test (OGTT), reference ranges varied by approximately 50%, and 30% of obtained results were inconsistent with the correct diagnosis (7). There is a compelling need for reliable GH assays based on robust reference standards.

A functional hallmark of a GH-secreting pituitary adenoma is the inability to respond appropriately to a glucose-induced neuroendocrine suppressive signal. The inability to suppress GH secretion to less than 1 μg/l during 2 hours after an oral glucose load (75 grams) is the current consensus for diagnosing acromegaly (8). However, this cutoff may in fact be insensitive, and patients have been identified with clinical features of acromegaly, elevated IGF1 levels, and nadir postglucose GH levels of less than 1 μg/l (9). Using ultrasensitive GH assays, a nadir GH cutoff of less than...
0.3 μg/l is effectively more discriminatory. Failure to suppress GH levels may also be encountered in patients with diabetes, renal or hepatic failure, and obesity or those receiving estrogen replacement or who are pregnant.

Screening of IGF1 levels is useful in obtaining a surrogate reflection of integrated GH secretion. IGF1 levels are relatively stable, correlate with clinical features of acromegaly (10), and exhibit a log-linear relationship with elevated GH levels (S3). Measured circulating IGF1 concentrations plateau when GH levels are greater than 20 μg/l, and subtle GH elevations do not uniformly induce IGF1. Accurate IGF1 evaluation requires age-matched control values, especially as levels may also be encountered in patients with diabetes, renal or heart disease (11). Malnourished patients and those with liver and renal failure or those receiving estrogen or who are pregnant.

The impact of recent multimodal therapy on mortality outcomes. 

A potential determinant of acromegaly mortality could be iatrogenic or endogenous hypopituitarism (failure of the pituitary gland to produce normal amounts of one or more of its hormones), resulting in deficiencies of pituitary-target hormone axes. Ideally, achievement of rigorously controlled GH and IGF1 levels would be expected to normalize SMRs. Accordingly, comorbidities associated with musculoskeletal degeneration and disfigurement, large organ hyperplasia, and cardiac and vascular dysfunction remain as therapeutic challenges.

### Morbidity impact of exposure to excess GH/IGF1

#### Mortality determinants

Large retrospective studies of acromegaly patients (14) indicate an average 10-year reduction in life expectancy, with at least a doubling of standardized mortality rates (SMRs) due to cardiovascular, cerebrovascular, metabolic, and respiratory comorbidities. Mean weight-adjusted SMRs in treated patients were 1.72 (1.62–1.83, 95% CI), with earlier studies showing higher ratios (15). Overall, achieving a post-treatment GH level of less than 2.5 μg/l results in maintaining normal life expectancy rates (2, 15). Independent survival determinants include the last recorded GH level (P < 0.001), hypertension (P < 0.02), heart disease (P < 0.03), and disease duration (P < 0.04) (14). In an outcomes study of 419 patients, cerebrovascular SMRs were elevated at 2.68 (1.73–4.15, P < 0.007), while malignancy-associated mortality was not enhanced (16). These results likely reflect the positive impact of recent multimodal therapy on mortality outcomes.

Radiotherapy directed at the GH-secreting pituitary adenoma may also be associated with increased mortality (P < 0.005) (16), especially from cerebrovascular disease. Although overall cancer incidence is not enhanced, there is a moderate risk of developing colorectal cancer (S4). Uncontrolled GH levels likely provide a growth advantage to neoplasms, resulting in more aggressive disease and increased cancer-associated mortality. Colonoscopy shows increased colon length and mucosal hypertrophy; up to 25% of polyps are right-sided and recur within 3 years.

A potential determinant of acromegaly mortality could be iatrogenic or endogenous hypopituitarism (failure of the pituitary gland to produce normal amounts of one or more of its hormones), resulting in deficiencies of pituitary-target hormone axes. Ideally, achievement of rigorously controlled GH and IGF1 levels would be expected to normalize SMRs. Accordingly, comorbidities associated with musculoskeletal degeneration and disfigurement, large organ hyperplasia, and cardiac and vascular dysfunction remain as therapeutic challenges.

### Comorbidities

The constellation of hypertension, cardiac arrhythmias, glucose intolerance, and diastolic dysfunction leads to heart failure, which may be intractable, especially if GH levels remain uncontrolled. Biventricular cardiac hypertrophy manifests early in response to elevated GH levels and is present in 20% of young acromegaly patients and in up to 90% of patients with long-standing disease independent of the presence of hypertension. Postexercise ventricular ejection fraction is increased in approximately 70% of patients (17), and approximately 50% are at intermediate-to-high risk for coronary arteriosclerosis (S5). The pathogenesis of hypertension is associated with plasma volume expansion and increased cardiac output (18). Although hypertension has been ascribed to increased peripheral vascular resistance, vessel growth and intimal thickness are not uniformly dysregulated. GH exerts antinatriuretic effects, leading to increased extracellular volume, soft tissue swelling, and organomegaly. GH acts at the aldosterone-sensitive distal nephron, and transepithelial sodium transport is attenuated by a GH receptor (GHR) antagonist, while cortical collecting duct epithelial sodium channel subunit transcription is induced by GH (19). Insulin resistance caused by GH excess results in glucose intolerance and diabetes (5), further exacerbating renal dysfunction.

Airway obstruction consequent to macroglossia (tongue enlargement) and hypothyropathy of laryngeal and pharyngeal mucosal tissues lead to upper airway obstruction, hyperventilation, snoring, and sleep apnea in approximately 50% of patients (S6).
Anterior pituitary development follows highly specialized precursor stem cell commitment, with restricted differentiation of hormone-secreting cell types. Somatotrophs account for more than 50% of pituitary hormone-secreting cells, and transcription factors paired-like homeodomain factor 1 (PROP1) and POU class 1 homeobox 1 (POU1F1) determine cell differentiation and commitment to synthesizing and secreting GH (20, 21). A family of genes located on the long arm of chromosome 17 encodes the GH peptides, encompassing pituitary human GH, a placental variant of human GH (hGH) known as hGH-V, placental lactogen, and PRL (22). An alternatively spliced pituitary GH molecule is devoid of aa 32–46 and is designated as 20-kDa GH. Structural characteristics of the 191-aa GH molecule that are important for peptide function include the third α-helix, comprising amphiphilic domain elements important for signaling, and integrity of the large helical loop is required for growth-promoting actions (23). GH mediates linear skeletal growth and also regulates carbohydrate, lipid, and mineral metabolism (24). Most of the growth-promoting actions of GH are enabled by IGF1.

Hypothalamic GH-releasing hormone (GHRH), ghrelin (mainly gut-derived), and somatostatin (SRIF) traverse the pituitary portal system to regulate GH production by anterior pituitary somatotroph cells (25) (Figure 2). GHRH, acting via the GHRH G protein-coupled receptor, induces and maintains somatotroph trophic function and induces GH gene transcription and secretion (26). Ghrelin, a gut-derived GH secretagogue (27), acts mainly at the hypothalamus and signals through the ghrelin secretagogue receptor type 1a (GHS-R1a) to induce GH secretion in synergy with GHRH (S7). GHRH also signals via the ghrelin receptor (28), acting as an allosteric coagonist for the GHS-R1a. GHRH and ghrelin thus act coordinately to regulate pituitary function as well as energy homeostasis. SRIF, acting via pituitary SSTR2 (where SSTR denotes SRIF receptor subtype) and SSTR5 subtypes, attenuates both the timing and amplitude of GH secretory pulses. GH secretion is characterized by sporadic secretory pulses interspersed with mostly minimal basal secretion determined by age, sex, specific nutrients, neurotransmitters, exercise, and stress. Random daytime GH measurements are usually very low for approximately 80% of the day and may range from undetectable to secretory peaks of up to 15 μg/l or higher in normal subjects, observed mainly at night. Increased BMI and obesity attenuate GH secretion, while malnutrition and prolonged fasting result in elevated GH pulse frequency and amplitude (29).

**GH signaling**

The gene encoding the GHR, a class I pleiotropic cytokine receptor (30), is ubiquitously expressed, especially in liver, fat, and muscle. The GH molecule interacts with a preformed dimer of identical GHR pairs, which undergoes rotation and triggers ligand-receptor complex signaling (31) (Figure 3). As a consequence, two JAK2 molecules undergo autophosphorylation and also phosphorylate the GHR cytoplasmic domain (S8). Subsequent JAK2-dependent and -independent intracellular signal transduction pathways...
evoke pleiotropic cell responses including IGF1 synthesis, glucose metabolism, cell proliferation, and cytoskeletal changes.

STAT5b is the key intracellular molecule required for GH mediation of postnatal growth, adipose tissue function, and sexual dimorphism of hepatic gene expression (24). Importantly, GH-activated STAT5b induces IGF1 gene transcription (S9), and several lines of evidence point to this pathway as being critical for initiating and maintaining skeletal growth. Male Stat5b−/− mice exhibit impaired growth, attenuated circulating IGF1 levels, and insensitivity to injected GH (S10). Hepatic IGF1 is induced by constitutively active STAT5b, while a dominant negative STAT5b construct prevents GH-induced IGF1 expression (S11). In humans, STAT mutations result in relative GH insensitivity and growth retardation (32). GH also induces early response genes that precede cell growth and differentiation signals (33) mediated by CCAAT enhancer-binding protein β and serum response element sites on the c-fos promoter.

The GHR may also translocate to the nucleus by the importin α/β pathway in conjunction with coactivator activator (CoAA). Gene targets for nuclear-mediated GHR action are predominantly proproliferative. Forced GHR targeting to the cell nucleus also enhances cell proliferation and transformation responsiveness to autocrine-derived GH. Thus, CoAA and activated STAT5 are both required for GH-dependent proproliferative actions of nuclear GHR (34).

STAT5b mediates sexually dimorphic GH signals. Females exhibit more frequent GH secretory pulses and shorter interpulse nadir intervals, leading to relative desensitization of female hepatic STAT5 induction by GH as compared with that of males. Targeted disruption of STAT5b leads to male-selective reduced growth rates and loss of gender-specific hepatic gene induction (35).

GH insensitivity may occur as a consequence of extracellular receptor domain cleavage as well as toxin-induced proteolysis,

Figure 2
Normal and disrupted GHRH–GH–IGF1 axis and molecular targets for therapy. Pituitary somatotroph cell development and gene expression are determined by the POU1F1 transcription factor. Net GH secretion is determined by integration of hypothalamic, nutritional, hormonal, and intrapituitary signals. GH synthesis and secretion are induced by hypothalamic GHRH and gut-derived ghrelin. GHRH may also act as a coagonist for the ghrelin receptor (28). Hypothalamic SRIF suppresses GH secretion mainly by high-affinity binding to SSTR2 and SSTR5 receptor subtypes expressed on somatotrophs (90). SSTR ligands (SRLs) signal through SSTR2 and SSTR5 to control GH hypersecretion and shrink tumor mass. GH secretion patterns in a normal subject and in acromegaly are depicted in the insets showing secretory bursts (mainly at night) and daytime troughs. Insets modified with permission from Expert opinion on biological therapy (S41).
which abrogates signaling (S11). GHR cell-surface translocation is also directly inhibited by IGF1, likely contributing to a local feedback loop (36) (Figure 3).

**IGF1**

IGF1, the polypeptide target hormone for GH, is synthesized in the liver and extrahepatic tissues (principally bone, muscle, and kidney) and also in the pituitary gland itself. IGF1 mediates most of the growth-promoting actions of GH (37). Acting at both kidney) and also in the pituitary gland itself. IGF1 mediates most peptide activity by regulating IGF1 cell-surface receptor access (39). As IGF1 receptors are ubiquitously expressed, widespread enhanced cell proliferation as well as metabolic actions are triggered by elevated IGF1 concentrations. IGF1 acts in an endocrine fashion to mediate tissue growth, or locally synthesized IGF1 acts in an autocrine/paracrine manner to regulate local GH target tissue growth. Ultimately, organ growth responses to IGF1 are determined by the intrinsic replicative potential of local tissues. Observations that doubly mutant Ghr<sup>−/−</sup> Igt<sup>−/−</sup> mice exhibit more severe growth retardation than animals with either single-gene deletion alone indicate that anabolic actions of GH, especially on muscle, may also be distinctively direct and not necessarily IGF1 dependent (40). GH acts directly to induce germinal epithelial cells, while IGF1 acts to induce chondrocyte proliferation (41), and based on results derived from transgenic mice with respective deletions of GHR or IGF1 (42), both GH- and IGF1-mediated signaling appear additive in enabling growth, while IGF1 may attenuate metabolic effects of GH (43).

**GH and IGF1 signaling in acromegaly**

In acromegaly, cellular responses elicited by high GH levels overwhelm intracellular mechanisms attenuating GH signaling, including those mediated by SOCS, Src kinases, and tyrosine phosphatase pathways (24). An in-frame deletion in exon 3 results in a GHR isoform devoid of 22 aa (known as d3-GHR), which is associated with enhanced GH responsiveness, as evidenced by higher STATS activation and accelerated growth (44). d3-GHR is also associated with a more florid clinical and biochemical acromegaly phenotype and relative resistance of IGF1 levels to acromegaly treatment interventions (45, S12).

Although mice overexpressing transgenic GH or IGF1 exhibit enhanced somatic growth reminiscent of acromegaly, several distinctive features point to unique independent target functions for GH and IGF1 (46, S13). For example, transgenic mice overexpressing GH, but not IGF1, exhibit liver, spleen, and kidney enlargement with features of renal glomerulosclerosis. In contrast, mice overexpressing IGF1 are obese, unlike GH transgenics (S13). This phenotype recapitulates acromegaly with reduced fat mass and increased lean body mass. To what extent GH-induced hyperinsulinemia, manifest in GH transgenic mice but not in IGF1 transgenic animals, contributes to the hypsomatomatrophic phenotype is unclear. The body of experimental evidence indicates that GH actions in bone and soft tissue require IGF1 to enable a maximally robust tissue response (47).

**Somatotroph adenoma pathogenesis**

Pituitary tumors are commonly encountered monoclonal adenomas that account for approximately 15% of all intracranial tumors. These invariably benign tumors arise from highly differentiated anterior pituitary cells expressing hormone gene products including GH, PRL, ACTH, TSH, and the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These tumors may secrete hormones excessively, leading to characteristic clinical features including acromegaly, Cushing disease, and hyperprolactinemia. More commonly, they are nonfunctional and lead primarily to hypogonadism and compressive pituitary failure (48). Mechanistic studies of human pituitary tumors have been constrained due to inaccessibility of the gland for biopsy, lack of functional cell lines, and unique differentiated tumor subtype behavior. In most cases of acromegaly, GH hypersecretion is derived from somatotroph cell tumors (see Sidebar 2). Autonomous GH secretion by distinct somatotroph adenomas derived from the POU1F1
transcription factor cell lineage characterizes a distinct balance of GH secretion versus somatotroph trophic activity. GH-secreting tumor formation ensues as a consequence of unrestrained somatotroph proliferation associated with intrinsic cell-cycle dysfunction as well as altered endocrine and/or paracrine factors regulating GH synthesis, GH secretion, and somatotroph cell growth.

GH-secreting adenomas very rarely exhibit activating ras mutations in invasive or metastatic lesions (49, S14). Uniquely, pituitary mitotic activity is relatively low, even in invasive adenomas. Several growth factors, including dysregulated receptors for fibroblast growth factors, dopamine, estrogen, and nerve growth factor (50), have been implicated predominantly in prolactinoma pathogenesis, but not uniformly in acromegaly (Table 1).

cAMP signaling
Several lines of evidence support the role of the GHRH-cAMP signaling pathway in mediating somatotroph tumorigenesis (Figure 4). Ectopic GHRH production by peripheral carcinoid inducing cAMP, which induces GH transcription mediated by GHRH receptor (GHRH-R), a G protein–coupled receptor, by cAMP response element–binding protein (CREB). A constitutively activated cAMP signaling pathway resulted in formation of murine tumors derived from the POU1F1 lineage (S17).

Cell-cycle disruption
Cyclin D1–dependent kinase 4 (CDK4) is required for postnatal somatotroph and lactotroph proliferation, and Cd4-null mice are resistant to the trophic effects of GHRH (56). In contrast, retinoblastoma gene (Rb) inactivation leads to endocrine tumorigenesis, and Rb+/- mice develop spontaneous pituitary tumors with almost 100% penetrance (57). Rb acts as a G1/S cell-cycle checkpoint control: cyclin-dependent kinases (CDKs) phosphorylate Rb, triggering the release of members of the E2F family of transcription factors, enabling the progression of S phase and cell proliferation. Loss of E2F1 reduces the frequency of pituitary tumors in the Rb+/- E2F1+/- mouse, further indicating that site-selective tumorigenesis in Rb+/- mice results from dysregulated E2F transcriptional activity (57).

MEN1. The multiple endocrine neoplasia type 1 (MEN1) syndrome (OMIM 131100) is an autosomal dominant disorder associated with germ-line mutations in MEN1, a tumor suppressor gene located on chromosome 11q13. The syndrome comprises a predisposition to parathyroid hyperplasia, pancreatic endocrine tumors, and pituitary adenomas. Up to 40% of affected individuals harbor pituitary tumors, and these comprise prolactinomas (60%), GH-secreting adenomas (20%), ACTH-secreting adenomas (<10%), and nonfunctional adenomas (<10%) (58, S18). The MEN1 nuclear protein controls genome stability by repression of telomerase activity via telomerase reverse transcriptase (S19). Mechanisms for pituitary tumor pathogenesis in patients with MEN1 syndrome and disrupted MEN1, apparent from animal
studies, include regulation of p27 and p18, both of which are implicated in pituitary tumor growth in transgenic mice models. Mice devoid of p27 exhibit striking features of gigantism with multiorgan hyperplasia and intermediate lobe pituitary tumors (S20). Thus, MEN1 enables suppression of pituitary and related neuroendocrine tumor formation, and disrupted MEN1 gene could facilitate development of these tumors. Mutations of MEN1, p18, or p27 have not been encountered in patients harboring sporadic pituitary adenomas.

When p18 homozygote mutant mice were crossed with heterozygous Men1 mutants, development of pituitary, parathyroid, thyroid, and pancreatic tumors was markedly accelerated (59). A germ-line mutation in p27 (also known as CDK inhibitor acting as a securin to inhibit separase and enable faithful sister chromatid separation (63, 64)). When p18 homozygote mutant mice were crossed with heterozygous Men1 mutants, development of pituitary, parathyroid, thyroid, and pancreatic tumors was markedly accelerated (59). A germ-line mutation in p27 (also known as CDK inhibitor acting as a securin to inhibit separase and enable faithful sister chromatid separation (63, 64)).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Mode of activation/ inactivation</th>
<th>Clinical context</th>
<th>Specificity for GH-secreting pituitary adenoma</th>
<th>Ref.</th>
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<tr>
<td>GNAS</td>
<td>Oncogene</td>
<td>Activating, imprinted</td>
<td>Nonfamilial, syndromic or sporadic</td>
<td>Relatively specific</td>
<td>52</td>
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<td>CREB</td>
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<td>Constitutive phosphorylation</td>
<td>Sporadic</td>
<td>Relatively specific</td>
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<td>Tumor suppressor</td>
<td>Inactivating</td>
<td>Familial, syndromic</td>
<td>Relatively specific</td>
<td>S46</td>
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<td>Inactivating</td>
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<td>Not specific</td>
<td>S18</td>
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<td>PRKAR1A</td>
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<td>Inactivating</td>
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<td>H-RAS (Harvey rat sarcoma virus oncogene)</td>
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<td>Overexpression</td>
<td>Sporadic</td>
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<td>FGFR4 (Fgf receptor 4)</td>
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<td>Alternative transcription</td>
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<td>Not specific</td>
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<td>Rb</td>
<td>Tumor suppressor</td>
<td>Epigenetic silencing</td>
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<td>Not specific</td>
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<td>Nonsense mutation</td>
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<td>Epigenetic silencing</td>
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Epigenetic mechanisms

Loss of gene expression due to DNA hypermethylation of both alleles in GH-secreting adenomas exemplifies an epigenetic mechanism by which the loss of genes that inhibit cell proliferation results in pituitary cell proliferation (S21). CDKN2A encodes CDK inhibitor 2A (also known as p16), which blocks
CDK4 from interacting with cyclin D1 and thereby preventing retinoblastoma protein (Rb) phosphorylation. Rb methylation in somatotroph adenomas is variable, with inconsistent effects on tumor proliferation (73). Epigenetic silencing of p16 and p27 expression or loss of heterozygosity on chromosome 13 is also associated with Rb inactivation in some human pituitary tumors (73). The growth arrest and DNA damage–inducible γ (GADD45G) and maternal expressed 3 (MEG3) genes and melanoma-associated antigen A3 are expressed in normal pituitary but not in pituitary adenomas (74–76).

Collectively, these observations suggest a model for pituitary adenoma growth whereby an initial proliferative phase occurs in response to growth stimuli and is then followed by irreversible growth arrest of the benign tumor. Thus, the vital hormonal functioning of the somatotroph for maintaining homeostasis control appears to be enabled by a senescent response to oncogenic stress restraining proliferation in an attempt to assure viable physiological functions.

Familial isolated pituitary adenomas. Less than 5% of pituitary adenomas are inherited on a familial basis (77). In familial isolated pituitary adenoma (FIPA) families, prolactinomas account for about half of the adenomas, with GH-secreting and mixed GH- and PRL-secreting adenomas accounting for the remainder. Homogenous familial acromegaly (also known as isolated familial somatotropinomas [IFS]) affects younger patients usually diagnosed as teenagers or in their 20s (78). About 25% of IFS patients present with gigantism and macroadrenomas, with most not harboring a known germline mutation. Mutations in the tumor suppressor aryl hydrocarbon receptor–interacting protein (AIP) predispose to somatotroph and lactotroph tumors in 15% of patients (79) (Table 1). Two of 21
The goal of surgery is to balance maximal tumor mass resection with preservation of normal pituitary secretory function when performed by skilled and experienced neurosurgeons (S23). Computerized image guidance and intraoperative MRI coupled with development of microinstrumentation and optics have resulted in safe, effective, and minimally traumatic procedures, often with minimally invasive endoscopic techniques. 90% of resections are performed via an endonasal transsphenoidal approach, often with minimally invasive endoscopic techniques. Microaneurysms also require surgical caution and alertness. Over resection. Tumor-associated internal carotid artery tortuosity and affected patients with GH-secreting pituitary tumors. shown to harbor relatively large intragenic AIP deletions (S22) and a 5818-bp deletion was detected in one of 7 families affected with mutations within these families, costly genetic screening is not yet convincingly warranted. Accurate relatively low-cost measurement (Table 2).

families with heterogenous pituitary adenoma predisposition were shown to harbor relatively large intragenic AIP deletions (S22) and a S818-bp deletion was detected in one of 7 families affected with acromegaly. Heterozygote germ-line AIP mutations were found in 47 subjects from 9 of 26 families with familial pituitary adenomas. Of these, 31 were diagnosed with gigantism or acromegaly (80).

Given the extremely low frequency of familial pituitary tumors, the small size of affected families, and the very low prevalence of mutations within these families, costly genetic screening is not yet convincingly warranted. Accurate relatively low-cost measurement of serum IGF1 levels is currently the most effective screening for affected patients with GH-secreting pituitary tumors.

### Acromegaly management

<table>
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<th>Mode</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>SRL</th>
<th>GHR antagonist</th>
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<tr>
<td>− GH &lt;2.5 μg/l</td>
<td>Transsphenoidal resection</td>
<td>Noninvasive</td>
<td>Monthly injection</td>
<td>Daily injection</td>
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<tr>
<td>− IGF1 normalized</td>
<td>Macroadenomas &lt;50%</td>
<td>− 50% in 10 years</td>
<td>−65%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Macroadenomas &gt;80%</td>
<td>&lt;30%</td>
<td>−65%</td>
<td>&gt;90%</td>
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<td>Rapid</td>
<td>Slow (yr)</td>
<td>Rapid</td>
<td>Rapid</td>
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<tr>
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<td>Ablated</td>
<td>Growth constrained or tumor shrinks −50%</td>
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<tr>
<td>Hypopituitarism</td>
<td>−10%</td>
<td>&gt;50%</td>
<td>None</td>
<td>Low IGF1</td>
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<td>Other</td>
<td>Tumor persistence or recurrence, diabetes insipidus, local complications</td>
<td>Local nerve damage, second brain tumor, visual and CNS disorders, cerebrovascular risk</td>
<td>Gallstones, nausea, diarrhea</td>
<td>Elevated liver enzymes</td>
</tr>
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</table>

The goals of acromegaly management include the following: (a) control of GH and IGF1 secretion and tumor growth; (b) relief of compressive effects on CNS and vascular structures, if present; (c) preservation or restoration of pituitary hormone reserve function; and (d) treatment of comorbidities and normalization of mortality rates. Table adapted from the New England journal of medicine (1).

### Acromegaly treatment

Several treatment options are currently available for acromegaly (Table 2).

#### Surgery

Resection of GH-secreting pituitary adenomas is technically challenging because of the anatomic inaccessibility of the pituitary and bony sellar confines and the proximity of vital brain and vascular structures. Functioning tumor microfoci often invade dural spaces, are not readily visible at surgery, and continue to secrete GH after tumor resection. GH-secreting tumors have a propensity to invade laterally into the cavernous sinus, precluding safe resection. Tumor-associated internal carotid artery tortuosity and microaneurysms also require surgical caution and alertness. Over 90% of resections are performed via an endonasal transsphenoidal approach, often with minimally invasive endoscopic techniques. Computerized image guidance and intraoperative MRI coupled with development of microinstrumentation and optics have resulted in safe, effective, and minimally traumatic procedures when performed by skilled and experienced neurosurgeons (S23). The goal of surgery is to balance maximal tumor mass resection with preservation of normal pituitary secretory function.

About 70% of patients harboring well-circumscribed GH-secreting microadenomas less than 10 mm in diameter achieve long-term biochemical control after surgery (81). Unfortunately, over 65% of GH-secreting adenomas are invasive macroadenomas at the time of diagnosis, and surgical outcomes for these patients are far less favorable, with an approximately 50% success rate reported from most experienced clinical centers (82, S24). Markers of surgical remission include biochemical control, normal pituitary and parasellar MRI visualization, and recurrence-free postoperative duration.Determinants of surgical remission include the experience of the surgeon in resecting these challenging adenomas (83), tumor size, and degree of invasiveness (82).

Transient side effects of surgery include local hemorrhage, CSF leak, diabetes insipidus, and rarely, local infection. Permanent side effects reported in less than 5% of patients include diabetes insipidus and pituitary hormone deficiency. Clearly, the major disadvantage of surgery is persistent postoperative GH hypersecretion.

#### Radiotherapy

Conventional external-beam radiotherapy is administered up to a maximum of 4000–5000 cGy in 180-cGy weekly doses spread over six weeks. Overall, about 50% of patients achieve biochemical remission (GH < 2 μg/l and normalized IGF1) after 10 years (84–86). In 77% of 884 irradiated patients, GH levels were attenuated to less than 2.5 μg/l by 20 years. The relatively long latency period required to achieve remission is a major disadvantage. Acquired residual pituitary damage is evident in approximately 50% of patients by 10 years. 27% exhibited TSH deficiency, 18% FSH/LH deficiency, and 15% ACTH deficiency (84). Rarely encountered local side effects include visual deficits, especially if the tumor abuts the optic chiasm, cerebral radionecrosis, cerebrovascular damage, and cognitive deficits. One percent of patients develop secondary intracranial tumors, with a latency up to 24 years (86). The reported incidence of these side effects is imprecise, due to absence of well-controlled studies and heterogeneity of radiation methodology.

#### Stereotactic radiosurgery

Using a 60Co Cobalt source, relatively narrow beams of high-dose, focused γ radiation are delivered with stereotactic precision to a small tumor, and the approach is particularly effective in tumors less than 3 cm in diameter and distant from the optic tract. Five
years after treatment, post-OGTT serum GH levels are less than 1 μg/l in approximately 50% of patients. Adenoma growth is arrested, tumor shrinkage observed in most patients, and subsequent pituitary failure occurs in approximately 25% of patients. Employing remission criteria of GH less than 2 μg/l and normalized IGF1, 17–35% of patients remitted after 24–36 months (87). In 1567 patients undergoing radiosurgery, half of whom had prior conventional radiotherapy, 13 patients developed cerebral radionecrosis (S29). Factors determining the risk of radiation-induced pituitary failure include prior surgery, the precision of stereotactic tumor target resolution, and pituitary stalk exposure to radiation.

**SSTR ligands**

The two forms of endogenous SRIF, comprising 14 or 28 aa, respectively, elicit cellular responses by five ubiquitously expressed SSTR receptor subtypes (88). SSTRs act to inhibit both endocrine and exocrine hormone secretions and, less compellingly, attenuate neuroendocrine tumor cell proliferation. SSTR signaling is mainly mediated by Gα subunits to inhibit adenylyl cyclase and reduce cAMP generation. Other actions include regulating phosphotyrosine phosphatase activity, K+ and Ca2+ channels, MAPK pathways, and Na+/H+ exchange activities (S26). SSTR2, SSTR5, and SSTR5 exhibit constitutive signaling to pituitary cells in a ligand-free environment (89). Thus, constitutive SSTR signaling may determine ambient pituitary hormone secretion.

The availability of SSTR subtype–selective ligands has enabled elucidation of specific SST functions (88). Thus, SSTR2, and to a lesser extent SSTR5, determine secretion of GH, thyroid-stimulating hormone, and ACTH (90). GH-secreting adenomas exhibit heterogenous SSTR expression (SSTR2 > SSTR5 > SSTR1 > SSTR5), while SSTR5 is notably undetectable in pituitary tumors (91, 92, S27). Several lines of evidence point to a cooperative functionality of SSTR2 and SSTR5 in suppressing GH and ACTH secretion (93–95). SSTR5 may also heterodimerize with SSTR2 to enhance availability of cell membrane receptors (96). Thus, analogs that activate both SSTR2 and SSTR5 receptors are more efficacious than respective monoselective SSTR analogs (91), and an SSTR antagonist reverses the GH-suppressive effects of biselective agonists or their respective combinations (95). Functional agonist-specific signaling may also determine cell responses of SSTR2, SSTR5, and SSTR5 (S26).

_Clinically available somatostatin receptor ligands_. Octreotide, a cyclic octapeptide, is administered by s.c. or i.v. injection. Octreotide binds avidly to SSTR2 with a Kd of approximately 0.4 μM, and to a lesser extent to SSTR5. The starting dose is 100–250 μg every 8 hours, and up to 1.5 mg/24 hours can be safely administered in patients with acromegaly (97, S28). Peak drug concentrations are attained within 40 minutes of injection, and the ligand exhibits a circulating half-life of up to 2 hours, as compared with approximately 2 minutes for endogenous SRIF. The long-acting release (LAR) intramuscular formulation is encapsulated within biodegradable D, L-lactic, and glycolic acid copolymer microspheres (88). The starting dose is usually 20 mg every 28 days, with safe maximal monthly doses up to approximately 60 mg or higher. Drug levels peak at 28 days, and plateau concentrations are sustained for approximately 14 days. When injected every 4 weeks, pharmacologically steady-state levels are achieved by the third injection. Lanreotide (BIM-23014) is incorporated into a biodegradable polymer for intramuscular injection (30 or 60 mg) every 7–14 days. With an approximately 5-day half-life, the molecule exhibits high SSTR2 affinity and also binds less avidly to SSTR5. The long-acting lanreotide Auto-gel (Somatuline Depot in the USA) is available as a water-soluble, prefilled 60-, 90-, or 120-mg syringe for deep s.c. injection. Pharmacologically effective therapeutic levels of approximately 1 ng/ml are maintained for 28 days and, with a 23- to 29-day half-life, steady-state is achieved after four monthly injections. Both octreotide and lanreotide activate the SSTR2 receptor with similar avidity, and head-to-head studies demonstrate nonsuperiority for safety and efficacy of either formulation (98).

Ubiquitous tissue distribution of SSTR receptor targets underlies the multitargeted therapeutic control elicited by somatostatin receptor ligands (SRLs) in acromegaly.

_Hypothalamus_. SRIF attenuates hypothalamic GHRH secretion and action by inhibiting GHRH induction of GH synthesis, secretion (99), and somatotroph cell replication (Figure 2) (S29). Ultra-
Pegvisomant is a 199-aa recombinant competitive GH antagonist mutated at Gly120Arg (Table 3). The drug abrogates GHR signaling and is pegylated to generate a stable molecule. PEG–hGH-G120K binds site 1 of the GHR and abrogates site 2 binding, preventing internal receptor conformational changes required for signaling. Eight additional mutations at site 1 enhance binding of the molecule to recombinant GHR-binding protein (GHBp) (120). Covalent pegylation delays renal clearance, prolonging the half-life to approximately 100 hours (121). The drug thus blocks IGF1 generation by specifically antagonizing peripheral GH action (122).

New SRL molecules
Pasireotide binds with high affinity to SSTR2, SSTR5, SSTR1, and SSTR3 (116). The molecule is currently being evaluated for treatment of octreotide-resistant GH-secreting adenomas (117). In addition to superior affinity for SSTR3 as compared with octreotide, pasireotide also acts to form unstable SSTR2 complexes with β arrestin, resulting in rapid receptor recycling (S37).

Clinical trials are ongoing using chimeric molecules activating both SSTR2 and D2 receptors and potently suppressing both GH and PRL. These hybrid molecules show comparable or superior GH suppression in hGH-secreting adenoma cells compared with octreotide treatment with monoselective D2 and SSTR2 analogs (118). Interestingly, a D2 antagonist also blocks GH suppression by the hybrid molecule, suggesting functional interaction between adenoma SSTR2 and the D2R ligand. Although D2R and SSTR2 heteroagomerize in stably transfected CHO-K1 cells (119), ligand-induced SSTR and D2R heterodimerization has not been shown in pituitary cells.

GHR antagonist
Pegvisomant is a 199-aa recombinant competitive GH antagonist mutated at Gly120Arg (Table 3). The drug abrogates GHR signaling and is pegylated to generate a stable molecule. PEG–hGH-G120K binds site 1 of the GHR and abrogates site 2 binding, preventing internal receptor conformational changes required for signaling. Eight additional mutations at site 1 enhance binding of the molecule to recombinant GH-binding protein (GHBp) (120). Covalent pegylation delays renal clearance, prolonging the half-life to approximately 100 hours (121). The drug thus blocks IGF1 generation by specifically antagonizing peripheral GH action (122).

<table>
<thead>
<tr>
<th>Table 4</th>
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<tr>
<td>Treatment outcomes</td>
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<tr>
<td><strong>Biochemical and clinical control:</strong></td>
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<tr>
<td>Basal GH &lt;1 μg/l after OGGT</td>
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<tr>
<td>Age-matched normal IGF1 level</td>
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<tr>
<td>Tumor stable</td>
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<tr>
<td><strong>Biochemical abnormality</strong></td>
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<tr>
<td>Basal GH &gt;0.4 μg/l</td>
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<td>Nadir GH &gt;1 μg/l after OGGT</td>
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<tr>
<td>Elevated IGF1 level</td>
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<tr>
<td>Tumor stable</td>
</tr>
<tr>
<td>No comorbidities</td>
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<tr>
<td><strong>Biochemically and clinically active:</strong></td>
</tr>
<tr>
<td>Basal GH &gt;0.4 μg/l</td>
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<tr>
<td>Nadir GH &gt;1 μg/l</td>
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<tr>
<td>Elevated IGF1 level</td>
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<tr>
<td>Tumor growing</td>
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<tr>
<td>Active comorbidities</td>
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Three outcomes each require a distinct treatment plan. Measurement of basal GH, GH after OGGT, and IGF1 levels determine degree of biochemical control. Clinical comorbidities require rigorous assessment and management to elicit optimal mortality outcomes. Based on recommendations published in ref. 8.
Using conventional assays, GH levels appear to increase after drug administration, likely due to attenuation of negative IGF1 feedback on somatotroph secretion.

**Efficacy.** In 177 patients receiving daily pegvisomant doses of 10–30 mg, 76% achieved normal IGF1 levels after 24 months (123), with improvement of symptoms, including soft-tissue swelling, perspiration, cardiomyopathy, and heart failure (S38). In 75% of patients resistant to maximal SRL doses, pegvisomant normalized IGF1 levels and improved cardiovascular risk markers and insulin sensitivity. Pegvisomant is additive with SRIF analogs in controlling IGF1 levels in patients resistant to SRIF alone. In 26 patients receiving monthly SRLs, addition of weekly pegvisomant injections normalized IGF1 levels in 95% of patients (S39). Thus, longer dosing intervals and combination therapy offer effective pharmacologic control for an overwhelming majority of patients.

**Side effects.** About 5% of patients receiving pegvisomant develop up to 3-fold or more increased hepatic transaminase levels (123), and this is invariably reversible. Other side effects include injection-site reactions and lipohypertrophy, likely reflecting local adipocyte GH insensitivity. As loss of IGF1 negative feedback on insulin sensitivity. Pegvisomant is additive with SRIF analogs in patients resistant to maximal SRL doses, pegvisomant normal with improvement of symptoms, including soft-tissue swelling, cardiomyopathy, and heart failure (S38). In 75% of patients resistant to maximal SRL doses, pegvisomant normalizes IGF1 levels and improved cardiovascular risk markers and insulin sensitivity. Pegvisomant is additive with SRIF analogs in controlling IGF1 levels in patients resistant to SRIF alone. In 26 patients receiving monthly SRLs, addition of weekly pegvisomant injections normalized IGF1 levels in 95% of patients (S39). Thus, longer dosing intervals and combination therapy offer effective pharmacologic control for an overwhelming majority of patients.

Novel GHR antagonists in development include small orally active molecules, recombinant GH antagonists, GHR antibodies, and antisense molecules directed against the GHR.

**Assessment of treatment outcomes**

Accurate biochemical assessment of surgical, medical, and radiotherapy treatment outcomes has been challenging due to inconsistency of reported assays (124) and lack of uniformity in defining treatment goals (8). Although tight medical control of GH improves clinical outcomes, a significant number of patients exhibit persistent GH hypersecretion. Cardiac failure and sleep apnea may partially resolve with disease control; however, intractable failure, arrhythmias, valvular dysfunction, and hypertension rarely resolve in patients achieving biochemical control, and aggressive ongoing treatment is required. Enhanced outcomes are achieved by increasing SRL doses, maximizing dose timing, and using combination treatments (Table 4).

Remarkable recent progress in understanding mechanisms underlying acromegaly pathogenesis has spawned novel peptide therapies to control the disease. New therapeutic molecules currently in trials will hopefully offer further safe benefit to those patients resistant to current therapeutic modes for this inexorably progressive disorder.

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