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.
Acromegaly is a disorder of disproportionate skeletal, tissue, and organ growth and occurs with an annual incidence of approximately five cases per one million individuals. Although the disorder has been recognized since antiquity, the pathology of pituitary “prospects” was first described by Andrea Verga in 1864 and the clinical features of acromegaly by Pierre Marie in 1886. Disease pathogenesis involves growth hormone (GH) hypersecretion by tumorous pituitary somatotroph cells, and the diagnosis is invariably preceded by about 10 years of active but unrecognized disease (1–3). Clinical presentation of acromegaly, in descending frequency 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 attenuation of 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.

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at 2.68 (1.73–4.15, 95% CI) in 419 patients, cerebrovascular SMRs were elevated. Incidence is not enhanced, with 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 hypertrophy of laryngeal and pharyngeal mucosal tissues lead to upper airway obstruction, hypoventilation, snoring, and sleep apnea in approximately 50% of patients (S6).

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### Sidebar 1

**Impact of long-term GH and IGF1 exposure**

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and joint</td>
<td>Acral changes, gigantism, prognathism, arthritis, osteopenia, vertebral fractures, carpal tunnel syndrome</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiomyopathy, hypertension, arrhythmias, valvulopathy, heart failure</td>
</tr>
<tr>
<td>Skin</td>
<td>Tags, excessive oily perspiration</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin resistance, diabetes</td>
</tr>
<tr>
<td>Lung</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Kidney</td>
<td>Antinatriuresis, fluid retention, increased aldosterone, renal failure</td>
</tr>
<tr>
<td>Gonads</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Goiter</td>
</tr>
<tr>
<td>Muscle</td>
<td>Proximal myopathy</td>
</tr>
<tr>
<td>Colon</td>
<td>Polyps</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Visceromegaly</td>
<td>Tongue, thyroid, salivary gland, liver, spleen, kidney, prostate</td>
</tr>
</tbody>
</table>

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 IGF1 concentrations plateau when GH levels are greater than 20 μg/l, results in maintaining normal SMRs. Failure to suppress GH levels are not uniformly dysregulated. GH exhibits 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 hypertrophy of laryngeal and pharyngeal mucosal tissues lead to upper airway obstruction, hypoventilation, snoring, and sleep apnea in approximately 50% of patients (S6).
GH secretion and action
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.
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> Igf1<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 STAT5 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 hypersomatotrophic 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

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**Figure 3**

GH action. GH binds to the GHR dimer, which undergoes internal rotation, resulting in JAK2 phosphorylation (P) and subsequent signal transduction. GH signaling is mediated by JAK2 phosphorylation of depicted signaling molecules or by JAK2-independent signaling including Src/ERK pathways (S42). Ligand binding to a preformed GHR dimer results in internal rotation and subsequent phosphorylation cascades. GH targets include IGF-I, c-fos, cell proliferation genes, glucose metabolism, and cytoskeletal proteins. GHR internalization and translocation (dotted lines) induce nuclear proliferation genes via importin α/β (Impα/Impβ) coactivator (CoAA) signaling. IGF-I may also block GHR internalization, acting in a feedback loop. The GHR antagonist, pegvisomant, blocks GH signaling; SRLs also attenuate GH binding and signaling (not shown).
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 cells activates CREB, a constitutively active cell lineage characterized by a distinct balance of GH secretion versus somatotroph trophic activity. 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).

Silent GH-secreting adenoma
GH-secreting extrapituitary tumor
Ectopic GH-cell adenoma

Cell-cycle disruption
Cyclin D1–dependent kinase 4 (CDK4) is required for postnatal somatotroph and lactotroph proliferation, and Cdk4-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 I (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
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Table 1
Genes that contribute to the molecular pathogenesis of GH-secreting adenomas

<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>
</tr>
</thead>
<tbody>
<tr>
<td>GNAS</td>
<td>Oncogene</td>
<td>Activating, imprinting</td>
<td>Nonfamilial, syndromic or sporadic</td>
<td>Relatively specific</td>
<td>52</td>
</tr>
<tr>
<td>CREB</td>
<td>Transcription factor</td>
<td>Constitutive phosphorylation</td>
<td>Sporadic</td>
<td>Relatively specific</td>
<td>54</td>
</tr>
<tr>
<td>AIP</td>
<td>Tumor suppressor</td>
<td>Inactivating</td>
<td>Familial, syndromic</td>
<td>Relatively specific</td>
<td>S46</td>
</tr>
<tr>
<td>MEN1</td>
<td>Tumor suppressor</td>
<td>Inactivating</td>
<td>Familial, syndromic</td>
<td>Not specific</td>
<td>S18</td>
</tr>
<tr>
<td>PRKAA1</td>
<td>Tumor suppressor</td>
<td>Inactivating</td>
<td>Familial, syndromic</td>
<td>Not specific</td>
<td>55</td>
</tr>
<tr>
<td>H-RAS (Harvey rat sarcoma virus oncogene)</td>
<td>Oncogene</td>
<td>Activating</td>
<td>Invasive or malignant</td>
<td>Not specific</td>
<td>S14</td>
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<tr>
<td>CCNB2</td>
<td>Cyclin</td>
<td>Induced by HMG A</td>
<td>Sporadic</td>
<td>Not specific</td>
<td>62</td>
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<tr>
<td>CCND1 (cyclin D1)</td>
<td>Oncogene</td>
<td>Overexpression</td>
<td>Sporadic</td>
<td>Not specific</td>
<td>56</td>
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<td>HMG12</td>
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<td>Sporadic</td>
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<td>61</td>
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<td>FGFR4 (FGF receptor 4)</td>
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<td>Alternative transcription</td>
<td>Sporadic</td>
<td>Not specific</td>
<td>S47</td>
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<tr>
<td>PTTG</td>
<td>Securin</td>
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<td>Sporadic</td>
<td>Not specific</td>
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<td>Rb</td>
<td>Tumor suppressor</td>
<td>Epigenetic silencing</td>
<td>Sporadic</td>
<td>Not specific</td>
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<td>CDKN1B</td>
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<td>Not specific</td>
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<td>GADD45H</td>
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<td>74</td>
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<tr>
<td>MEG3</td>
<td>Proliferation inhibitor</td>
<td>Epigenetic silencing</td>
<td>Sporadic</td>
<td>Not specific</td>
<td>75</td>
</tr>
</tbody>
</table>

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 1B [CDKN1B]) has been reported in a family exhibiting features of a recessive MEN1-like phenotype (60). The index patient harbored a GH-secreting pituitary adenoma and a parathyroid adenoma. This mutation may thus account, at least in part, for the subset of apparent MEN1 subjects who do not exhibit MEN1 mutations.

HMG12. Several lines of evidence support the role of high-mobility group AT-hook 2 (HMG12), a nuclear architectural protein, in murine and human pituitary tumorigenesis. Transgenic mice overexpressing HMG12 exhibit highly prevalent pituitary tumors induced by (a) displacing histone deacetylase from the pRB complex; (b) acetylation and liberation of E2F1; and (c) driving pituitary cells into S phase (61). HMG12 also induces pituitary tumor cyclin B2 (CCNB2) and directly induces CCNB2 promoter transcriptional activity. GH-secreting tumors coexpress high levels of CCNB2, HMG1A, and HMG1B (61, 62).

PTTG. Pituitary tumor–transforming protein (PTTG), isolated from pituitary tumor cells, facilitates the spindle checkpoint by acting as a securin to inhibit separase and enable faithful sister chromatid separation (63, 64). Ptg mediates in vitro transformation and in vivo tumorigenesis in mice, and PTTG overexpression induces aneuploidy with dysregulated G0/M checkpoint surveillance, resulting in abnormal mitosis and chromosomal instability (65). PTTG modulates p53, participating in DNA damage/repair and apoptosis (66–68). PTTG is abundantly expressed in pituitary adenomas (69) and correlates with tumor invasiveness and recurrence; it is induced early in estrogen-induced pituitary tumorigenesis. PTTG elicits pituitary tumorigenesis in a transgenic model of pituitary-directed Ptg overexpression, resulting in focal pituitary hyperplasia and functional adenoma formation (70).

Pituitary senescence. Pituitary carcinomas are exceedingly rare, and only isolated cases of pituitary metastases derived from GH-secreting adenomas have been reported. GH-secreting adenomas thus represent an intriguing model for studying triggers of malignant transformation. Cellular senescence mediated by oncogenic pathways is associated with the activation of inhibitors of cell-cycle progression (such as p53-mediated p21), which protect the cell from proproliferative signals and act as a buffer against malignant transformation (71). Premature senescence may account for the overwhelming predominance of benign versus malignant GH-secreting pituitary tumors, as more than 70% of GH-secreting tumors overexpress PTTG, leading to aneuploidy and induction of senescence markers including p21 and senescence-associated β-galactosidase (72). In contrast, p21 is weakly expressed in normal pituitary tissue and undetectable in pituitary carcinomas. Senescence features of GH-secreting pituitary adenomas likely constrain malignant transformation of these invariably benign adenomas. Slow replicative pituitary cell-cycle progression is distinct from the rapid cell cycle of skin or digestive tract regenerative tissues (56), consistent with observations that pituitary tumors rarely exhibit malignant phenotypes. Thus, accumulated pituitary DNA damage and senescence, hallmarks of GH-secreting adenomas, likely enable a benign phenotype.

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 macroadomas, 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. Ninety percent 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 local complications cerebrovascular risk. 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. 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.

Table 2
Acromegaly management

<table>
<thead>
<tr>
<th>Mode</th>
<th>Surgery Transsphenoidal resection</th>
<th>Radiotherapy Noninvasive</th>
<th>SRL Monthly injection</th>
<th>GHR antagonist Daily injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>− GH &lt;2.5 μg/l</td>
<td>Macroadenomas &lt;50% Microadenomas &gt;80%</td>
<td>− 50% in 10 years</td>
<td>−65%</td>
<td>0</td>
</tr>
<tr>
<td>− IGF1 normalized</td>
<td>Macroadenomas &lt;50% Microadenomas &gt;80%</td>
<td>&lt;30%</td>
<td>−65%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Onset Rapid</td>
<td>Tumor mass Debucked or resected</td>
<td>Slow (yr) Ablated</td>
<td>Rapid Growth constrained or tumor shrinks −50%</td>
<td>Rapid Unknown</td>
</tr>
</tbody>
</table>

Disadvantages
Hypopituitarism −10% Tumor persistence or recurrence, diabetes insipidus, local complications

Other Tumor mass >50% Local nerve damage, second brain tumor, visual and CNS disorders, cerebrovascular risk

None Gallstones, nausea, diarrhea

Low IGF1 Elevated liver enzymes

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).

families with heterogenous pituitary adenoma predisposition were shown to harbor relatively large intragenic AIP deletions (S22) and a 6818-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. One percent of patients develop secondary intracranial tumors, mostly cranial and pituitary hormone deficiency. Clearly, the major disadvantage of surgery is persistent postoperative GH hypersecretion.

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 paracellar 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. Determinants of surgical remission include the experience of the surgeon in resecting these challenging adenomas (83), tumor size, and degree of invasiveness (82).

Stereotactic radiosurgery
Using a 60Cobalt 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 (S25). Factors determining the risk of radiation-induced pituitary dysfunction 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 adenyl 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, SSTR3, 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 SSTR functions (88). Thus, SSTR2, and to a lesser extent SSTR5, determine secretion of GH, thyroid-stimulating hormone, and ACTH (90). GH-secreting adenosmas exhibit heterogenous SSTR expression (SSTR2 > SSTR5 > SSTR4 > SSTR3), while SSTR6 is notably undetectable in pituitary tumors (91, S27). Several lines of evidence point to a cooperative functionality of SSTR1 and SSTR2 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 SSTR3 (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, t-lactic, and glycolic acid copolymer microspheres (S88). 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 97–92% bioavailability, drug levels peak at 28 days, 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 97–92% bioavailability, drug levels peak at 28 days, 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 SSTR1 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-
dian rat GH rhythm (where ultradian rhythms are recurrent periods or cycles repeated throughout a 24-hour circadian day) is mediated by tonic SRIF secretion, antagonizing GHRH action (100). SRLs or cycles repeated throughout a 24-hour circadian day) is mediated in up to 80% of patients. Efficacy may be moderately improved by approximately 33% of patients could be defined as controlled. In therapy impact to manifest. Biochemical control by primary SRL

**Table 4**

<table>
<thead>
<tr>
<th>Observed outcomes</th>
<th>Treatment plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical and clinical control:</td>
<td></td>
</tr>
<tr>
<td>Nadir GH &lt;1 μg/l after OGTT</td>
<td>None or no change in current treatment</td>
</tr>
<tr>
<td>Age-matched normal IGF1 level</td>
<td>Evaluate pituitary axes</td>
</tr>
<tr>
<td>Tumor stable</td>
<td>Annual MRI</td>
</tr>
<tr>
<td>No comorbidities</td>
<td></td>
</tr>
<tr>
<td>Biochemical abnormality</td>
<td></td>
</tr>
<tr>
<td>Basal GH &gt;0.4 μg/l</td>
<td>Weigh treatment benefit vs. risks</td>
</tr>
<tr>
<td>Nadir GH &gt;1 μg/l after OGTT</td>
<td>Consider new treatment if being treated</td>
</tr>
<tr>
<td>Elevated IGF1 level</td>
<td>Evaluate pituitary axes</td>
</tr>
<tr>
<td>Tumor stable</td>
<td>MRI as indicated</td>
</tr>
<tr>
<td>No comorbidities</td>
<td></td>
</tr>
<tr>
<td>Biochemically and clinically active:</td>
<td></td>
</tr>
<tr>
<td>Basal GH &gt;0.4 μg/l</td>
<td>Actively treat or change treatment</td>
</tr>
<tr>
<td>Nadir GH &gt;1 μg/l</td>
<td>Evaluate pituitary function</td>
</tr>
<tr>
<td>Elevated IGF1 level</td>
<td>Assess cardiovascular, metabolic, and tumor comorbidity</td>
</tr>
<tr>
<td>Tumor growing</td>
<td>MRI as indicated</td>
</tr>
<tr>
<td>Active comorbidities</td>
<td>Treat</td>
</tr>
</tbody>
</table>

Three outcomes each require a distinct treatment plan. Measurement of basal GH, GH after OGTT, 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.

**New SRL molecules**

Pasireotide binds with high affinity to SSTR4, SSTR5, SSTR3, and SSTR2 (116). The molecule is currently being evaluated for treatment of octreotide-resistant GH-secreting adenomas (117). In addition to superior affinity for SSTR2 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 cotreatment 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 heterooligomerize in stably transfected CHO-K1 cells (119), ligand-induced SSTR2 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).
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 adipoocyte GH insensitivity. As loss of IGF1 negative feedback on the somatotroph could conceivably lead to persistent cell proliferation, possible continued pituitary tumor growth should be monitored by MRI, especially in those patients in whom SRLs have been discontinued. Although GH antibodies may form, pegvisomant tachyphylaxis is not observed. Pegvisomant-mediated lowering of IGF1 levels to below normal limits may result in features of adult GH deficiency.

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 measures for this inexorably progressive disorder.

Acknowledgments

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