AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF ACROMEGALY—2011 UPDATE

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **BEL** = "best evidence" level; **BMD** = bone mineral density; **CPAP** = continuous positive airway pressure; **CPG** = clinical practice guidelines; **CSF** = cerebrospinal fluid; **EL** = evidence level; **GH** = growth hormone; **GHRH** = growth hormone-releasing hormone; **IGF-I** = insulinlike growth factor-I; **IS** = international standard; **LAR** = long-acting release; **LFTs** = liver function tests; **MEN 1** = multiple endocrine neoplasia type 1; **MRI** = magnetic resonance imaging; **OGTT** = oral glucose tolerance test; **R** = recommendation; **RT** = radiation therapy; **SSAs** = somatostatin analogues

1. INTRODUCTION

Acromegaly is a disorder characterized by growth hormone (GH) hypersecretion, multisystem-associated morbidities, and increased mortality. In 2004, the American Association of Clinical Endocrinologists (AACE) published medical guidelines for the clinical management of acromegaly **(1 ["evidence level" or EL 4])**. Those guidelines summarized the then-current literature on the management of acromegaly and have been used for the clinical approach to patients with that disorder. Since publication of those guidelines, a number of studies have addressed further the biochemical diagnostic criteria for acromegaly and the appropriate biochemical assessment for therapeutic monitoring. In addition, the literature regarding medical therapy, in particular the use of combination medical therapy for acromegaly, has expanded. The goals of these guidelines are to update clinicians regarding all aspects in the current management of acromegaly and to use methods of current clinical practice guidelines (CPG) to support the recommendations.

2. GUIDELINES FOR CPG

Current guidelines in clinical medicine emphasize an evidence-based approach rather than simply expert opinion **(2 [EL 4], 3 [EL 4])**. Even though a purely evidence-based approach lacks applicability to all actual clinical scenarios, its incorporation in these CPG provides objectivity.

3. TRANSPARENCY: LEVELS OF SCIENTIFIC SUBSTANTIATION AND RECOMMENDATION GRADES

All clinical data that are incorporated in these CPG have been evaluated in terms of levels of scientific substantiation (evidence levels [EL]; Table 1). This evidence rating system has one minor modification in comparison with the original AACE protocol **(3 [EL 4])** in that level 2 (EL 2) prospective studies now may be randomized or nonrandomized to allow for well-designed cohort studies. This modification was incorporated because it is difficult to perform well-controlled, randomized clinical trials in surgery, unlike what physicians have been accustomed to in pharmaceutical trials. Another point worth mentioning is that when consensus statements are cited, even if based on a synthesis of evidence as in a published "evidence-based report," then an evidence level 4 [EL 4] is assigned. Clinical references have been assigned an evidence rating, which is provided in brackets at the end of the citation in both the Appendix and Reference sections. The "best evidence" level (BEL) corresponds to the best conclusive evidence found. The BEL accompanies the recommendation Grade in the Executive Summary and maps to the text in the Appendix section, where transparency is paramount.

Final recommendation grades incorporate EL ratings (Table 2), and in situations in which there is no clinical evidence, various subjective factors are considered: physician preferences, costs, risks, and regional availability of specific technologies and expertise. Hence, recommendation grades are generally based on strong BEL (Grade A; BEL 1), intermediate BEL (Grade B; BEL 2), weak BEL (Grade C; BEL 3), or subjective factors when there is no clinical evidence, inconclusive clinical evidence, or contradictory clinical evidence (Grade D; BEL 4). All recommendations result from a consensus among the AACE primary writers and influenced by input from reviewers. If subjective factors take priority over the BEL based on the expert opinion of the task force members, then this is described explicitly. Thus, some recommendations may be "upgraded" or "downgraded" according to explicitly stated subjective factors. Furthermore, the correctness of the recommendation Grades and EL is subject to review at several levels. In addition, recommendation Grades are assigned only if a specific action is recommended. The action may be ordering a particular diagnostic test, using a particular drug, performing a particular procedure, or adhering to a particular algorithm.

Shortcomings of this evidence-based method in this CPG are as follows: (*1*) relative paucity of strong (EL 1 and 2) scientific data, leaving the majority of recommendations based on weaker, extant EL 3 data and EL 4 consensus opinion; (*2*) potential subjectivity of the primary writers when weighing positive and negative, or epidemiologic versus experimental, data to arrive at an evidence-based recommendation grade or consensus opinion; (*3*) potential subjectivity of the primary writers when weighing subjective attributes, such as cost-effectiveness and risk-benefit ratios, to arrive at an evidence-based recommendation grade or consensus opinion; (*4*) potentially incomplete review of the literature by the primary writers despite extensive diligence; and (*5*) bias in the available publications, which originate predominantly from experienced

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Table 1
Levels of Scientific Substantiation in Evidence-Based Medicine[a]

Level	Description	Comments
1	Prospective, randomized, controlled trials—large	Data are derived from a substantial number of trials, with adequate power involving a substantial number of outcome data subjects Large meta-analyses using raw or pooled data or incorporating quality ratings Well-controlled trial at one or more centers Consistent pattern of findings in the population for which the recommendation is made (generalizable data) Compelling nonexperimental, clinically obvious evidence (for example, use of insulin in diabetic ketoacidosis); "all-or-none" indication
2	Prospective with or without randomization—limited body of outcome data	Few number of trials, small population sizes in trials Well-conducted single-arm prospective cohort study Meta-analyses are limited but are well conducted Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with 1 or more major or 3 or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in above necessitate an expert panel's synthesis of the literature and a consensus Experience-based Theory-driven

[a] Levels 1-3 represent a given level of scientific substantiation or proof. Level 4 represents unproven claims. It is the "best evidence" based on individual ratings of clinical reports that contributes to a final grade recommendation.

pituitary endocrinologists and neurosurgeons and therefore may not reflect the experience at large. These shortcomings have been addressed by the primary writers through an a priori method and multiple levels of review by a large number of experts.

4. EXECUTIVE SUMMARY OF RECOMMENDATIONS

*Each recommendation is labeled "**R**" in this summary.*

The following recommendations are evidence-based (Grades A, B, and C) or based on expert opinion because of a lack of conclusive clinical evidence (Grade D) (see Tables 1 and 2). Details regarding the mapping of clinical evidence ratings to these recommendation grades are provided in the Appendix (Discussion) section.

4.1. Presenting Features and Assessment of Comorbidities

- **R1.** Patients should be queried regarding and examined for typical signs and symptoms of acromegaly, including somatic enlargement, excessive sweating, jaw overgrowth, joint pains, cardiomyopathy, carpal tunnel syndrome, sleep apnea syndrome, osteoarthropathy,

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diabetes mellitus, menstrual irregularities in women and sexual dysfunction in men, headache, and visual field loss (attributable to optic chiasmal compression) and diplopia (due to cranial nerve palsy) **(Grade C; "best evidence" level or BEL 3)**.

- **R2.** Headaches and painful osteoarthritis are common in patients with acromegaly, and appropriate analgesic management should be considered. Definitive therapy for acromegaly is the most helpful intervention to diminish or prevent worsening of such comorbidities **(Grade C; BEL 3)**.
- **R3.** The finding of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of multiple endocrine neoplasia type 1 (MEN 1). Likewise, the presence of multiple family members with pituitary tumors should prompt investigation into a genetic predisposition to pituitary tumors, including MEN 1, familial acromegaly, or familial isolated pituitary adenomas **(Grade C; BEL 3)**.
- **R4.** Corrective orthopedic or plastic surgical procedures should be postponed until serum concentrations of GH and insulinlike growth factor-I (IGF-I) normalize **(Grade C; BEL 4)**.
- **R5.** Performance of a sleep study for evaluation of sleep apnea syndrome, which is frequently associated with acromegaly, should be considered **(Grade C; BEL 3)**.

Table 2
Grade-Recommendation Protocol
Adopted by the American Association of Clinical Endocrinologists[a]

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Action based on **strong** evidence Action can be used with other conventional therapy or as "**first-line" therapy**
B	No conclusive level 1 publication ≥1 conclusive level 2 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any Action based on **intermediate** evidence Can be recommended as "**second-line" therapy**
C	No conclusive level 1 or 2 publication ≥1 conclusive level 3 publications demonstrating benefit >> risk *or* No risk at all and no benefit at all	Action recommended for indications reflected by the published reports *If* the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; **"no objection" to recommending their use** *or* **"No objection" to continuing their use** Action based on **weak** evidence
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit	**Not recommended** Patient is advised to **discontinue use** Action not based on any evidence

[a] The final recommendation grades are determined by the primary writers by consensus based on (*1*) "best evidence" ratings and (*2*) subjective factors (see text section 3 on Transparency).

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- **R6.** Measurements should be performed for assessment of diabetes mellitus, and appropriate therapy should be administered if diabetes is diagnosed **(Grade A; BEL 3)**.
- **R7.** Blood pressure should be measured, and appropriate therapy should be administered if hypertension is present **(Grade A; BEL 3)**.
- **R8.** Cardiovascular risk status, including measurement of a lipid profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), should be assessed **(Grade C; BEL 3)**.
- **R9.** Cardiac evaluation including an electrocardiogram and an echocardiogram may be considered, particularly if the patient has signs or symptoms suggestive of cardiac involvement, such as arrhythmias and shortness of breath **(Grade C; BEL 4)**.
- **R10.** Patients with known cardiac disease should be considered for a formal cardiology consultation before a surgical procedure is performed **(Grade C; BEL 4)**.
- **R11.** Although there is insufficient evidence to state that patients with acromegaly have an increased risk of colon cancer, there is evidence of an increased prevalence of colon polyps. Therefore, colonoscopy is recommended **(Grade C; BEL 4).**

4.2. How Is the Diagnosis Made?

- **R12.** Acromegaly is a clinical syndrome that, depending on its stage of progression, may not manifest with clear diagnostic features. Clinicians should think of this diagnosis in patients with 2 or more of the following comorbidities: new-onset diabetes, diffuse arthralgias, new-onset or difficult-to-control hypertension, cardiac disease including biventricular hypertrophy and diastolic or systolic dysfunction, fatigue, headaches, carpal tunnel syndrome, sleep apnea syndrome, diaphoresis, loss of vision, colon polyps, and progressive jaw malocclusion **(Grade A; BEL 1)**.
- **R13.** A serum IGF-I level, if accompanied by a large number of results from age- and sex-matched normal subjects, is a good tool to assess integrated GH secretion and is excellent for diagnosis, monitoring, and especially screening. A random IGF-I value (a marker of integrated GH secretion) should be measured for diagnosis and for monitoring after a therapeutic intervention **(Grade B; BEL 2)**.
- **R14.** Serum GH assays are not standardized and should not be used interchangeably. Multiple samples, random GH, and GH after glucose administration have considerable variability and are useful, but they must be used in the clinical context **(Grade C; BEL 3)**.
- **R15.** A GH value <1 ng/mL after an oral glucose tolerance test (OGTT) (75 g of glucose orally followed by GH measurements every 30 minutes for 120 minutes) is considered normal **(Grade C; BEL 3)**.
- **R16.** This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing **(Grade D; BEL 4)**.
- **R17.** Currently, there are insufficient data to recommend additional testing with insulinlike growth factor-binding protein-3 measurement or use of a thyrotropin-releasing hormone test (which can lead to a paradoxical increase in GH levels in patients with acromegaly) **(Grade A; BEL 1)**.

4.3. Further Evaluation After Diagnosis of Acromegaly

- **R18.** Once a biochemical diagnosis of acromegaly has been made, a magnetic resonance imaging (MRI) scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases. A computed tomographic scan of the pituitary offers less anatomic detail and is not suggested, but it may be necessary if the patient has a contraindication for MRI, such as the presence of a cardiac pacemaker **(Grade B; BEL 1)**.
- **R19.** Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or if the patient has complaints of reduced peripheral vision **(Grade A; BEL 1)**.
- **R20.** Further biochemical testing should include a serum prolactin level (to evaluate for hyperprolactinemia) and assessment of anterior and posterior pituitary function (for potential hypopituitarism) **(Grade A; BEL 1)**.
- **R21.** All patients should undergo a comprehensive medical history, physical examination, and appropriate laboratory testing **(Grade C; BEL 4)**.

4.4. What Are the Therapeutic Options?

- **R22.** There should be a thorough discussion with the patient regarding the risks and benefits of surgical, medical, and radiotherapeutic options **(Grade C; BEL 4)**.
- **R23.** The pros and cons of pituitary surgery should be discussed, with emphasis on the value of surgical intervention as the primary therapy in most patients because it is the most effective option for inducing rapid and complete biochemical cure of acromegaly in patients who meet surgical criteria **(Grade C; BEL 3)**.
- **R24.** The pros and cons of primary medical therapy should be discussed, particularly in those patients who have a tumor that cannot be completely removed surgically, who have no compressive tumor effects, who are poor surgical candidates, or who have a preference for medical management **(Grade C; BEL 3)**.
- **R25.** The pros and cons of radiation therapy (RT) should be discussed, with an emphasis on its use as adjuvant

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treatment, the potential efficacy, and the long-term side effects **(Grade C; BEL 3)**.
- **R26.** Financial counseling should be provided regarding the various therapeutic options **(Grade C; BEL 4)**.

4.5. What Are the Goals of Therapy?
- **R27.** There should be a thorough discussion with the patient regarding the goals of therapy, which include normalization of biochemical variables, reversal of mass effects of the tumor, improvement in signs, symptoms, and comorbidities of the disease, and minimization of long-term mortality risk **(Grade B; BEL 3)**.
- **R28.** Treatment goals include assessment and management of the comorbidities, such as aggressive control of lipid abnormalities, type 2 diabetes mellitus, obstructive sleep apnea, arthritic complications, and cardiac dysfunction as well as surveillance for colon polyps **(Grade C; BEL 2)**.

4.6. Therapeutic Options
- **R29.** There is sufficient evidence for recommending pituitary surgery as the primary treatment in patients with microadenomas and in patients with macroadenomas that are associated with local mass effects or are enclosed and potentially curable surgically because surgery can lead to durable control of the tumor mass and associated biochemical effects **(Grade B; BEL 2)**.
- **R30.** In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention **(Grade B; BEL 2)**.
- **R31.** A role of primary medical therapy, especially with somatostatin analogues (SSAs), has been suggested in patients with macroadenomas who have no local mass effects and have a minimal chance of surgical cure (because of extrasellar extension of the tumor, especially into the cavernous sinus) or in patients who are poor surgical candidates or who prefer medical treatment **(Grade B; BEL 3)**.
- **R32.** RT is recommended as adjuvant treatment in patients with active disease despite surgery and medical therapy or in patients who prefer RT in light of the cost of long-term medical treatment **(Grade C; BEL 3)**.

4.7. Surgery
- **R33.** There is sufficient evidence linking surgical experience (number of pituitary surgical procedures performed) with surgical cure rate as well as morbidity and mortality **(Grade A; BEL 2)**.
- **R34.** There is sufficient evidence to recommend surgery as the primary therapy for all patients with microadenomas **(Grade A; BEL 2)**.
- **R35.** Surgery is indicated for all patients with a macroadenoma and mass effects, including visual loss **(Grade A; BEL 1)**.
- **R36.** There is sufficient evidence to recommend surgery as the primary therapy for all patients who have macroadenomas with a high predicted chance for cure (that is, no invasion of local structures such as the cavernous sinus) **(Grade A; BEL 2)**.
- **R37.** In the patients with macroadenomas that are not likely to be cured with surgery, and without compressive effects on local structures, surgery may be recommended for debulking to improve the response to subsequent medical therapy or RT. There should be a thorough discussion with the patient regarding the use of primary medical therapy as an alternative in this setting **(Grade B; BEL 3)**.

4.7.1. How Should Patients Be Prepared for Surgery?
- **R38.** The preoperative evaluation must include a comprehensive medical history, physical examination, and appropriate laboratory testing **(Grade C; BEL 4)**.
- **R39.** Laboratory testing should include an evaluation for hypopituitarism, and the hormone axes, particularly adrenal and thyroid, should be replaced as indicated **(Grade C; BEL 4)**.
- **R40.** A role for medical therapy with SSAs preoperatively has been suggested to reduce surgical risk, although further studies are necessary to support general use **(Grade C; BEL 4)**.
- **R41.** A role for presurgical medical therapy with SSAs to improve biochemical outcomes with surgery has been suggested, although further studies are needed to support general use **(Grade B; BEL 2)**.
- **R42.** Consideration should be given to careful perioperative airway management because patients with acromegaly often have a compromised airway **(Grade C; BEL 3)**.
- **R43.** Cardiovascular risk assessment should be performed preoperatively in accordance with standard protocol. Routine echocardiography is not recommended preoperatively, although a role for echocardiography may be suggested, depending on attributable signs and symptoms **(Grade C; BEL 4)**.

4.7.2. Management After Surgery
- **R44.** Postoperative management should include monitoring for electrolyte abnormalities, including diabetes insipidus and syndrome of inappropriate secretion of antidiuretic hormone, for up to 2 weeks **(Grade C; BEL 3)**.
- **R45.** In the postoperative setting, the presence of diuresis may reflect obligate natriuresis after a rapid reduction in GH and IGF-I values **(Grade C; BEL 3)**.
- **R46.** Adrenal function should be monitored and replaced as appropriate **(Grade C; BEL 3)**.

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- **R47.** It is recommended that a fasting GH level be measured early postoperatively; a postoperative day 1 GH level less than 2 ng/mL correlates with long-term remission. An OGTT can be performed 1 to 2 weeks after surgery for further diagnostic confirmation, although this procedure is not generally performed at this point **(Grade C; BEL 2)**.
- **R48.** A serum IGF-I level should be remeasured at 12 weeks; a normal IGF-I value is consistent with surgical remission **(Grade C; BEL 2)**.
- **R49.** A repeated OGTT may be performed at 12 weeks; a GH value <1 ng/mL is consistent with surgical remission **(Grade C; BEL 2)**.
- **R50.** This panel suggests that the serum GH nadir after glucose administration be lowered to 0.4 ng/mL to increase the sensitivity of testing **(Grade D; BEL 4)**.
- **R51.** Repeated imaging with an MRI scan should be performed at 12 weeks after surgery to assess for residual tumor and establish a postoperative baseline **(Grade C; BEL 3)**.
- **R52.** Repeated pituitary hormone testing, including the thyroid and gonadal axes, should be performed at 6 to 12 weeks postoperatively in order to assess pituitary function and the need for hormone replacement therapy **(Grade C; BEL 3)**.
- **R53.** If the repeated serum IGF-I value is reduced from baseline but still elevated at 12 weeks, repeated testing in another 9 to 12 weeks should be considered to determine whether there may be delayed biochemical normalization, before proceeding with potential surgical reexploration, medical therapy, or RT **(Grade C; BEL 3)**.
- **R54.** For patients who use a nasal continuous positive airway pressure (CPAP) device for management of sleep apnea syndrome, the CPAP device is generally withheld postoperatively for a temporary period, as recommended by the neurosurgeon and sleep specialist **(Grade C; BEL 4)**.

4.8. Medical Therapy

- **R55.** Medical therapy is appropriate as adjuvant treatment in patients with residual disease after surgery **(Grade A; BEL 2)**.
- **R56.** There are 3 classes of medical therapy: dopamine agonists, SSAs, and a GH receptor antagonist **(Grade A; BEL 1)**.
- **R57.** There should be a thorough discussion with the patient regarding the risks and benefits of each medication. This discussion should include financial counseling, and the physician should be able to provide clinical material for information on the medications as well as their costs **(Grade A; BEL 2)**.

4.8.1. Dopamine Agonists

- **R58.** There are 2 dopamine agonists, cabergoline and bromocriptine, available for patients in the United States **(Grade A; BEL 1)**.
- **R59.** Cabergoline may be more effective and better tolerated than bromocriptine **(Grade C; BEL 3)**.
- **R60.** Dopamine agonists may be considered as first-line medical therapy because these agents are orally administered and relatively inexpensive in comparison with the other medical therapy options **(Grade C; BEL 3)**.
- **R61.** Dopamine agonists may be considered particularly in patients with mild biochemical activity, such as in the setting of modestly elevated serum IGF-I levels in the absence or concomitant presence of SSA therapy **(Grade B; BEL 3)**.
- **R62.** The response of GH to cabergoline is not clearly demonstrated to be related to the presence or absence of hyperprolactinemia **(Grade C; BEL 3)**.
- **R63.** Patients should be counseled about the potential side effects of dopamine agonists, including gastrointestinal upset, orthostatic hypotension, headache, and nasal congestion **(Grade A; BEL 1)**.
- **R64.** Patients should be counseled that cabergoline, when administered in high doses to patients with Parkinson disease, has been associated with echocardiographically evident valve abnormalities. The clinical effect of this finding in patients with acromegaly is unclear **(Grade C; BEL 3)**.
- **R65.** Repeated GH, prolactin, and IGF-I levels should be determined 4 to 6 weeks after each dose change for a dopamine agonist **(Grade B; BEL 3)**.

4.8.2. Somatostatin Analogues

- **R66.** There are 2 long-acting, depot SSAs available: octreotide LAR (long-acting release, administered as an intramuscular injection) and lanreotide Autogel (administered as a deep subcutaneous depot injection) **(Grade A; BEL 1)**.
- **R67.** A 2-week trial of octreotide is recommended before institution of octreotide LAR therapy (based on the US package insert), although this panel feels that a single test dose to rule out a severe reaction is sufficient **(Grade D; BEL 3)**.
- **R68.** SSAs are effective in normalizing IGF-I and GH levels in approximately 55% of patients. The clinical and biochemical responses to SSAs are inversely related to tumor size and degree of GH hypersecretion. Octreotide LAR and lanreotide Autogel have similar efficacy profiles **(Grade B; BEL 2)**.
- **R69.** SSAs reduce pituitary tumor size modestly in approximately 25% to 70% of patients, depending on whether they are used as adjuvant or de novo therapy,

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respectively. Patients should be counseled that, although tumor shrinkage can occur, SSAs should not be relied on for decompression of local structures in the presence of mass effects **(Grade B; BEL 3)**.

- **R70.** Patients should be counseled about the potential side effects of SSAs, including gastrointestinal upset, malabsorption, constipation, gallbladder disease, hair loss, and bradycardia. It is not recommended that patients have close radiologic imaging surveillance for symptomatic gallbladder disease, but patients should be queried about potential symptoms during follow-up appointments. Octreotide LAR and lanreotide Autogel have similar side effect profiles **(Grade B; BEL 2)**.
- **R71.** In patients with an inadequate response to SSAs, the addition of cabergoline or pegvisomant may be effective for further lowering of GH or IGF-I levels (or both) **(Grade B; BEL 3)**.
- **R72.** The short-acting subcutaneously administered SSA octreotide is effective and may be used, especially in the setting of financial constraints or the need for rapid onset of action **(Grade C; BEL 3)**.

4.8.3. GH Receptor Antagonist

- **R73.** Pegvisomant is a GH receptor antagonist that competes with endogenous GH for its receptor and prevents functional dimerization and signal transduction by the GH receptor **(Grade A; BEL 2)**.
- **R74.** Pegvisomant is highly effective in normalizing IGF-I values (>90%), including patients who are partially or completely resistant to other medical therapies **(Grade A; BEL 2)**.
- **R75.** Pegvisomant is effective at improving glucose homeostasis in patients with associated diabetes mellitus **(Grade C; BEL 2)**.
- **R76.** Pegvisomant is often used as a medical therapy in patients with inadequate response to or tolerability of SSAs **(Grade A; BEL 2)**.
- **R77.** Patients should be counseled that pegvisomant is administered as a subcutaneous injection daily, although alternative protocols, including twice-a-week or once-a-week administration, have been suggested in specific patients **(Grade B; BEL 3)**.
- **R78.** Patients should be counseled about the side effects of pegvisomant, including flulike illness, allergic reactions, and increase in liver enzymes. Therefore, serial monitoring of results of liver function tests (LFTs) is suggested at monthly intervals for the first 6 months, quarterly for the next 6 months, and then biannually. Patients with elevated baseline results of LFTs need more frequent monitoring **(Grade B; BEL 3)**.
- **R79.** Patients should be counseled that tumor enlargement has been infrequently associated with use of pegvisomant. Therefore, serial monitoring with pituitary MRI scans is suggested **(Grade C; BEL 3)**.
- **R80.** Pegvisomant therapy may be effective regardless of baseline tumor size or degree of GH hypersecretion **(Grade B; BEL 2)**.
- **R81.** Because endogenous GH levels increase with pegvisomant administration and pegvisomant may be cross-measured in GH assays, serum GH levels are not specific and should not be monitored in patients receiving pegvisomant **(Grade A; BEL 2)**.

4.8.4. Combination Therapy

- **R82.** In patients with a partial response to SSA therapy, the addition of cabergoline may be useful for further lowering of GH or IGF-I levels **(Grade C; BEL 3)**.
- **R83.** In patients with a partial response to SSA therapy, the addition of daily, weekly, or twice weekly pegvisomant may be beneficial **(Grade C; BEL 3)**.

4.9. Radiation Therapy

- **R84.** Pituitary RT in acromegaly should be considered an adjunctive treatment in patients not fully responding to surgical or medical treatments (or both) **(Grade C; BEL 4)**.
- **R85.** Because RT may lead to normalization of biochemical indices of acromegaly, this modality may be used in an effort to limit lifelong use of GH and IGF-I suppressive medical therapy **(Grade C; BEL 4)**.
- **R86.** Patients may be counseled about the options of RT, including conventional fractionated RT versus stereotactic radiosurgery, which can be administered by means of Gamma Knife, proton beam, CyberKnife, or a linear accelerator **(Grade C; BEL 4)**.
- **R87.** Because of the technical advances and convenience, stereotactic radiosurgery may be considered the preferred mode of RT over conventional RT in patients with acromegaly, unless the technique is not available, there is substantial residual tumor burden, or the tumor is too close (<5 mm) to the optic chiasm **(Grade C; BEL 4)**.
- **R88.** Patients should be counseled that the benefits of RT on GH hypersecretion may be delayed, up to years, and medical therapy will be needed until the radiation effect is sustained. Intermittent withdrawal of medical therapy will be necessary in order to assess GH secretion **(Grade C; BEL 4)**.
- **R89.** Patients should be counseled that serial pituitary function follow-up is necessary to evaluate for hypopituitarism. This follow-up includes assessment of adrenal, thyroid, and gonadal function, testing that should be performed at least annually **(Grade B; BEL 2)**.

4.10. Acromegaly and Pregnancy

- **R90.** In a pregnant patient with acromegaly, biochemical monitoring with measurement of GH or IGF-I levels is of limited use **(Grade B; BEL 3)**.

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- **R91.** Serial visual field monitoring should be performed during pregnancy, at intervals dictated by the tumor size and location before pregnancy **(Grade C; BEL 3)**.
- **R92.** MRI scans should not be routinely performed during pregnancy unless there is evidence of new or worsening visual field compromise. If performed, the MRI scan should be done without administration of a contrast agent **(Grade A; BEL 1)**.
- **R93.** In pregnant patients who have tumor growth with chiasmal compression and visual field compromise, transsphenoidal surgery should be considered **(Grade A; BEL 1)**.
- **R94.** Medical therapy with a long-acting SSA should be discontinued 2 to 3 months before a planned pregnancy, depending on the clinical status of the patient **(Grade D; BEL 3)**.
- **R95.** If the patient conceives while receiving SSA therapy, she should have a discussion with her physician about discontinuing the SSA, with further monitoring as described in **R89 (Grade D; BEL 3)**.
- **R96.** Institution of medical therapy should be considered during pregnancy if there is suggestive evidence of worsening disease **(Grade D; BEL 3)**.

4.11. Approach to Gigantism in Children and Adolescents

- **R97.** Gigantism is a rare clinical syndrome that is associated with dramatic linear growth acceleration **(Grade A; BEL 1)**.
- **R98.** A random serum IGF-I value, normalized for age and sex, should be measured for diagnosis; an elevated IGF-I value is consistent with the diagnosis **(Grade B; BEL 2)**.
- **R99.** Once a biochemical diagnosis of gigantism has been made, an MRI scan of the pituitary gland (the physician should order a dedicated pituitary MRI with and without use of contrast medium) should be performed because a pituitary GH-secreting adenoma is the cause in most cases **(Grade B; BEL 1)**.
- **R100.** Visual field testing should be performed if there is optic chiasmal compression noted on the MRI or the patient has complaints of reduced peripheral vision **(Grade A; BEL 1)**.
- **R101.** The goals of therapy are to control the biochemical variables and reduce tumor volume, as in acromegaly. Another goal of therapy is to control the accelerated linear growth **(Grade A; BEL 1)**.
- **R102.** Transsphenoidal surgery is the primary treatment, where possible **(Grade C; BEL 3)**.
- **R103.** Use of medical therapy as an adjunctive treatment after incomplete surgery is similar to that with adults **(Grade C; BEL 4)**.
- **R104.** In patients with gigantism, RT is often not used **(Grade C; BEL 3)**.

4.12. How Should Medical Comorbidities Be Monitored?

- **R105.** Any corrective surgical procedure, such as maxillofacial correction of dental malocclusion, should be postponed until GH and IGF-I levels normalize for at least 6 months **(Grade D; BEL 4)**.
- **R106.** Patients should be monitored for signs and symptoms of carpal tunnel syndrome, and directed care, including a release procedure, should be considered for persistent or progressive symptoms **(Grade C; BEL 3)**.
- **R107.** Arthropathy should be managed aggressively with physical therapy, systemic or intra-articular anti-inflammatory medications, and consideration of joint replacement, when appropriate **(Grade C; BEL 3)**.
- **R108.** The presence of hypercalcemia should prompt an evaluation for primary hyperparathyroidism and, if present, consideration of MEN 1 **(Grade B; BEL 3)**.
- **R109.** Bone densitometry should be performed in patients with a history of hypogonadism or fracture. If osteoporosis is present and does not improve with correction of hypogonadism, hypercalcemia, GH and IGF-I excess, or any combination of these factors, antiresorptive therapy should be considered **(Grade C; BEL 3)**.
- **R110.** Formal overnight polysomnography or home overnight oximetry (as a screening test for sleep apnea) followed by formal overnight polysomnography should be performed if symptoms are suggestive in patients with either active or biochemically controlled acromegaly **(Grade C; BEL 3)**.
- **R111.** Standard therapy should be used for patients with left ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease, or ischemic heart disease **(Grade C; BEL 4)**.
- **R112.** Routine echocardiography should be considered in patients who have evidence of left ventricular hypertrophy by electrocardiography or who are symptomatic with shortness of breath **(Grade C; BEL 3)**.
- **R113.** Blood pressure should be monitored because hypertension may persist despite biochemical control of acromegaly **(Grade C; BEL 3)**.
- **R114.** All patients should be monitored for evidence of glucose intolerance or overt type 2 diabetes mellitus, and corrective measures should be taken as needed **(Grade C; BEL 3)**.
- **R115.** In patients in whom SSA therapy worsens glucose control, reduction of the SSA dose, addition of or substitution with a GH receptor antagonist, or diabetes management with glucose-lowering agents should be considered **(Grade C; BEL 3)**.
- **R116.** Goals for high-risk cardiac patients should be adopted, including blood pressure less than 130/80 mm Hg and hemoglobin A_{1c} less than 6.5% **(Grade C; BEL 2)**.

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- **R117.** Colonoscopy should be performed after diagnosis of acromegaly. Patients with polyps at screening or with persistently elevated IGF-I levels should undergo follow-up colonoscopy. Other patients should undergo follow-up colonoscopy, with a schedule based on current general recommendations **(Grade C; BEL 4)**.
- **R118.** Standard screening guidelines for other cancers should be rigorously followed **(Grade B; BEL 4)**.
- **R119.** In patients with active acromegaly and those in remission, attention to quality-of-life issues is recommended **(Grade C; BEL 4)**.

APPENDIX: DISCUSSION OF THE CLINICAL EVIDENCE

5. CLINICAL SIGNS AND SYMPTOMS: WHY TREAT?

5.1. Epidemiology

Acromegaly is an uncommon disorder, with an estimated prevalence of 40 to 125 per million and an incidence of 3 to 4 new cases per million **(4 [EL 3])**, although a more recent study in Belgium suggested a higher incidence of approximately 13 cases per 100,000 **(5 [EL 3])**. In a recent study that involved measurement of serum IGF-I levels in a primary care population, a higher incidence of 1,034 per million patients was demonstrated **(6 [EL 2])**. This study suggests that acromegaly may often be underdiagnosed **(Grade C)**.

5.2. Initial Clinical Presentation

Acromegaly is diagnosed in approximately equal numbers of men and women, and the mean age at diagnosis for both sexes is in the early to mid-40s **(7 [EL 3], 8 [EL 4], 9 [EL 3], 10 [EL 3])**. Only a fraction of patients with acromegaly are actually diagnosed after presentation with a chief complaint attributable to acral overgrowth (Table 3). For example, amenorrhea may be the most common presenting complaint in women **(9 [EL 3])**. In a review of 164 patients with acromegaly, only 58 (35%) presented because of a change in features **(4 [EL 3])**. In that study, 56 patients (34%) presented because of disturbances associated with acromegaly, including visual field defects, carpal tunnel syndrome, and headaches. The remaining 50 patients had no complaints related directly to the acromegaly and were diagnosed when seeking medical attention for an unrelated complaint. Therefore, it is relatively uncommon that patients present with complaints attributable to the more classic signs of acromegaly, including bony or soft tissue overgrowth.

Because the features of acromegaly progress insidiously, the diagnosis is often delayed for approximately 7 to 10 years after the estimated onset of symptoms **(11 [EL 3])**. These findings emphasize the need to educate primary care physicians and other medical groups, including orthopedists, otorhinolaryngologists, rheumatologists, cardiologists, and dentists, about the constellation of signs and symptoms of acromegaly in order to facilitate earlier detection of the disease, with the hope of minimizing the long-term consequences of this debilitating disorder.

5.3. Clinical Consequences Related to Tumor Mass

The majority of pituitary somatotroph tumors are macroadenomas (>10 mm) at the time of diagnosis, presumably reflecting the usual delay in diagnosis. In a recent report from a Spanish Acromegaly Registry, macroadenomas were detected in 77% of the 1,196 subjects **(12 [EL 3])**. These data highlight the concern that somatotroph adenomas, because of their size and extension at the time of diagnosis, may cause major signs and symptoms due to local mass effect.

Headache is a common presenting feature and is reported in approximately 55% of patients. Headaches are generally thought to be due to tumor growth with suprasellar extension and stretching of the dura mater, cavernous sinus invasion with trigeminal nerve irritation, or factors associated with GH hypersecretion as well **(7 [EL 3], 8 [EL 4], 13 [EL 4], 14 [EL 4])**. Although recent studies have suggested that headache may be unrelated to tumor size or local invasion, tumor size has an important role in headaches in these patients **(13 [EL 4], 15 [EL 3])**. Pituitary tumor apoplexy should be considered in patients with acute onset of headache, should be visible on the precontrast MRI scan, and has been described in approximately 3.5% of patients with acromegaly **(9 [EL 3])**.

Table 3
Presenting Clinical Features of Acromegaly

Feature	Percent
Acral enlargement	86
Maxillofacial changes	74
Excessive sweating	48
Arthralgias	46
Headache	40
Hypogonadal symptoms	38
Visual deficit	26
Fatigue	26
Weight gain	18
Galactorrhea	9

Adapted from Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. *J Clin Endocrinol Metab*. 2000;85:168-174.

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Visual field defects due to mass effects on the optic chiasm are a particular concern in the setting of suprasellar extension by the tumor **(16 [EL 3], 17 [EL 3])**. In a series of 256 patients who underwent assessment with Goldmann perimetry, a visual field defect that could be attributed to the pituitary adenoma was observed in 18% at the time of diagnosis and was bilateral in 61.3% **(18 [EL 3])**. In light of these data, visual field testing should be performed in all patients with a macroadenoma and suprasellar extension and compression of the optic chiasm.

5.4. Endocrinopathy

Hypopituitarism attributable to compression of the normal pituitary gland, particularly in the setting of a macroadenoma, is prevalent as well in patients with acromegaly. Adrenal insufficiency and central hypothyroidism have been described in up to 20% and 9% of cases, respectively **(8 [EL 4], 19-22 [EL 3])**. Hypogonadism can be detected in up to 70% of women of childbearing age and may be accompanied by hyperprolactinemia in up to 45% of patients **(16 [EL 3], 23 [EL 3])**. The source of the hyperprolactinemia is often the tumor itself, and up to 50% of somatotroph tumors cosecrete prolactin, versus hyperprolactinemia from the normal lactotroph cells due to stalk compression from the tumor itself **(24 [EL 4], 25 [EL 4])**. Menstrual irregularities, often associated with hirsutism, are common in acromegaly and are due to a combination of hyperprolactinemia, androgen excess, and, less often, compressive hypogonadotropic hypogonadism from the tumor itself **(26 [EL 3])**. Testosterone deficiency may be present in up 50% of men, attributable to both hyperprolactinemia and hypogonadotropic hypogonadism **(16 [EL 3])**. Symptoms of sexual dysfunction are common and should be assessed in men with acromegaly **(Grade B)**.

Thyroid gland enlargement frequently occurs in patients with acromegaly, particularly due to multinodular goiter. Thyroid nodules were detected in 73% of patients by ultrasonography in one study and in 87% of patients by palpation in another study **(27 [EL 3], 28 [EL 3])**. Despite the high prevalence of thyroid nodules, no convincing data indicate an increased risk of thyroid cancer in patients with acromegaly above that expected in the general population with thyroid nodules **(29 [EL 4])**. Therefore, thyroid nodules in patients with acromegaly should be monitored according to standard guidelines. Most patients have normal thyroid function, although the presence of hyperthyroidism ranges from 4% to 14% **(30 [EL 3])**. In a patient with elevated serum thyroxine levels, the presence of an inappropriately normal or elevated serum thyrotropin level may signify cosecretion of thyrotropin by the pituitary adenoma **(31 [EL 3], 32 [EL 3])**.

5.5. Clinical Consequences of GH Hypersecretion

Chronic hypersecretion of GH and IGF-I can lead to a myriad of soft tissue and bone overgrowth manifestations, medical comorbidities, and accompanying clinical features.

5.5.1. Somatic Overgrowth

Soft tissue overgrowth is a universal manifestation of acromegaly. Hand volume and heel pad thickness are often increased, and patients frequently describe increased ring and glove sizes as well as shoe width. Thickening of the skin, due to edema and deposition in the papillary and upper reticular dermis of hydrophilic glycosaminoglycans, hyaluronic acid, and chondroitin 4, is common in acromegaly **(8 [EL 4], 33 [EL 3])**. Excessive perspiration and seborrhea occur in 60% to 80% of patients **(34 [EL 3])**. Somatic enlargement, particularly of the hands, feet, and skull (including frontal bossing), is a classic finding, and these changes can be disfiguring. The dental changes, including maxillary and mandibular widening with separation of the teeth, mandibular overgrowth, jaw malocclusion, and overbite, may be disabling for patients **(35 [EL 3])**. Arthropathy develops early in the course of acromegaly and, with progression, resembles active osteoarthritis and often results in substantial disability **(36 [EL 3], 37 [EL 4], 38 [EL 3])**. Joint pains may be present in up to three-quarters of the patients **(39 [EL 3])**.

Bony overgrowth can lead to an increase in both cortical and trabecular bone mineral density (BMD), although trabecular BMD is more consistently influenced by gonadal status because patients with acromegaly who have hypogonadism may have a reduction in trabecular BMD **(40-43 [EL 3])**. The effect of bony changes on vertebral fractures is unclear, but a recent study of 40 male patients with acromegaly, including 15 with active disease, showed that the prevalence of radiographic vertebral fractures was significantly higher in patients with acromegaly than in control subjects (58% versus 23%, respectively), although it is possible that hypogonadism influenced these findings **(40 [EL 3], 44 [EL 3])**. Hypercalcemia, hypercalciuria, and hyperphosphatemia can uncommonly occur with GH excess and are due to altered vitamin D metabolism **(45 [EL 3])**. In addition, the presence of hypercalcemia should trigger consideration of measurement of the parathyroid hormone concentration because the presence of primary hyperparathyroidism suggests that an evaluation for MEN 1 is indicated **(Grade C)**.

5.5.2. Neurologic Disorders

An increased incidence of cerebral aneurysms in patients with pituitary adenomas, particularly in

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acromegaly, has been described largely in the form of case reports **(46 [EL 3])**. These aneurysms are often diagnosed incidentally during the initial evaluation of pituitary adenomas, but they may manifest with hemorrhage as a result of rupture **(47 [EL 3])**.

Symptomatic carpal tunnel syndrome, due to an increase in median nerve edema within the carpal tunnel, may be described in up to 64% of patients and is a frequent source of disability and discomfort **(48 [EL 3], 49 [EL 3])**.

5.5.3. Respiratory Conditions

Sleep apnea syndrome is present in approximately 70% of patients with acromegaly and is present in more than 90% of patients with acromegaly who snore **(50 [EL 3])**. The cause of sleep apnea syndrome is primarily obstruction due to pharyngeal thickening and macroglossia, but a central component has been described as well. Sleep apnea is a common cause of daytime somnolence in patients and must be managed aggressively **(Grade C)**. Patients with acromegaly and sleep apnea may have sinus arrhythmias and sometimes life-threatening arrhythmias **(51 [EL 3])**.

Upper airway obstruction due to jaw deformity, macroglossia, hypertrophy of the epiglottis, and narrowing of the opening between the vocal cords can lead to difficulties with airway management during surgical procedures. Airway obstruction after induction of general anesthesia may interfere with visualization of the vocal cords during laryngoscopy and intubation **(52 [EL 3])**. Therefore, airway management should be carefully considered preoperatively **(Grade C)**.

5.5.4. Cardiovascular Disease

Insulin resistance is a frequent consequence of acromegaly. The prevalence of impaired glucose tolerance is up to 46%, and type 2 diabetes mellitus is detected in up to 56% of patients with acromegaly **(12 [EL 3], 53 [EL 3], 54 [EL 2])**. Hypertension is detected in up to 40% of patients, presumably attributable to an increase in plasma volume along with an increase in sodium retention **(55 [EL 3])**. Suppressed plasma renin activity and aldosterone concentrations in acromegaly are consistent with a primary increase in total body sodium **(56 [EL 3])**. Of interest, acromegaly may be associated with an increase in carotid artery intima-media thickness, although the prevalence of atherosclerosis may be similar to that in the general population **(57 [EL 3], 58 [EL 3])**. This finding suggests that GH, IGF-I, or both may limit the progression of atherosclerosis, despite the coexistence of hypertension and glucose intolerance.

An acromegalic cardiomyopathy, characterized by biventricular cardiac hypertrophy, is a hallmark finding in patients with acromegaly **(59 [EL 4])**. Both age and duration of disease correlate with the presence and the degree of the hypertrophy **(60 [EL 2], 61 [EL 4], 62 [EL 3])**. Early in acromegaly, the cardiomyopathy may include diastolic dysfunction or insufficient systolic performance with effort. With progression of acromegaly, the cardiomyopathy may progress to systolic dysfunction at rest and, rarely with advanced disease, to a dilated congestive cardiomyopathy **(63 [EL 4], 64 [EL 4])**. Cardiac valve abnormalities, particularly in association with left ventricular hypertrophy, may occur **(65 [EL 3])**. Arrhythmias, including atrial fibrillation, supraventricular tachycardia, and bundle branch blocks, may be detected in approximately 40% of patients **(66 [EL 3])**. The presence of a cardiomyopathy may lead to fatigue and dyspnea, particularly during exercise. Use of an echocardiogram in the routine assessment of a patient with acromegaly is controversial, although it may be warranted in patients with fatigue and dyspnea, especially in those patients who are older **(Grade D)**.

5.5.5. Psychologic Alterations

Acromegaly appears to be associated with psychologic changes and alterations in personality, attributable to impairment in self-esteem, distortion of body image, disruption in interpersonal relationships, social withdrawal, and anxiety **(67 [EL 3])**. Patients often have depression, which may inhibit recovery **(68 [EL 4])**. Furthermore, patients with acromegaly may describe loss of initiative and spontaneity in conjunction with considerable lability of mood **(69 [EL 4], 70 [EL 3])**. These published studies have not demonstrated a clear correlation of psychologic symptoms with biochemical activity. In addition, a recent study in 17 patients with newly diagnosed acromegaly showed that, in comparison with 16 control subjects, there was a reduction in memory functions, including working memory, learning, and recall processes **(71 [EL 3])**. Although this study suggests that acromegaly may be associated with impaired cognitive processes, further investigations of neurocognitive function and the influence of other hormone dysfunctions on such function need to be performed.

5.5.6. Constitutional Symptoms

Fatigue and weakness are commonly described by patients with acromegaly and may be prominent symptoms. These symptoms may reflect the associated medical consequences of acromegaly, including sleep apnea syndrome, cardiomyopathy with reduced function, hypopituitarism, hyperthyroidism, depressed mood, and diabetes mellitus.

5.5.7. Neoplasms

An increased risk of cancer, particularly of the colon, in patients with acromegaly has been suggested largely by retrospective studies, although this finding is controversial **(14 [EL 4], 29 [EL 4])**. Moreover, when colon cancer is present in a patient with acromegaly, the colon cancer mortality rate (standardized mortality ratio, 2.47) is higher than expected for the general population **(72 [EL 2])**. In addition,

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many, but not all, studies have reported that colonic polyps are more prevalent in patients with acromegaly than in control subjects **(73 [EL 2], 74 [EL 2], 75 [EL 3])**. These findings are highly suggestive of a connection between GH hypersecretion and growth of neoplasms, particularly those of the colon. Screening colonoscopy should be performed in patients with active acromegaly, and follow-up should be scheduled in accordance with standard guidelines **(14 [EL 4]) (Grade C)**.

5.5.8. Mortality

Acromegaly is associated with a 2 to 2.5 times increased mortality risk, and normalization of GH or IGF-I levels (or both) has been shown to abrogate the mortality risk **(10 [EL 3], 76 [EL 2])**. The exact GH cutoff level required for normalization of risk, however, remains unclear. A recent meta-analysis suggested that a random GH measurement of <2.5 ng/mL on radioimmunoassay, which is roughly equivalent to <1 ng/mL as measured by modern more sensitive immunoassays, results in mortality rates similar to expected levels **(76 [EL 2])**. Of note, epidemiologic studies in acromegaly regarding correlation of GH levels with mortality rates have largely been based on either fasting or random serum GH levels. No epidemiologic studies have predicted mortality rates based on GH suppression after glucose administration. For this reason, random or fasting GH values or multiple samples have merit in the diagnosis and monitoring of acromegaly, although because of the variability in GH levels, random GH values are considered less reliable **(11 [EL 3], 76 [EL 2], 77 [EL 3], 78 [EL 4]) (Grade C)**. Overall, GH and IGF-I biochemical control must be an important focus of therapy for acromegaly, in particular for management of the mortality risk **(Grade C)**.

5.5.9. Summary

Acromegaly is associated with a spectrum of comorbidities, which result in significant and debilitating clinical manifestations. Therefore, the frequent delay in diagnosis can magnify the consequences of this disease. Education about the clinical spectrum of acromegaly is imperative in order to promote earlier detection.

6. DIAGNOSIS OF ACROMEGALY

The diagnosis of acromegaly begins with a clinical suspicion by the physician that the patient has this disease. On many occasions, the suspicion originates from a physician who is working in a field other than endocrinology. For example, a dentist may recognize a bite malocclusion typical of a patient with acromegaly whose lower jaw is protruding further than the upper jaw, or an ophthalmologist may find a visual field defect consistent with chiasmal compression caused by a pituitary tumor. Currently, many rheumatologists are testing for disorders that potentially can cause osteoarthritis and thus measure serum IGF-I levels as part of their overall assessment of the patient **(14 [EL 4], 59 [EL 4])**. Biochemical confirmation is rarely difficult once the diagnosis has been considered; the major challenge, however, is to consider acromegaly as part of the differential diagnosis for the numerous manifestations with which it can present **(Grade D)**.

The presenting symptoms of acromegaly are of insidious onset and lack specificity—such as lethargy, headache, and increased sweating, which are often mistaken as signs associated with aging. Because there are no pathognomonic early features of this disease, the most reliable history and physical findings suggesting acromegaly relate to abnormal growth, such as hand and foot enlargement, facial bone enlargement, and acral or soft tissue changes **(79 [EL 4])**. Therefore, clinicians must actively look for this disorder in patients with multiple features or components of the syndrome rather than just one presenting feature **(Grade A)**. A review of the features **(9 [EL 3], 80 [EL 3])** present at diagnosis provides clues about the medical specialists likely to be encountered by patients with undiagnosed acromegaly (Table 3). Patients should be encouraged to bring old photographs to an appointment in an attempt to determine the chronicity of the disease **(Grade D)**.

For the biochemical confirmation of acromegaly, measurement of serum IGF-I and glucose-suppressed GH levels is recommended **(Grade B)**. GH is produced by the somatotroph cells of the pituitary gland in a pulsatile fashion. Circulating GH stimulates hepatic secretion of IGF-I. Total serum IGF-I serves as an integrated marker of GH secretory status, which is important in the assessment of GH hypersecretion **(81 [EL 2]) (Grade B)**. In general, there is a linear relationship between serum GH and IGF-I levels, especially with serum GH levels less than 20 ng/mL. IGF-I levels plateau at serum GH concentrations above 40 ng/mL **(82 [EL 3])**. Both assays should have adequate sensitivity (for GH, at least 0.05 ng/mL), established validity, specificity, reliability, and uniform reproducibility.

6.1. IGF-I Measurement

Although serum IGF-I levels are subject to circadian changes to a much lesser degree than GH levels, IGF-I has the advantage over GH when determined as a single sample because it provides a measure of integrated GH secretion. Furthermore, IGF-I levels can be determined at any time of the day without the patient having to fast and therefore are more convenient for the patient and the physician. False-positive elevations of serum IGF-I levels may be seen in pregnancy, during which the placenta makes large quantities of a smaller **(83 [EL 2])** yet biologically active GH molecule. IGF-I levels should be compared with age-dependent normative data generated across all age-groups in both sexes **(84 [EL 1], 85 [EL 2]) (Grade B)**. Systemic illness, including catabolic states **(86 [EL 1], 87-90 [EL 2])**, hepatic **(91 [EL 2], 92 [EL 2])** or renal

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failure **(93 [EL 2], 94 [EL 2])**, malnutrition **(95 [EL 2], 96 [EL 2])**, and diabetes mellitus **(97 [EL 2], 98 [EL 2])**, may lower the IGF-I level and result in false-negative values. In those patients with poorly controlled diabetes attributable to acromegaly, serum IGF-I levels should be remeasured at a later time when the glycemic control has improved **(97 [EL 2])** **(Grade C)**. Orally administered estrogen antagonizes GH actions and can lower IGF-I into the normal range in patients with acromegaly who have mildly elevated IGF-I levels **(99 [EL 2])**. Obtaining serum IGF-I values by using a CLIA (Clinician Laboratory Improvement Amendments)-approved laboratory method is highly recommended **(31 [EL 3], 100 [EL 2])**. Major concerns about IGF-I measurement are the lack of agreement between assays and the lack of validated normal ranges **(101 [EL 4], 102 [EL 2])**. Therefore, it is advisable to use the same assay in the same patient for serial measurements **(103 [EL 3])** **(Grade C)**. Additional components of the IGF-I circulating complex, such as insulinlike growth factor-binding protein-3 and acid-labile subunit, have been used as other diagnostic markers to reflect GH secretion. Their sensitivity and specificity, however, are not nearly as good as those of IGF-I; thus, they have been used predominantly as research tools and not as markers for clinical management of acromegaly **(104 [EL 3], 105 [EL 3])** **(Grade C)**. Because IGF-I levels may be more predictive of clinical symptom scores **(106 [EL 3])**, greater emphasis for diagnosis and disease control is placed on monitoring random IGF-I levels for clinical care **(Grade C)**. Measurement of free IGF-I and IGF-binding proteins is not considered useful for the diagnosis of acromegaly **(107 [EL 3])** **(Grade C)**.

The serum IGF-I is considered an excellent screening tool for the diagnosis of acromegaly. If the IGF-I level is elevated and clinical features of the disease are present, GH measurement after an OGTT may be omitted **(Grade D)**.

6.2. GH Measurement

GH secretion in normal persons is pulsatile and diurnal and can also be stimulated by exercise and sleep. Because the half-life of GH is short (approximately 20 minutes), the clearance of GH from plasma is rapid **(108 [EL 4])**. Therefore, GH concentrations fluctuate throughout the day, such as after meals. GH levels may be elevated in the presence of liver disease, malnutrition, and uncontrolled diabetes mellitus. The interpretation of serum GH levels must take these variables into account **(Grade B)**. Rather than the OGTT, frequent sampling of GH levels every 30 minutes for 3 hours has been used **(109 [EL 2])**, and the criterion for normal GH levels during this period is any serum GH value less than 1 ng/mL. This testing, however, may be cumbersome and time-consuming for patients, and it is unclear whether this adds further information to the aforementioned testing for either diagnosis or therapeutic monitoring **(110 [EL 3])** **(Grade D)**. Because of the lack of a well-defined normal or safe range, a random GH level is not thought to add appreciably to the evaluation **(Grade C)**.

6.2.1. Oral Glucose Tolerance Testing

The nadir GH suppression after administration of glucose is considered the "gold standard" test for acromegaly **(Grade B)**. The panel recommends that GH measurements be performed at baseline, then every 30 minutes for a total of 120 minutes after administration of glucose **(Grade C)**. Currently, there are no data contrasting the sensitivity and specificity of the 75-g and 100-g dose of glucose for the OGTT; it is proposed that 75 g should be used to achieve a level of standardization **(111 [EL 3])** **(Grade C)**. In addition, although GH levels are influenced by age, sex, and weight, these variables are not taken into account in the biochemical interpretation of disease activity **(112 [EL 2], 113 [EL 4])**. In a recent comparison of commercial GH assays, the investigation found that the various assays may not have the same result even though the same split samples were used **(112 [EL 2])**. False-positive responses to the OGTT may be seen in puberty and in patients with diabetes mellitus, liver disease, renal disease, or anorexia nervosa **(114 [EL 3], 115 [EL 4], 116 [EL 4])**. These issues need to be considered in interpretation of serum GH values **(Grade C)**.

The inability to suppress serum GH to less than 1 ng/mL after glucose administration is considered the diagnostic criterion for acromegaly **(106 [EL 3], 110 [EL 3], 117 [EL 3], 118 [EL 2])** **(Grade B)**. This cutoff nadir GH value, however, is controversial, particularly because of the development of more sensitive GH assays that result in lower serum GH levels **(119 [EL 4])**. The development of such GH assays has led to consideration for use of a lower nadir GH cutoff for the diagnosis of acromegaly. In a consensus guideline in 2000, the diagnosis of acromegaly was excluded if the patient had a random GH measurement less than 0.4 ng/mL and a normal IGF-I value **(120 [EL 3])**. This issue was especially relevant because of studies that suggested that a nadir GH cutoff level of 1 ng/mL was insufficient for diagnosis in a proportion of patients with acromegaly **(110 [EL 3], 121 [EL 2], 122 [EL 1])**. This is particularly the case in patients with mild GH hypersecretion, as shown by Dimaraki et al **(123 [EL 3])** who reported random GH levels of less than 1 ng/mL in 8 of 16 patients with acromegaly who had elevations in serum IGF-I levels. This finding was substantiated in another study in which 50% of patients with acromegaly and mildly elevated fasting GH levels demonstrated nadir GH suppression below 1 ng/mL **(124 [EL 2])**. These data suggest that the 1 ng/mL nadir GH cutoff value may be inadequate. Another consensus statement in 2005 suggested that the nadir GH level be lowered to 0.4 ng/mL for diagnosis of acromegaly **(125 [EL 4])**. Although a nadir GH concentration of less than 1

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ng/mL after administration of glucose is the standard recommendation for a normal response, this panel suggests consideration of a lower nadir GH cut point at 0.4 ng/mL after glucose administration because of the enhanced assay sensitivity and more frequent finding of modest GH hypersecretion **(110 [EL 3], 112 [EL 2], 121 [EL 2], 122 [EL 1]) (Grade D)**.

6.2.2. Additional GH Assay Considerations

The differences in the assay performance of GH may also pose some problems for the application of international consensus criteria to local practice. The factors that influence assay performance include heterogeneity of human isoforms in circulating serum, epitope specificity of polyclonal antibodies used, and susceptibility to interference by endogenous GH-binding protein. Additionally, the use of different units (mU/L versus μg/L) to report GH levels further compounds the problems of standardizing GH results because various conversion factors are used. Therefore, results from one laboratory cannot be compared with results from another laboratory **(112 [EL 2]) (Grade C)**. Various standards have been used in commercial assays. For example, the Immulite 2000 uses the World Health Organization second international standard (IS) of 87/518, the Nichols Advantage uses the National Institute for Biological Standards and Control second IS of 98/574, and the Diagnostic Systems Laboratories assay uses the World Health Organization reference preparation of human growth hormone of 88/624. In a comparison of these assays **(112 [EL 2])**, the Immulite 2000 results were 2.3 times those obtained with the Nichols Advantage and 6-fold higher than those obtained by the Diagnostic Systems Laboratories. Even though most assays are now calibrated against international reference preparations of the hormone **(126 [EL 1], 127 [EL 2])**, the comparative measurements of serum samples by different immunoassays still produce heterogeneous results **(128 [EL 3])**. Use of the first and second IS for recombinant GH (IS 88/624 and 98/574), which consist of 24-kDa GH of more than 95% purity, instead of pituitary-derived IS 80/505, which contains a mixture of isoforms, has been suggested **(126 [EL 1]) (Grade C)**. It has also been suggested that GH be expressed in mass units instead of international units **(127 [EL 2]) (Grade C)**.

6.2.3. Interpretation of Discordant Laboratory Test Results

In general, GH and IGF-I levels correlate closely with each other in patients with acromegaly **(129 [EL 3], 130 [EL 3])**. Divergent GH and IGF-I values, however, may be seen in up to 30% of patients **(131-133 [EL 3])**. The most common discrepancy involves an elevated IGF-I level with normal GH values, and this is thought most frequently to reflect earlier disease **(123 [EL 3])**. Less commonly, an elevated GH value (such as an abnormal OGTT result) with an associated normal IGF-I concentration may be seen. Such discrepancies may reflect lack of assay standardization, the effects of age and gonadal status on GH and IGF-I secretion, genetic differences in binding proteins, or stress at the time of sampling **(132 [EL 3], 134 [EL 2], 135 [EL 1])**. If the discrepancy is substantial, repeated testing may be warranted, particularly if the clinical impression is suggestive of a diagnosis of acromegaly **(Grade D)**.

6.3. Further Evaluation

Other tests that do not offer additional routine information for the diagnosis of acromegaly include growth hormone-releasing hormone (GHRH) and gonadotropin-releasing hormone stimulation **(120 [EL 3]) (Grade C)**. Serum prolactin should be measured in all patients diagnosed as having acromegaly because prolactin cosecretion is common **(136 [EL 3])** and conflicting data exist about whether prolactin cosecretion predicts response to dopamine agonist therapy **(137 [EL 2], 138 [EL 3], 139 [EL 3]) (Grade C)**. Similarly, thyroid-stimulating hormone and free thyroxine levels are useful to exclude the possibility of inappropriate thyroid-stimulating hormone secretion from a thyrotropin-cosecreting tumor. After diagnosis of acromegaly, an MRI scan of the pituitary gland should be obtained to ascertain tumor size, location, and invasiveness **(140 [EL 3]) (Grade B)**. If there is no evidence of a pituitary tumor by imaging studies, a search for an ectopic source should be undertaken with use of imaging studies such as a chest CT scan and Octreoscan **(141 [EL 3]) (Grade B)**. If the sellar contents are generally enlarged without a clear focus of tumor, consistent with somatotroph hyperplasia, a serum GHRH level should be measured **(141-144 [EL 3]) (Grade B)**. Ectopic GH- or GHRH-producing tumors are rare but are most commonly bronchial carcinoid tumors **(141 [EL 3])**. Preoperative consideration of a GH-secreting pituitary carcinoma would be exceedingly rare **(145 [EL 3])**.

6.4. Key Summary of Diagnosis

- Acromegaly is a clinical syndrome that does not manifest with clear diagnostic features; clinicians must think of the diagnosis in the setting of various clinical presentations **(Grade A)**.
- Serum GH assays are not standardized and should not be used interchangeably **(Grade C)**. The GH nadir after administration of 75 g of glucose orally should be less than 1.0 ng/mL to define normal, and this is the "gold standard." This panel, however, recommends consideration of lowering this cutoff to 0.4 ng/mL because of the increased sensitivity of current GH assays **(Grade D)**. Clinicians should investigate the assay being used to know the sensitivity **(Grade A)**.
- Serum IGF-I assays, if accompanied by a large number of results from age- and sex-matched normal subjects, are good tools to assess integrated GH secretion and

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are excellent for diagnosis, monitoring, and screening **(Grade B)**.

The diagnosis of acromegaly depends on clinical and laboratory features. Assays for GH and IGF-I and a dedicated pituitary MRI complement each other to arrive at a diagnosis **(Grade B)**. The important features for diagnosis of the patient with acromegaly, as summarized in Table 4, include history, physical findings, imaging features, and laboratory results **(7 [EL 3], 8 [EL 4], 9 [EL 3], 16 [EL 3], 110 [EL 3], 112 [EL 2], 120 [EL 3], 146 [EL 1], 147 [EL 1], 148 [EL 3])**. Experience with the assay used locally by the clinical endocrinologist is important, and clinical correlation is often required.

7. TREATMENT

The goals of therapy for acromegaly are to (*1*) control biochemical indices of activity, (*2*) control tumor size and prevent local mass effects, (*3*) reduce signs and symptoms of disease, (*4*) prevent or improve medical comorbidities, and (*5*) prevent early mortality **(Grade B)**. The primary mode of therapy is surgery, which is recommended for all patients with microadenomas and for all patients who have macroadenomas with associated mass effects **(Grade B)**. In patients with macroadenomas without mass effects, and with low likelihood of surgical cure, a role for surgical debulking of macroadenomas to improve the response to subsequent medical therapy has been advocated, as well as primary medical therapy alone **(Grade C)**. Medical therapy is generally used in the adjuvant setting, although a role for medical treatment as primary therapy in selected patients with macroadenomas not likely to be cured by surgery and without associated mass effects may be considered **(Grade C)**. Irradiation, either conventional fractionated RT or stereotactic radiosurgery, is largely relegated to an adjuvant role **(Grade C)**. Availability of specific therapeutic options and cost of these interventions are taken into account with decisions regarding therapy. A treatment algorithm is presented in Figure 1.

Table 4
Summary of Diagnostic Features of Acromegaly

Category	Major diagnostic features	Additional diagnostic features
Symptoms	Headache Heat intolerance Ring and shoe sizes Facial bony changes	Hypogonadism (amenorrhea, impotence) Visual changes Sleep apnea
Signs	Prominent forehead Broad nose Prominent lower jaw Visual field loss	Large hands and feet Skin tags Bite abnormalities Carpal tunnel Oily skin
Magnetic resonance imaging findings	Dedicated pituitary magnetic resonance imaging Commonly, macroadenoma	Microadenoma (rarely) Extension lateral to carotid predicts incomplete resection
Biochemical results	Elevated level of insulinlike growth factor-I Growth hormone nadir >1.0 ng/mL after oral glucose dose Panel suggests lower growth hormone nadir (>0.4 ng/mL) after oral glucose dose	Elevated prolactin level Random growth hormone <0.4 ng/mL and normal insulinlike growth factor-I make the diagnosis highly unlikely
Pathologic findings	Growth hormone-staining pituitary adenoma	Somatostatin resection subtype characterization to predict response to somatostatin analogue therapy

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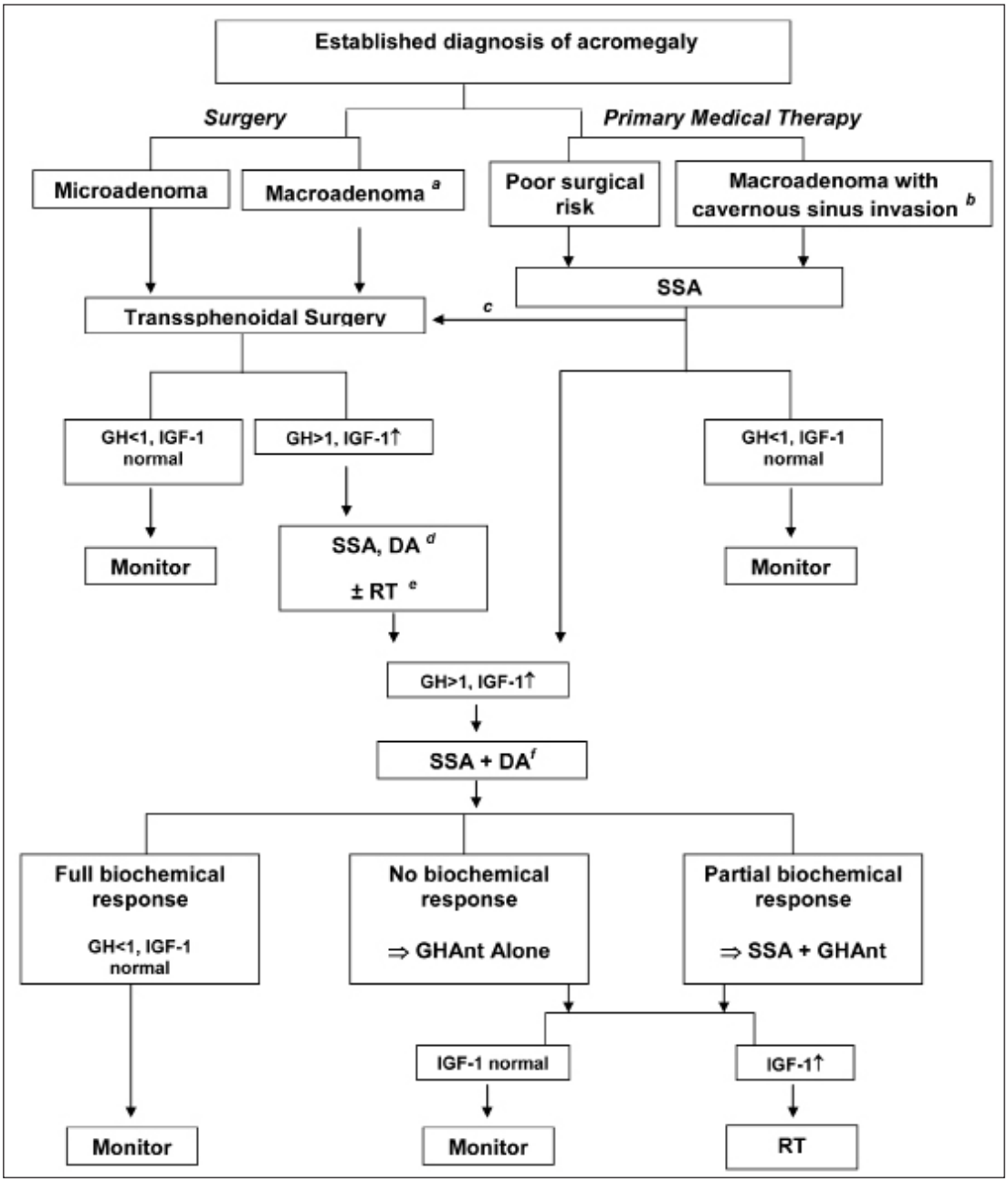


Fig. 1. Algorithm for the approach to therapy in patients with acromegaly. *a* = Visual field compromise is absolute indication for surgery. *b* = Primary medical therapy can be considered if there is no visual field deficit and there is no possibility of surgical cure because of cavernous sinus involvement. *c* = Reconsider surgery to debulk tumor to improve response to medical therapy, to reduce medical comorbidities, or to comply with patient preference. *d* = Consider a dopamine agonist (*DA*) in the setting of modest disease. *e* = Consider radiotherapy (*RT*) in patients with residual tumor after surgery. This decision is based on several factors, including age, reproductive status, pituitary function, insurance coverage, and patient preference regarding long-term medical therapy. *f* = Addition of a DA in the setting of modest disease. *GH* = growth hormone; *GHAnt* = growth hormone antagonist; *IGF-1* = insulinlike growth factor-I; *SSA* = somatostatin analogue.

8. SURGERY

8.1. Goals of Surgical Treatment

1. To decrease the tumor burden and yield a cure, if possible, with attempted preservation of normal pituitary function. A cytoreduction strategy is also a goal in maximizing further adjuvant medical, radiation, or radiosurgical attempts at endocrinologic control, by diminishing tumor volume and GH hypersecretion.
2. To decompress the mass effect of macroadenomas on any normal remaining pituitary gland tissues, the optic chiasm or nerves, or the surrounding critical structures.

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3. To lower rapidly or minimize GH and IGF-I levels, slow or arrest the progression of disease, and alleviate associated comorbidities.
4. To obtain important pathologic tissue for immunohistochemical study, ultrastructural analysis, and molecular biology to aid in understanding tumor biologic processes and serve as a substrate for current and future therapeutic strategies.

8.2. Surgical Approach

Empirical evidence strongly suggests that a well-coordinated team approach—anchored by an endocrinologist and an experienced neurosurgeon and assisted by a dedicated neuroradiologist and radiation therapist—will offer optimal treatment strategies with better outcomes and lower morbidity **(149 [EL 4], 150 [EL 4]) (Grade C)**. There is ample experiential evidence suggesting that high-volume medical centers with dedicated pituitary surgeons who perform 50 or more transsphenoidal procedures per year yield the best surgical outcomes with low morbidity and mortality **(151 [EL 3], 152 [EL 3]) (Grade C)**. The strongest preoperative factors predictive of a surgical cure are the following: (*1*) MRI size and appearance of the tumor and (*2*) GH and IGF-I levels. Despite some differences in agreement about what represents early surgical cure or remission **(153 [EL 3], 154 [EL 2])**, numerous surgical series have demonstrated that surgical efficacy is inversely proportional to (*1*) preoperative GH and IGF-I levels and (*2*) tumor size (especially in those without evidence of cavernous sinus involvement) **(155-160 [EL 3]) (Grade C)**. Three-tesla magnets yield improved anatomic imaging, an inherent quality of the physics involved **(161 [EL 3])**. Under optimal conditions, microadenomas revealing no involvement of the cavernous sinus on MRI and lower levels of GH and IGF-I excess yield an approximately 80% or higher early biochemical cure, which may serve as a surgical benchmark **(Grade B)**. Tumor size and biochemical activity affect surgical response, and surgery is curative in 40% to 50% of macroadenomas larger than 2 cm. In addition, higher GH and IGF-I preoperative levels (GH >30 ng/mL) correlate with cavernous sinus invasion and demonstrably lower surgical cure (20% to 50%). Preoperative GH levels >200 ng/mL are surgically incurable, as is obvious MRI evidence of cavernous sinus invasion **(155-160 [EL 3]) (Grade B)**.

Surgeons using transsphenoidal approaches are rapidly adopting minimally invasive, endonasal strategies. There are still reasons for offering craniotomy in selected cases, particularly for huge, extrasellar lesions. Transnasal endoscopic procedures are rapidly replacing the sublabial transseptal approaches because of lower patient morbidity and improved optic light sources with smaller endoscopes. No randomized controlled trials have compared outcomes between the conventional sublabial transseptal approach and the transnasal endoscopic approach. There are studies, however, that have compared outcomes in matched cohorts of patients who underwent a transnasal endoscopic approach versus a sublabial transseptal approach. Transnasal endoscopic procedures reveal improved patient satisfaction and shorter hospital stay over the traditional sublabial procedures without compromising surgical success when performed by experienced surgeons **(162 [EL 3], 163 [EL 3])**. The majority of dedicated pituitary surgeons now perform variations of the transnasal endoscopic approaches, which are rapidly becoming the surgeon and patient procedure of choice **(164-166 [EL 3], 167 [EL 4]) (Grade D)**. Surgical removal of fibrous tumors may be deliberately staged by resection of the inferior component of the tumor to allow the suprasellar component to descend into the excavated area, followed by complete removal by a second procedure at a later date **(168 [EL 3])**.

Surgical adjuncts to improve outcomes are dependent on the surgeon and available resources but include (*1*) intraoperative imaging, (*2*) neuronavigation, and (*3*) intraoperative determination of GH levels.

Intraoperative MRI is a very expensive technique but offers high-quality imaging by using higher field strength magnets. Few medical centers offer this expensive modality, which is best used for large and geometrically complex tumors **(169 [EL 3]) (Grade D)**. Ultrasonography is the only real-time intraoperative imaging procedure. Removal of a small portion of the skull and use of the newer, higher powered machines offer real-time tumor visualization that is quite good. This technique may optimize removal of large complex tumors **(170 [EL 3]) (Grade D)**.

Neuronavigation—the wedding of preoperative imaging to trajectory at surgery—is a good strategy for anatomic variations, such as in the case of patients who have undergone previous surgery, the presence of abnormal bone, narrow carotid apertures, or the probability of misdirection due to confusing surgical landmarks **(171 [EL 3]) (Grade C)**.

Intraoperative measurement of GH levels is also an expensive technique; the variable half-life of GH can prolong a surgical procedure and be misleading **(172 [EL 3])**. Thus far, intraoperative GH levels have not been found to be clinically useful **(Grade C)**.

Pediatric cases of acromegaly are uncommon, and such cases may represent more aggressive and larger tumors. As a result, pediatric cases may require more intensive management **(173 [EL 3], 174 [EL 3])**. Elderly patients with acromegaly may have a generally good surgical outcome **(175-177 [EL 3])**, and reoperation for recurrent or residual disease in selected cases is appropriate **(178 [EL 3]) (Grade C)**. Some evidence suggests that very large cerebrospinal fluid (CSF) leaks at the time of pituitary surgery may benefit by lumbar drainage and CSF diversion **(179 [EL 3])**, but this is a surgeon- and experience-dependent option.

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8.3. Is There a Role for Preoperative Medical Therapy?

8.3.1. Does SSA Administration Improve Surgical Outcome?

There has been considerable discussion about a role of preoperative medical therapy, especially with SSAs, to affect the quality of the tumor, with resultant enhanced surgical resection and consequently biochemical remission. A study conducted by Abe and Lüdecke **(180 [EL 3])** compared GH and IGF-I levels in patients with or without preoperative octreotide therapy and found higher rates of normalization of GH and IGF-I levels in the group pretreated with octreotide. In contrast to that study, a larger but retrospective analysis of 286 patients demonstrated that surgical remission and complication rates in patients with acromegaly who received treatment with either octreotide or lanreotide preoperatively were not significantly different from those of matched patients who did not receive these agents **(181 [EL 2])**.

Subsequently, a multicenter study in Norway revealed that 6-month pretreatment with octreotide LAR (20 mg/mo) resulted in surgical remission (defined as a normal level of IGF-I) in 50% of patients with macroadenomas, versus 16% of those who underwent surgery without pretreatment ($P = .02$) **(182 [EL 2])**. In this study, when a normal level of GH (less than 1 ng/mL) after glucose suppression was added to the definition of biochemical remission, the difference between the 2 groups was no longer significant. Therefore, the value of pretreatment with octreotide was significant only when IGF-I was used as the marker. In a single-center study, 98 patients with macroadenomas were randomly assigned to lanreotide therapy for 4 months before surgery or directly to surgery, and surgical remission (defined by IGF-I level) was achieved in 49% versus 18%, respectively ($P = .001$) **(183 [EL 2])**. In this study, the difference in remission rates remained significant when a glucose-suppressed GH level less than 1 ng/mL was also used to define remission. These randomized studies suggest that preoperative treatment with SSAs may improve surgical remission rates **(Grade C)**. Further study is needed to determine whether routine SSA administration should be considered preoperatively and whether selected patients will benefit more from this combined approach.

8.3.2. Can Preoperative Medical Therapy Diminish Cardiopulmonary Comorbidities and Anesthesia-Related Risks of Surgical Treatment?

As discussed in section 5.5, cardiovascular disease, pulmonary dysfunction, and metabolic disorders, including hyperglycemia, are prevalent in acromegaly. In addition to the morbidity caused by these complications themselves, these conditions place patients at increased anesthesia-related and operative risk. Thus, control of these comorbid conditions may reduce surgical risk and improve postoperative outcomes **(Grade D)**. Indeed, patients with acromegaly are at increased risk of anesthesia-related complications including hemodynamic changes, with a significantly higher incidence of difficulty with intubation because of laryngeal and pharyngeal soft tissue swelling and vocal cord swelling **(184 [EL 3])**. Up to 30% of anesthesia intubations for surgical procedures in patients with acromegaly have been reported to be difficult **(185 [EL 3])**. The oropharyngeal swelling and macroglossia result in an increased frequency of sleep apnea syndrome, which has been reported in 20% to 80% of this population **(185 [EL 3])**. Sleep apnea itself is associated with an increased risk of coronary artery disease and hypertension and may complicate both the preoperative and the postoperative status of the patient and delay extubation. SSAs can reduce soft tissue swelling within days after onset of treatment, with some studies demonstrating resolution of sleep apnea after 6 months of treatment with octreotide. As a result, preoperative SSA therapy might be expected to result in reduction of intubation-related complications **(Grade D)**. This issue, however, warrants further direct examination for higher quality of evidence.

Patients with acromegaly are also at risk of cardiac complications, including left ventricular hypertrophy, increased stroke volume and cardiac index, biventricular concentric cardiomyopathy, and, in advanced cases, reduced ejection fraction or cardiac failure. Up to 10% of patients with newly diagnosed acromegaly present with high-output heart failure **(186 [EL 3])** and an increased prevalence of ventricular dysrhythmias **(187 [EL 3])**. Treatment with SSAs improves cardiac function, reduces ventricular mass, reduces the incidence of cardiac dysrhythmias, and thus may potentially have beneficial effects on surgical outcome, although this result has not been formally proved **(187 [EL 3], 188 [EL 3])** **(Grade C)**.

8.4. Postoperative Course

8.4.1. Biochemical Testing

Assessment of GH secretion may begin as early as postoperative day 1. In a study by Krieger et al **(189 [EL 3])** in 116 patients with acromegaly, 99% with a postoperative day 1 fasting serum GH level less than 2 ng/mL had both a normal IGF-I value and clinical evidence of disease remission at 5 years. Therefore, there may be a role for immediate postoperative GH measurement as a prognostic marker in the biochemical assessment of surgical efficacy. A postoperative serum GH level, however, may have more limited prognostic value because the stress of surgery may stimulate the remaining normal pituitary gland to elevate GH levels **(Grade D)**. The OGTT can be performed early in the postoperative period and can be relied on as early as 1 week postoperatively **(190 [EL 2])** **(Grade C)**. A nadir

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GH value less than 0.4 ng/mL may be used to define disease control postoperatively **(131 [EL 3], 191 [EL 3], 192 [EL 4], 193 [EL 2])**.

Assessment of biochemical activity at 3 to 6 months after surgery is considered more valid in determining surgical efficacy **(131 [EL 3], 194 [EL 3]) (Grade C)**. After surgery in a patient with acromegaly, the serum IGF-I may take months to decline into the normal range despite cure **(190 [EL 2])**. The reasons for this are unclear but are probably related to increased liver sensitivity to GH, resulting in persistent elevation of IGF-I levels and delayed reduction in IGF-binding protein levels. Surgical remission is generally defined as achievement of a normal level of IGF-I and a nadir GH less than 1.0 ng/mL during an OGTT by 3 to 6 months, although use of a lower nadir GH of less than 0.4 ng/mL is suggested **(110 [EL 3], 195 [EL 4]) (Grade C)**. Because divergent GH and IGF-I values may be seen in up to 30% of patients **(131 [EL 3], 132 [EL 3])** (see section 6.2.3), repeated testing may be warranted. The most common discrepancy involves an elevated IGF-I level with normal GH values; this finding is thought most commonly to reflect minimal residual disease **(123 [EL 3])**. With this scenario, repeated testing may be done if there is a high clinical suspicion of persistent disease, such as evidence of residual tumor on imaging or persistent symptoms **(Grade D).**

If early postoperative imaging is required, such as to assess remaining tumor or to rule out infection, then a T1-weighted MRI with gadolinium is the most useful technique, although a scan at this time may be difficult to interpret. Studies suggest that Gelfoam packing may require 3 to 5 months to involute, and fat packing may require even longer. Therefore, a postoperative MRI scan to identify residual tumor is generally performed at least 12 weeks after surgery **(196 [EL 3]) (Grade C)**.

At a minimum, IGF-I levels should be measured annually in all patients after surgery because recurrences have been reported as long as 10 to 20 years after apparent cure **(106 [EL 3]) (Grade C)**. An OGTT may also be performed annually for the assessment of recurrence of acromegaly **(Grade D)**.

8.4.2. Pathologic Analysis

An important goal of surgery is to obtain tissue intraoperatively for pathologic studies by the surgical team **(Grade D)**. Depicting the invasive or proliferative potential of the tumor reflected by the Ki-67 index may aid in selecting early adjuvant therapy for aggressive or less-differentiated tumors or suspected failures, such as dural invasion, cavernous sinus invasion, or atypical appearance of the cells **(197 [EL 3], 198 [EL 3])**. Pituitary tumors that stain for GH without circulating excess of the hormone are considered clinically silent, but such adenomas may harbor the aggressive growth features of biologically active tumors. In addition, GH-staining tumors may respond to medical treatments similar to their biologically active counterparts **(199 [EL 3], 200 [EL 3])**. Tumors that stain for prolactin may similarly predict potential response to dopamine agonist therapy (see section 9.3.1). Sparsely granulated GH tumors need to be distinguished from the more common densely granulated variety. The latter are significantly more likely to respond to SSAs in comparison with the other types of GH-producing adenomas **(201 [EL 3], 202 [EL 3])**.

8.4.3. Postoperative Management

Postoperatively, adrenal function should be monitored and treated appropriately. Posterior pituitary function must also be monitored during the immediate postoperative period and for approximately 2 weeks **(Grade C)**. Hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone may manifest 5 to 14 days postoperatively in 5% to 10% of the patients after any transsphenoidal procedure. Mild cases respond to fluid restriction, and severe cases may necessitate hospitalization and intravenous administration of hypertonic saline **(203 [EL 2], 204 [EL 2]) (Grade B)**. Diabetes insipidus is a common transient event in perhaps 20% of patients who undergo a transsphenoidal procedure, necessitating at least one treatment of desmopressin in about 10% and long-term treatment in perhaps 2% to 7% of all transsphenoidal procedures. There may be a higher association of diabetes insipidus with intraoperative CSF leaks **(205 [EL 2])**. Of note, patients often have a brisk diuresis postoperatively because the reduction in serum GH level results in a natriuresis. The clinician needs to consider this in the postoperative management of polyuria; this diuresis is not associated with excessive thirst and will not necessitate desmopressin management **(Grade B)**. The thyroid and gonadal axes should be reevaluated 6 to 12 weeks postoperatively **(Grade C)**. In patients with sleep apnea syndrome, the CPAP device is generally withheld postoperatively for a period to prevent the risk of pneumocephalus and meningitis due to high intranasal pressures, particularly in the setting of a CSF leak **(206-208 [EL 3]) (Grade D)**.

New-onset permanent pituitary dysfunction, given the resiliency of the remaining gland, should be less than 5% **(162 [EL 3], 163 [EL 3], 189 [EL 3], 209 [EL 3])**. The prevalence of postoperative complications is inversely correlated with the experience of the neurosurgeon **(210 [EL 2]) (Grade C)**.

9. MEDICAL THERAPY FOR ACROMEGALY

9.1. Role of Medical Therapy: Primary Versus Adjunctive Treatment

Surgical resection of the pituitary tumor has traditionally represented the cornerstone of management for most patients with acromegaly. Primary surgical intervention, however, has been challenged because a strict target

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of age-normalized IGF-I level and a glucose-suppressed GH level is difficult to achieve with surgery, particularly in patients with macroadenomas and extrasellar extension **(Grade C)**. Because complete resection is not always feasible, adjunctive therapy is frequently necessary. This outcome has prompted the view that primary medical therapy, in particular with SSAs, may be a suitable option to consider for some patients **(211 [EL 4])**. Primary medical therapy with an SSA may lead to biochemical control (a normal IGF-I level) in up to 70% of patients and is well tolerated **(212 [EL 3])**. In a recent study, three-quarters of the patients had at least 25% tumor shrinkage after 12 months of SSA therapy, and tumor shrinkage correlated with biochemical response **(213 [EL 2])**. As such, primary medical therapy may be considered, particularly for those patients who are at high surgical risk, those with tumors that exhibit extrasellar involvement (without chiasmal compression) and low likelihood of cure with surgery, and those who express a preference for medical management **(Grade C)**. It should also be recognized that synergy between medical and surgical approaches must be considered. Indeed, transsphenoidal pituitary surgery has been shown to enhance SSA efficacy in comparison with primary medical therapy alone **(158 [EL 3])**. These latter findings indicate that a possible role exists for surgical tumor debulking in a combination treatment approach for patients with advanced disease **(Grade C)**.

With these caveats in mind, a suggested management paradigm is presented in Figure 1. SSAs have a role as *primary medical therapy* in patients who have a low likelihood of surgical remission or who are poor surgical candidates and as *adjuvant therapy* in patients with persistently nonsuppressible GH or elevated IGF-I levels (or both) after pituitary surgery or during the interim period after RT. The use of a GH antagonist alone or in combination with an SSA is pharmacologically rational and of proven effectiveness in patients in whom surgery or SSA therapy (or both) is not completely effective.

9.2. Biochemical Monitoring During Medical Therapy

1. For SSA and dopamine agonist administration, serum GH and IGF-I levels are the appropriate biochemical markers for monitoring activity **(131 [EL 3]) (Grade C)**. At a minimum, serum IGF-I monitoring is the test of choice **(Grade C)**. Of note, IGF-I levels plateau at serum GH concentrations above 40 ng/mL **(82 [EL 3])**. Therefore, in the setting of very high serum GH levels, there may be a delay in the reduction of serum IGF-I because the GH levels are progressively lowered **(Grade C)**.

   GH monitoring:

   a. Glucose-suppressed GH levels to less than 1 ng/mL have been shown to be useful for monitoring the efficacy of medical therapy **(133 [EL 3], 214 [EL 3], 215 [EL 3])**, although a recent study has questioned the additional benefit of this test for monitoring purposes **(131 [EL 3]) (Grade C)**.

   b. Frequent sampling of GH levels every 30 minutes for 3 hours has been used for therapeutic monitoring **(109 [EL 2])**, and the criterion for controlled GH levels during this period is any serum GH level of less than 1 ng/mL. This testing, however, may be cumbersome and time-consuming for patients, and it is unclear whether this adds further information to the aforementioned testing **(110 [EL 3]) (Grade D)**.

2. With administration of pegvisomant, serum IGF-I should be measured alone to monitor the dose efficacy **(Grade B)**. There is no benefit from measurement of serum GH in conjunction with pegvisomant therapy. GH levels increase when pegvisomant is administered, and the GH levels have no effect on pegvisomant dosing **(216 [EL 2], 217 [EL 2]) (Grade B)**.

9.3. Specific Agents

9.3.1. Dopamine Agonists

Dopamine agonists have long been used in the treatment of acromegaly because they have some efficacy in decreasing GH hypersecretion. Although bromocriptine was shown to provide benefit in a minority of patients with acromegaly in earlier studies, more recent studies suggest that cabergoline, a more selective dopamine-2 receptor agonist, may be effective in a larger percentage of patients **(137 [EL 2], 138 [EL 3], 218 [EL 3]) (Grade B)**. In a series of 64 patients with acromegaly treated with cabergoline for 3 to 40 months at dosages between 1.0 and 1.75 mg/wk, decreases in GH and IGF-I levels were noted in almost 40% of patients **(137 [EL 2])**. A recent meta-analysis has further supported these findings **(219 [EL 3])**. In contrast to management of prolactinoma, higher doses of cabergoline—up to 7 mg weekly—may be needed for normalization of GH and IGF-I levels in acromegaly **(220 [EL 3])**. The response to treatment appeared to be more pronounced in those cases with minimal elevation of IGF-I levels or with cosecretion of prolactin (or both). Other studies, however, have not indicated that cosecretion of prolactin predicts a dopamine agonist response **(138 [EL 3], 220 [EL 3]) (Grade C)**. Repeated GH, prolactin, and IGF-I levels should be determined 4 to 6 weeks after each dose change for a dopamine agonist **(137 [EL 2]) (Grade B)**. Overall, dopamine agonists are less effective than SSAs, and there are limited data available on tumor shrinkage **(Grade C)**. Because of the lower cost of cabergoline in comparison with either SSAs or pegvisomant and the finding that cabergoline may be useful in a subset of patients, however, cabergoline may be considered as first-line medical therapy in patients with modest IGF-I elevations or in the

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setting of combination therapy with SSAs **(218 [EL 3], 219 [EL 3]) (Grade C)**. Side effects include gastrointestinal upset, nasal congestion, fatigue, orthostatic hypotension, and headache. Cabergoline may be better tolerated than bromocriptine **(Grade C)**. When administered in higher doses (for example, more than 3 mg daily) in patients with Parkinson disease, cabergoline has been associated with an increased risk of echocardiographically evident valvular abnormalities **(221 [EL 2]) (Grade C)**. Although there are no definitive data that link cabergoline with echocardiographically evident valvular abnormalities in acromegaly and there are no systematic reports that have determined that these changes translate into hemodynamically significant valvulopathies, the extent to which this finding applies to patients with acromegaly remains unclear **(Grade D)**.

9.3.2. Somatostatin Analogues

The physiologic rationale for the use of SSAs in the management of acromegaly is based principally on the inhibitory effects of native somatostatin on GH secretion. Although the initial formulations for SSAs (octreotide and lanreotide) were administered subcutaneously up to 3 or 4 times a day, the newer formulations are longer acting and necessitate intramuscular or deep subcutaneous injections once monthly. The package insert for octreotide LAR includes a recommendation that short-acting subcutaneously administered octreotide should be given for 2 weeks at a dosage of 0.1 mg 3 times daily before initiation of treatment with the long-acting octreotide LAR depot in order to assess the response to and systemic tolerability of octreotide. In general practice, however, this recommendation is not followed; 1 or 2 doses of short-acting octreotide are administered subcutaneously to assess for major toxic effects **(222 [EL 3]) (Grade C)**. SSAs successfully reduce GH and IGF-I levels in 50% to 70% of patients, with an IGF-I normalization rate of approximately 30% in patients in whom pituitary surgery has failed **(223 [EL 2])**. In patients whose GH levels return to baseline before the end of the dosing interval, the frequency of administration can be further increased **(Grade C)**. With use of the short-acting subcutaneous preparations, an increase in the daily dose beyond 300 to 600 μg rarely achieves a greater effect **(223 [EL 2]) (Grade C)**. The short-acting agents offer the advantages of being self-administered, rapid acting, and considerably less expensive than longer-acting preparations. Nevertheless, with long-term use, most patients requiring SSA treatment typically use the longer-acting depot preparations that include octreotide LAR and lanreotide Autogel, whose features will be described next.

9.3.2.1. Effect on biochemical control

After administration of a new dose of a long-acting SSA, the serum IGF-I level should be measured 3 months later, and there is evidence that further declines in GH and IGF-I values may occur for up to 6 months **(Grade B)**. The effectiveness of SSAs in achieving biochemical remission was assessed in a meta-analysis of 44 trials **(223 [EL 2])**. The criteria for efficacy of treatment with octreotide LAR generally involved normalization of the IGF-I concentration, a mean GH value less than 2.5 ng/mL, a GH level less than 1 ng/mL during an OGTT, or some combination of these factors. Among all patients treated with octreotide LAR, 57% had normalization of the GH value, and 67% reached normal IGF-I levels. It must be emphasized that such meta-analyses were based primarily on studies in which SSAs were used in the adjunctive setting. Octreotide LAR and lanreotide Autogel have similar pharmacologic and efficacy profiles **(224 [EL 2]) (Grade B)**. Increasing the SSA dosage to 60 mg/mo of octreotide LAR may improve results in patients resistant to conventional doses **(225 [EL 3])**. Conversely, in some cases in which IGF-I levels decline excessively, SSAs may be administered at 6-week intervals or longer **(Grade B)**. Although data from studies powered for primary medical therapy have demonstrated benefit in the de novo setting **(212 [EL 3])**, meta-analyses comparing short-term and long-term outcomes in the primary versus adjunctive setting are required.

9.3.2.2. Predictors of response

SSA responsiveness has been correlated in some, but not all, studies with somatostatin receptor subtype 2 density, although somatostatin receptor subtype analysis is not routinely performed on the tumors **(202 [EL 3]) (Grade C)**. Maximal suppression with the short-acting SSAs is reached within 2 hours and typically lasts for approximately 6 hours. Because the GH decline is rapid after injection of a short-acting SSA, an assessment may be conducted at the outset to identify potential responsiveness to octreotide. An immediate GH decrement after a single subcutaneous dose of octreotide, however, has not been shown to be accurate in predicting biochemical remission **(226 [EL 2]) (Grade C)**. Radiolabeled octreotide imaging has also been used for potential prognostic capability, although the long-term SSA response does not clearly correlate with radiotracer uptake **(226 [EL 2]) (Grade C)**. Important predictors of response include smaller, less invasive pituitary tumors and lower baseline GH and IGF-I levels **(201 [EL 3]) (Grade C)**. Pathologic analysis may have prognostic value as well; the GH inhibitory effects of octreotide appear to be significantly better in patients who are found to have densely granulated somatotroph adenomas in comparison with those harboring sparsely granulated GH adenomas **(201 [EL 3]) (Grade C)**.

9.3.2.3. Effect on tumor size

An important goal in the management of acromegaly is tumor size shrinkage, if not complete resolution. Several studies have examined the effect of primary therapy with SSAs on tumor size. A systematic review of 15 studies was conducted to examine the extent of tumor shrinkage with

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primary SSA therapy **(227 [EL 2]) (Grade B)**. Results from 14 of the studies showed that 36.6% of patients had a significant (10% to >45%) reduction in tumor size. Of note, there did not appear to be a significant difference in the groups receiving short-acting versus long-acting octreotide. The weighted mean reduction for patients who experienced significant tumor shrinkage based on 7 of the studies was approximately 50% **(227 [EL 2], 228 [EL 3])**. Moreover, the frequency of tumor shrinkage seems to be nearly equal in those with microadenomas and those with macroadenomas **(222 [EL 3]) (Grade C)**.

9.3.2.4. Adverse events

Early adverse events associated with use of SSAs include transient abdominal cramps and malabsorptive diarrhea. Long-term use of SSAs is also associated with an increased incidence of gallbladder sludge and gallstone formation, but these effects are not typically of clinical significance **(223 [EL 2]) (Grade B)**. Less frequently, hair loss or, even more uncommonly, bradycardia or constipation is experienced. SSAs appear to cause a moderate impairment of glucose tolerance, and overt diabetes mellitus may be infrequently detected **(229 [EL 3]) (Grade C)**. In patients in whom SSA therapy worsens glucose control, reduction of the SSA dose, addition of or substitution with a GH receptor antagonist, or diabetes management with glucose-lowering agents should be considered **(230 [EL 3], 231 [EL 3]) (Grade C)**. Long-acting SSAs are also expensive, a factor that may limit accessibility (see section 9.6 on cost considerations).

9.3.3. Pegvisomant (GH Receptor Antagonist)

Pegvisomant is a recombinantly derived analogue of human GH that acts as a highly selective GH receptor antagonist **(216 [EL 2], 217 [EL 2]) (Grade B)**.

Under normal circumstances, GH binds to a preformed GH receptor dimer at 2 distinct sites to provoke cellular signaling and GH effect. Pegvisomant abrogates functional receptor dimerization and subsequent intracellular signaling. Treatment with pegvisomant results in a dose-dependent reduction of serum IGF-I levels but an increase in circulating GH levels. Therefore, serum IGF-I, and not GH, is used to monitor the biochemical response to therapy **(Grade B)**.

9.3.3.1. Long-term results

Several studies have assessed the long-term effects of pegvisomant therapy in acromegaly. One of the relatively large double-blind, randomized, placebo-controlled trials involved 111 patients with acromegaly who received treatment for 12 weeks with placebo or 1 of 3 dosages of pegvisomant, including 10, 15, or 20 mg administered subcutaneously daily **(216 [EL 2])**. Patients treated with the highest dose had a reduction of IGF-I levels of up to 60% and a normalization of IGF-I in 89% of cases. These patients also experienced a reduction in their symptom and sign scores in a dose-dependent manner.

In an open-label follow-up to this first study, 152 patients were treated with pegvisomant for up to 18 months **(217 [EL 2])**. In the group of patients treated for 12 months (N = 90), the IGF-I level was normalized in 97% of patients, reflecting a success rate higher than other existing pharmacotherapies. In addition to the reduced level of IGF-I, there was a parallel increase in GH values that plateaued by 6 months of pegvisomant treatment. On average, GH levels increased 12 to 14 ng/mL. This increase in GH concentration is likely the result of augmented pituitary GH secretion due to interrupted negative feedback resulting from diminished IGF-I production and cross-reactivity by the assay of the drug.

A recent study showed that a mean daily pegvisomant dose of 17.4 mg was required for IGF-I normalization, although some patients may require much higher doses, such as up to 40 mg daily **(232 [EL 3])**. Paradigms of administration of weekly or twice-a-week formulations of pegvisomant have been used, and less frequent administration may prove easier for patient use **(233 [EL 3]) (Grade C)**. In recent studies, pegvisomant administration resulted in improvement in glucose homeostasis, in contrast to a subset of patients receiving SSAs **(229 [EL 3])**. Therefore, pegvisomant may be useful in patients with glucose intolerance or overt type 2 diabetes mellitus **(Grade C)**.

9.3.3.2. Adverse events

Unlike SSAs and dopamine agonists, pegvisomant does not target the tumor or have tumor antiproliferative effects. Although several cases of tumor growth during pegvisomant therapy have been reported **(217 [EL 2])**, observational studies have shown this to be an uncommon finding that may reflect the presence of more aggressive tumors or may possibly be a rebound effect due to withdrawal of SSAs **(234 [EL 2]) (Grade C)**. Therefore, patients receiving this GH receptor antagonist require close observation with serial MRI scans, such as at 6-month intervals during the first year of management and then at annual intervals **(Grade C)**. Pegvisomant should probably not be the first-line pharmacologic therapy in patients with large macroadenomas or tumors of any size near the optic chiasm **(Grade C)**. Pegvisomant therapy is associated with abnormal results of LFTs, and in the German Pegvisomant Observational Study, transaminase levels greater than 3 times normal were noted in 5.2% of patients **(235 [EL 3]) (Grade B)**. Of note, 58% of these patients had normalization of transaminase levels with continued treatment, and another 33% had normalization after discontinuation of pegvisomant therapy. These transaminase elevations are usually asymptomatic, and often transient and self-limiting, despite continued administration of pegvisomant **(235 [EL 3])**. Nevertheless, results of LFTs need to be monitored regularly in patients receiving pegvisomant treatment

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(Grade B). Other more uncommon side effects include a flulike illness, local allergic reactions, and local lipohypertrophy **(236 [EL 3]) (Grade C)**.

9.4. Estrogens or Selective Estrogen Receptor Modulators as Alternative Considerations

Orally administered estrogens have long been recognized for their ability to attenuate GH-induced IGF-I production. Indeed, their use for this application was more common decades before the availability of the more current agents **(237 [EL 3])**. In a recent study of female patients with persistent active acromegaly, the addition of a ethinyl estradiol/levonorgestrel combination to octreotide LAR resulted in IGF-I normalization in 6 of 7 patients **(238 [EL 4])**. In another report of 8 men with active disease, the short-term use of the selective estrogen receptor modulator raloxifene normalized IGF-I levels in 2 patients without affecting GH levels **(239 [EL 2])**. More effective therapies and concerns regarding the safety of long-term estrogenic compounds have diminished interest in this approach. Nevertheless, orally administered estrogens and selective estrogen receptor modulators are worthy of consideration in selected cases.

9.5. Combination Medical Therapy

In patients with a partial biochemical response to SSA therapy, addition of either cabergoline or pegvisomant should be considered **(Grade C)**.

9.5.1. Combination of SSA and Cabergoline

Some published studies have indicated that the dopamine agonist cabergoline may be useful as an adjunct to SSAs in patients who are resistant to SSAs **(218 [EL 3])**. In one study of 19 patients with a partial response to SSA treatment, the addition of cabergoline resulted in normalization of IGF-I levels in 8 (42%) **(138 [EL 3])**. In this study, the presence of positive tumor immunocytochemistry for prolactin or hyperprolactinemia did not correlate with GH and IGF-I reduction. Therefore, the combination of cabergoline and SSA therapy may be effective in a subset of patients, even in the absence of associated hyperprolactinemia **(Grade C)**.

9.5.2. Combination of SSA and Pegvisomant

Studies have been conducted to examine the use of a combination of SSA and pegvisomant. The combination of these 2 medications appeared to be more effective in lowering IGF-I levels in comparison with either SSA or pegvisomant treatment alone **(233 [EL 3], 240 [EL 3]) (Grade C)**. The addition of weekly pegvisomant therapy at a mean dosage of 60 mg per week for 42 weeks to patients with resistance to SSAs resulted in normalization of IGF-I levels in 95% of patients **(240 [EL 3])**. No enlargement of pituitary tumors was seen, but mild increases in liver enzymes were noted in 38% of patients (elevated results of LFTs are more common in the setting of combination therapy versus pegvisomant monotherapy). The improved glucose homeostasis versus SSA therapy alone **(229 [EL 3])** and the benefit of tumor volume control over pegvisomant monotherapy **(235 [EL 3])** may lead to an advantage for this combination therapy **(Grade C)**. Thus, for patients exhibiting partial sensitivity to SSAs, the addition of pegvisomant therapy should be considered **(Grade C)**. In a recent study focused on those patients who were resistant to SSAs, however, the combination of these 2 agents was equally as effective as pegvisomant therapy alone in reducing IGF-I levels **(241 [EL 3]) (Grade C)**. Those patients showing more complete resistance to SSAs should be considered for pegvisomant monotherapy **(Grade C)**. Such recommendations should harmonize optimal IGF-I responses and tumor size restraint with cost-effective, fiscally responsible long-term treatment plans.

9.6. Cost Considerations

Acromegaly is also a disease with a substantial economic burden. Longitudinal assessment of the economic costs relative to clinical and biochemical outcomes was examined for a 4-year period in 53 Canadian patients **(242 [EL 2])**. The mean annual cost per patient in Canadian dollars was $8,111 (95% confidence interval, $5,848 to $10,374). GH- and IGF-I-reducing medications constituted the largest component (nearly 38%) of the overall cost of management **(Grade C)**. It should be emphasized that although surgical costs per patient were high ($2,800 to $9,200), the 4-year mean annual cost was approximately $2,400 less than the cost of medications. Furthermore, treatment of patients with macroadenomas costs considerably more annually ($11,425) than treatment of those with microadenomas ($4,442); this fact emphasizes the importance of earlier diagnosis **(Grade C)**. In addition, a recent study indicated that, to be cost-effective, the price of pegvisomant should be reduced by a third **(243 [EL 2]) (Grade C)**. Although these are considerable costs, they are not significantly higher than those associated with other chronic diseases. Short-acting SSAs, administered as subcutaneous injections, are appreciably less expensive than long-acting depot preparations and may be considered in the setting of financial constraints **(Grade C)**. There has also been consideration that the combination of the GH receptor antagonist, pegvisomant, and an SSA may result in lower doses of each medication, eventuating in lower annual costs **(240 [EL 3]) (Grade D)**. There is a significant cost differential between cabergoline and SSAs. In the United States, the annual retail cost of generic cabergoline (assuming a dosage of 2 mg weekly) is approximately a fifth that of Sandostatin LAR (assuming a dosage of 20

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mg monthly) **(244 [EL 1])**. Cost is one of the factors that is considered for use of cabergoline as first-line medical therapy in patients with moderate disease **(Grade D)**.

10. ROLE OF RADIATION THERAPY

Pituitary irradiation in acromegaly is generally considered an adjunctive therapy in patients not fully responding to surgical and medical treatments **(14 [EL 4], 194 [EL 3], 245 [EL 4]) (Grade C)**. It may be administered to control excess GH secretion or tumor expansion (or both) **(245 [EL 4]) (Grade C)**. With the availability of effective medical therapy, the role of RT for patients with acromegaly has diminished. Nevertheless, it has been used to limit lifelong medical therapy and with a goal of disease cure **(194 [EL 3], 246 [EL 4]) (Grade C)**. Although the effect on tumor growth can be quite rapid, the full therapeutic effect to control excess GH secretion, if it occurs, can take from several years to more than a decade, depending on what modality has been used **(247-249 [EL 3])**. For this reason, RT is rarely used as primary treatment in patients with acromegaly unless there are contraindications to surgical intervention or a poor response to or tolerability of medical therapy **(194 [EL 3]) (Grade C)**. The techniques of RT have improved over the years, with better targeting of the therapy to the tumor and avoidance of unnecessary radiation exposure to surrounding tissues.

10.1. Types of Radiation Treatments

There are 2 main types of RT used for patients with acromegaly: conventional fractionated RT and stereotactic radiosurgery. Fractionated RT is typically administered in dosages of 160 to 180 centigray (cGy) 4 to 5 days per week over a 5- to 6-week period up to a total dose of 4,500 to 5,000 cGy **(Grade B)**. This RT technique concentrates the beam on the target mostly from 2 to 3 portals, with the patient being immobilized in a tight-fitting mask that has a relocation accuracy of 2 to 5 mm **(250 [EL 4])**. Fractionated RT may also include use of proton particles administered by means of a cyclotron.

Stereotactic radiosurgery includes several modalities, such as Gamma Knife, CyberKnife, and a linear accelerator, which delivers high-energy photons. Some centers use proton particles for stereotactic radiosurgery **(251 [EL 3])**. In acromegaly, the preponderance of experience with stereotactic radiosurgery involves Gamma Knife radiotherapy, which is usually delivered by a cobalt 60 gamma radiation source as a single treatment through a hemisphere, which is placed around the patient's head. Greater precision is achieved by using a firmer immobilization and delivery of RT through a larger number of conformal beams. Only limited data are available on the use of linear accelerator, CyberKnife, and proton beam radiosurgery in patients with acromegaly **(252-255 [EL 3])**.

10.2. Choice of RT

10.2.1. Conventional RT

Conventional RT has been used for years in treatment of patients with acromegaly. With the change in sensitivity of GH assays and definition of acromegaly biochemical control over the years, the reported remission rate after RT has also changed. Moreover, published studies must be scrutinized carefully because reported remission rates may include patients with biochemical variables controlled with or without concomitant medical therapy **(Grade B)**. Most studies before 1995 that used a GH cutoff value of <5 to 10 ng/mL reported a >80% remission rate **(256 [EL 3], 257 [EL 4]) (Grade C)**. In patients with more than 10 to 15 years of follow-up and with use of more restricted remission criteria (random GH measurement <2.5 ng/mL [or GH level <1 ng/mL during OGTT] and normal age- and sex-adjusted IGF-I value), however, most studies indicate a 10% to 60% remission rate **(247-249 [EL 3], 255 [EL 3], 258-261 [EL 3]) (Grade C)**.

The mean time to remission after conventional RT is about 10 years, which is usually longer in patients with higher initial GH and IGF-I levels **(247-249 [EL 3], 255 [EL 3], 262 [EL 3])**. Most patients will require medical therapy during the long latency period, which is one of the drawbacks of RT **(Grade B)**. Periodic withdrawal of medical therapy is recommended in order to assess the effect of RT and the need for continuation of medical therapy **(245 [EL 4]) (Grade B)**. In patients achieving a normal IGF-I level, it is reasonable to schedule an annual "drug holiday" with reassessment of GH and IGF-I values **(Grade C)**. The medications need to be withheld for 1 to 3 months, depending on the medical agent (or agents) used for reassessment of hormone variables **(249 [EL 3], 258 [EL 3]) (Grade C)**. Conventional RT achieves tumor control in more than 90% and 85% of patients with acromegaly at 10 and 20 years, respectively, and a decrease in tumor volume is expected in about 50% of patients **(259 [EL 3], 263 [EL 3], 264 [EL 2], 265 [EL 3])**. Tumor progression after fractionated RT is rare **(257 [EL 4], 263 [EL 3])**.

10.2.2. Stereotactic Radiosurgery

Because most of the literature regarding use of stereotactic radiosurgery for acromegaly involves use of the Gamma Knife, this section will focus on studies involving this modality. Gamma Knife surgery delivers narrow beams with stereotactic precision and accuracy on the target tumor with the aim of minimizing injury to surrounding tissues. Because of the technical advances and convenience of Gamma Knife over fractionated RT, there has been a trend toward use of radiosurgery in most patients being considered for RT unless the technology is not available locally, there is a substantial residual tumor burden, or the tumor is too close to the optic chiasm **(247 [EL 3], 250 [EL 4]) (Grade C)**.

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Some of the older studies reported a 90% remission rate (defined as a GH level <5 ng/mL), but with use of more strict remission criteria (random GH measurement <2.5 ng/mL [or GH level <1 ng/mL during OGTT] and normal age- and sex-adjusted IGF-I value), the reported remission rate is 17% to 50% during a follow-up period of 2 to 5 years without medical therapy **(266-271 [EL 3])**. A more prolonged follow-up is necessary, however, to define the actual remission rate. In some studies, the mean time to biochemical remission for Gamma Knife radiosurgery is about 2 years, which is shorter in comparison with conventional RT **(266-269 [EL 3], 271 [EL 3], 272 [EL 4], 273 [EL 3])**. Because patients undergoing Gamma Knife radiosurgery usually have lower baseline GH levels in comparison with those treated with conventional RT, however, the rate of decline in GH level may not be different **(272 [EL 4])**, and it remains unclear whether Gamma Knife radiosurgery leads to more rapid biochemical control **(Grade C)**. Periodic withdrawal of medical therapy after radiosurgery will be necessary for biochemical assessment, similar to the situation with conventional RT (see section 10.2.1).

Because of the technical improvement in Gamma Knife radiosurgery, currently tumors as close as 5 mm to the optic chiasm are considered potentially eligible for this mode of treatment **(250 [EL 4]) (Grade C)**. Similar to conventional RT, studies show tumor stabilization after radiosurgery and a decrease in tumor size in up to 75% of the patients **(267-270 [EL 3])**.

There are scattered data in different case series regarding the use of repeated RT in patients with uncontrolled acromegaly who had undergone irradiation previously within a window of 2 to 17 years **(266-269 [EL 3], 274 [EL 3])**. Repeated irradiation of a pituitary adenoma may be considered after careful consideration of alternative treatment options, the interval from prior RT, and the details of the prior RT (including technique, dose, and site of irradiation, as well as the fractionation schedule) **(Grade D)**. There is no clear consensus about the time interval for considering repeated RT **(Grade D).** There appears to be an increased incidence of side effects, including hypopituitarism, visual deficit, and radionecrosis, after such combination RT procedures **(266 [EL 3], 269 [EL 3], 274 [EL 3], 275 [EL 3], 276 [EL 4])**. There is a distinct need for further studies, however, in order to provide a clearer perspective **(Grade C)**.

10.2.3. Complications of RT

The main limitations for RT in patients with acromegaly are the development of hypopituitarism and long-term safety **(Grade A)**. In most studies, the rate of occurrence of hypopituitarism is more than 50% after 5 to 10 years and seems to increase further with time **(247 [EL 3], 249 [EL 3], 255 [EL 3], 260-262 [EL 3], 266 [EL 3], 268 [EL 3], 269 [EL 3], 277 [EL 3], 278 [EL 2])**. Therefore, long-term follow-up and evaluation of pituitary function at intervals are necessary **(278 [EL 2]) (Grade B)**. The incidence and severity of hypopituitarism after RT seem to be dose dependent **(279 [EL 4], 280 [EL 2])**. Hypopituitarism has been linked to increased mortality, mainly attributable to cardiovascular and cerebrovascular events **(281-283 [EL 3])**. With the caveat that the mean duration of follow-up for most studies involving Gamma Knife radiosurgery has been less than 6 years, the prevalence of hypopituitarism after stereotactic radiosurgery has been similar to that after conventional RT **(250 [EL 4], 266-269 [EL 3], 271 [EL 3], 273 [EL 3], 284-288 [EL 3])**. The risk of hypopituitarism needs special consideration in young patients, particularly with regard to fertility issues **(Grade B)**.

Fractionated RT may be associated with an increased risk of cerebrovascular disease, depending on the dose delivered **(12 [EL 3], 217 [EL 2], 281 [EL 3], 283 [EL 3], 289 [EL 3], 290 [EL 3])**. In a recent study by Sherlock et al **(291 [EL 3])** involving 501 patients with acromegaly, there was a significant increase in all-cause mortality in patients who received RT (N = 237) in comparison with those who did not (N = 264) during 14 years of follow-up. The associated increased mortality continued to be significant after correcting for GH level, sex, hypopituitarism, attained age, period of follow-up, and pretreatment GH level. Among those patients exposed to RT, there was an approximate 4 times increased risk of cerebrovascular death **(291 [EL 3])**. Because of the selection bias in those undergoing RT (more aggressive disease, poorer acromegaly control), the independent role of RT in occurrence of cerebrovascular disease needs to be examined further. Long-term data on such risks in patients undergoing Gamma Knife radiosurgery are not available **(194 [EL 3])**. There is also a concern regarding the rare but feared loss of vision in patients undergoing RT; in the majority of studies, this complication has been reported in 0% to 3% of the patients **(248 [EL 3], 255 [EL 3], 264 [EL 2], 266 [EL 3], 267 [EL 3], 269 [EL 3], 270 [EL 3], 275 [EL 3], 292 [EL 3]) (Grade C)**. Optic neuropathy seems to be an unlikely event if there is less than 8 to 10 Gy exposure to the optic pathways **(245 [EL 4], 269 [EL 3])**. Performance of debulking surgery before RT and the use of modern MRI techniques, allowing for more precise delivery of RT, are believed to be among the reasons for the decreased risk of optic neuropathy after RT **(245 [EL 4])**.

The risk of cerebrovascular disease in patients with acromegaly undergoing RT appears to be increased in comparison with those treated otherwise **(12 [EL 3])**. Radiation-induced secondary tumors and radionecrosis have been reported in ≤2% of patients undergoing conventional RT **(293-296 [EL 2], 297 [EL 3])**. In a review among 1,567 patients treated with Gamma Knife radiosurgery, 0.8% developed radionecrosis **(276 [EL 4])**. About half of these patients had been treated previously with

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conventional irradiation. The risk of cognitive deficit after RT continues to be controversial **(194 [EL 3], 298-300 [EL 3]) (Grade C)**.

Of note, most data in the literature about complications of RT in patients with acromegaly have been derived from retrospective case series, and underreporting may be a confounding factor. On the other hand, most published data are based on older radiation techniques with imprecise target definition, and newer delivery systems may potentially yield a better side effect profile **(194 [EL 3])**.

10.2.4. Role of Medical Therapy as Radioprotective or Radiosensitizer Agents

The role of SSAs and, to a lesser degree, dopamine agonists as radioprotective agents at the time of RT has been suggested by some, but not all, studies and continues to be a controversial subject **(266 [EL 3], 267 [EL 3], 269 [EL 3], 301 [EL 3])**. Although SSAs are often withheld at the time of RT, this practice is not based on well-controlled studies **(Grade C)**.

11. ACROMEGALY AND PREGNANCY

Pregnancy in a woman with acromegaly presents particular issues for management. These issues relate to concern about the effects of pregnancy on acromegaly activity, questions regarding therapy for acromegaly during pregnancy, and concerns about neonatal outcome.

11.1. Effect of Pregnancy on Biochemical and Tumor Variables and Neonatal Outcomes in Acromegaly

11.1.1. Effect of Acromegaly on Serum GH and IGF-I Levels During Pregnancy

The physiologic aspects of GH secretion are altered during normal pregnancy. Pituitary GH is the primary circulating GH during the first trimester, although placental GH variant becomes the major circulating form during the remainder of the pregnancy **(302 [EL 2])**. The increase in placental GH causes an increase in the IGF-I levels during normal pregnancy **(303 [EL 2])**. Therefore, the rise in serum IGF-I during pregnancy does not appear to be pituitary dependent. In patients with acromegaly, GH hypersecretion by the pituitary adenoma remains autonomous, and GH levels remain elevated and largely unchanged during the pregnancy **(304 [EL 3], 305 [EL 3])**. Serum IGF-I levels increase throughout pregnancy in patients with acromegaly as well **(304 [EL 3], 305 [EL 3])**. There is substantial overlap of serum IGF-I levels, however, in normal pregnant patients and pregnant patients with acromegaly, and serum IGF-I levels are not as useful for monitoring activity during pregnancy **(Grade C)**. Nevertheless, as a guide, IGF-I levels typically do not increase by more than 25% to 50% above prepregnant levels **(304-306 [EL 3])**.

11.1.2. Effect of Pregnancy in Acromegaly on Somatotroph Tumor Size

Because estrogen receptors are found on GH-secreting tumors **(307 [EL 1])**, particularly in tumors that concurrently secrete prolactin **(308 [EL 1])**, there is concern about tumor growth during pregnancy. It is reassuring that tumor size does not increase in most patients. In a study of 27 patients in whom MRI scans were performed 6 months after delivery, the adenoma volume increased in 3 patients with macroadenomas—2 women with visual complications and another who required surgery when she had been pregnant for 3 months **(306 [EL 3])**. In this same study, the tumor was stable in 23 patients (85%). In another series, 1 of 2 GH-secreting macroadenomas increased in size during pregnancy **(309 [EL 3])**. Because there is a risk of tumor growth during pregnancy, particularly in patients with macroadenomas, serial visual field monitoring should be performed during pregnancy in patients who had detectable tumor before pregnancy **(Grade C)**.

11.1.3. Effect of Acromegaly on Maternal and Neonatal Outcomes

In many patients, signs and symptoms of acromegaly are not exacerbated during pregnancy, and in one series, they worsened in only 4 of 24 patients (17%) **(310 [EL 3])**. A potential explanation for the relatively infrequent worsening of signs and symptoms of acromegaly during pregnancy is a relative decrease in IGF-I secretion attributable to the GH-antagonistic effect of estrogen **(237 [EL 3], 311 [EL 3])**. This may result in a state of relative GH resistance. With regard to maternal outcomes, gestational diabetes mellitus was diagnosed in 7% and gestational hypertension in 14% in one French series of 59 pregnant patients with acromegaly—both more frequent than found in the French general population **(306 [EL 3])**. These pregnancy-related complications, although aggravated by the GH hypersecretion, have not had a substantial effect on maternal health. Such maternal comorbidities should be managed as in a population of pregnant patients without acromegaly **(Grade 4)**. Neonatal outcome is largely unaffected by the acromegaly; no major fetal malformation risk has been reported **(310 [EL 3], 312 [EL 3])**.

11.2. Management of Acromegaly During Pregnancy

Although most patients with acromegaly are able to reach full-term pregnancy without major complications, pregnancy can adversely affect tumor size and signs and symptoms of acromegaly in a subset of patients. Therefore, surgery or medical therapy may be used in the management of such patients.

11.2.1. Surgery in the Pregnant Patient With Acromegaly

In a situation of pituitary tumor enlargement with visual field loss, surgery may be necessary for visual

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sparing, similar to the situation in the nonpregnant state. There are limited available data, mostly as case reports, about surgery in the pregnant patient with acromegaly. With regard to the safety of surgery in patients with pituitary tumors, one series found no difference in spontaneous abortion and prenatal mortality rates. An increased incidence of prematurity (37% versus 8%), however, was observed in the offspring of patients undergoing intrapartum pituitary surgery in one study **(313 [EL 3])**. More current studies are needed to address this subject.

11.2.2. Medical Management During Pregnancy

11.2.2.1. Dopamine agonist therapy

In light of the experience with use in patients with prolactinoma, bromocriptine administration during pregnancy has not been associated with an increase in neonatal risk or congenital malformations **(314 [EL 2])**. Bromocriptine has been used during pregnancy in patients with acromegaly, and has been useful for managing signs and symptoms of acromegaly, without neonatal complications **(305 [EL 3], 306 [EL 3])**. There is limited experience with the use of cabergoline for acromegaly management during pregnancy.

11.2.2.2. SSA therapy

Because SSAs can cross the placenta and reach the fetal circulation **(312 [EL 3])**, there has been concern regarding the safety of SSA use during pregnancy. Although a subcutaneous injection of octreotide can cause an acute decrease in uterine artery blood flow, longer use of octreotide does not appear to cause adverse effects on the course of pregnancy, on delivery, or on fetal development. There have been a number of cases in which octreotide was used in pregnant patients **(305 [EL 3], 306 [EL 3], 315 [EL 3])**, and most of these pregnancies were uneventful. In a few cases of pregnant patients given SSA therapy, the resultant infants were small for gestational age, although the causality was not clear **(306 [EL 3])**.

11.2.2.3. Pegvisomant therapy

Data for pegvisomant use during pregnancy are limited to a single case in which pegvisomant administration was well tolerated, the patient's condition was well controlled, and the infant was normal in size and health **(316 [EL 3])**. At this point, no further recommendations can be made relative to the use of pegvisomant in a pregnant patient with acromegaly **(Grade D)**.

11.3. Use of Medical and Surgical Therapy in Pregnant Patients With Acromegaly

The management of pregnant patients with acromegaly depends on the tumor size, the presence of mass effects, and the degree of acromegaly activity. For better stratification of patient management, an MRI scan should be performed and GH and IGF-I hormonal status should be determined just before pregnancy. In a patient with a microadenoma, it is advised to discontinue medical therapy when pregnancy is determined **(Grade C)**. This recommendation is based on the aforementioned findings (see sections 11.1.2 and 11.1.3) that the risks of both fetal malformation and growth of a macroadenoma are small in untreated pregnant patients with acromegaly. In a patient with acromegaly who has a macroadenoma without mass effects, medical therapy may be withheld at conception **(305 [EL 3]) (Grade C)**. Close follow-up with serial visual field testing during pregnancy, particularly in the setting of a macroadenoma, should be performed because of the small risk for tumor expansion. If the patient develops worsening of symptoms, medical therapy can be reinitiated, with a goal to ameliorate the specific concerns **(310 [EL 3])** and not to normalize the level of IGF-I, inasmuch as IGF-I values are not useful as a benchmark of acromegaly activity during pregnancy **(306 [EL 3]) (Grade C)**. Evidence of visual field compromise should necessitate performance of an MRI scan (without gadolinium—for maternal safety) to assess tumor anatomy, and further treatment, such as surgical or medical therapy, should be considered in the setting of visual loss **(Grade C)**. It has also been advised that medical therapy with a long-acting SSA should be discontinued 2 to 3 months before a planned pregnancy **(305 [EL 3])**, depending on the clinical status of the patient **(Grade D)**.

12. PITUITARY GIGANTISM

Gigantism refers to excess GH secretion that occurs during childhood when growth plates are open, leading to accelerated vertical growth. This is in contrast to acromegaly, in which GH hypersecretion occurs after epiphyseal plate closure and stature is not affected. During adolescence, vertical growth is aggravated by hypogonadotropic hypogonadism and the resulting lack of gonadal steroids, which delays epiphyseal closure. True gigantism is rare and usually caused by a pituitary mammosomatotroph adenoma **(317 [EL 3], 318 [EL 4])**. In one series of 2,367 children and adolescents with a pituitary adenoma, pituitary gigantism was found in only 0.6% **(173 [EL 3])**. Boys and girls are equally affected.

12.1. Clinical Presentation

In children, an evaluation should be considered after an unexpected change in growth velocity. This accelerated growth beyond pubertal limits may be accompanied by mild to moderate obesity. Patients may have progressive macrocephaly, especially during infancy. The clinical presentation is accompanied by oligomenorrhea or amenorrhea in girls and by mass effects, such as visual field compromise, in boys **(317 [EL 3])**. Because of the insidious onset of acromegaly, the diagnosis can be delayed by 6 to 8 years, presenting a diagnostic challenge **(11 [EL 3])**. In contrast, the late presentation of a patient with gigantism

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is dramatic, and the diagnosis becomes more straightforward **(318 [EL 4])**. The diagnosis is usually made earlier in girls than in boys, presumably because of the menstrual dysfunction and the socially unacceptable vertical growth **(317 [EL 3], 318 [EL 4], 319 [EL 3])**.

12.2. Diagnosis of Gigantism

Diagnostic measures include growth charts that demonstrate clear shifts from normal in height and weight curves. Biochemical tests with use of GH, IGF-I, and the OGTT are similar to those used for adults with suspected acromegaly. The important distinction is the use of appropriate normal age- and sex-based IGF-I concentrations **(Grade B)**. GH responses to glucose suppression are similar to those in adults **(317 [EL 3])**. It is important to consider, however, that the GH response to glucose suppression may be abnormal in the setting of tall adolescents without pathologic GH hypersecretion. In one prospective study of 126 tall adolescents without progressive GH hypersecretion, 31% had abnormal results of an OGTT **(320 [EL 3])**. Therefore, multiple factors, such as IGF-I values and physical examination findings including complete growth charts, are important in the diagnosis of gigantism **(Grade B)**.

Concurrent secretion of prolactin is more common in gigantism than in acromegaly **(317 [EL 3])**. Cardiovascular, respiratory, neoplastic, and metabolic complications are rare **(59 [EL 4])** in gigantism, and only one case of ketoacidosis **(321 [EL 3])** has been reported. The lack of severe comorbidities may reflect the shorter time to diagnosis in such patients **(318 [EL 4])**. Gigantism is usually associated with a macroadenoma, and microadenomas are rare. In children with gigantism, GH-secreting adenomas may be more aggressive and invasive than in adults with acromegaly **(173 [EL 3], 319 [EL 3])**. Genetic conditions such as McCune-Albright syndrome should be suspected when appropriate and confirmed with genetic testing. Long-term mortality rates are presumably similar to those in adults with acromegaly when GH and IGF-I levels are controlled, but long-term data are lacking. Many of these patients will need long-term medical treatment because irradiation is seldom used.

12.3. Treatment of Gigantism

Treatment goals with gigantism are similar to those in adult patients with acromegaly (see section 7), except for urgency to achieve biochemical control and arrest the potentially irreversible musculoskeletal deformities and pathologic tall stature **(Grade B)**. Treatment consists of surgery, medical therapy, and RT. RT, however, is used less frequently than in acromegaly because of the long-term consequences of irradiation during a longer life expectancy, including hypopituitarism and possible cognitive dysfunction **(Grade D)**. SSAs, dopamine agonists, and, more recently, pegvisomant **(322 [EL 3], 323 [EL 3])** have all been used successfully, with the same success rates as in adults with acromegaly. Use of combination SSAs plus dopamine agonist therapy is reasonable in tumors cosecreting GH and prolactin.

13. MONITORING AND TREATING COMORBIDITIES

The morbidities associated with GH-secreting pituitary adenomas are due to local mass effects of the tumor, sequelae of GH and IGF-I excess, and sequelae of other pituitary hormone deficiencies. In an effort to decrease the excess mortality attributable to cardiovascular disease, respiratory disease, and cancer, aggressive modification of risk factors and screening for early diagnosis should be implemented **(Grade C)**.

13.1. Skeletal and Dental Manifestations

Unlike the soft tissue changes, the bone enlargement that occurs with excess secretion of GH is not reversible with successful treatment **(324 [EL 2], 325 [EL 3], 326 [EL 3])**. Any corrective surgical procedure, such as maxillofacial correction of dental malocclusion, should be postponed until GH and IGF-I levels normalize **(327 [EL 3])** **(Grade D)**. Joint discomfort may, in part, be due to enlargement of soft tissues and retention of fluid, and symptoms of carpal tunnel syndrome may be the result of median nerve edema, both of which may improve with reduction of excess GH secretion **(36 [EL 3], 38 [EL 3], 48 [EL 3], 49 [EL 3], 324 [EL 2], 325 [EL 3], 326 [EL 3], 328 [EL 4], 329 [EL 3], 330 [EL 3], 331 [EL 4], 332 [EL 3], 333 [EL 3])**. Persistent carpal tunnel syndrome may necessitate further management, including surgical release **(Grade C)**. Established degenerative arthritis may be irreversible **(325 [EL 3], 326 [EL 3], 334 [EL 3])**. Painful arthropathy often persists despite biochemical control, and joint complaints are a major contributor to a perceived reduced quality of life despite long-term biochemical remission **(335 [EL 3], 336 [EL 3])**. Therefore, musculoskeletal complications should be managed aggressively with physical therapy, antiinflammatory and analgesic medications, and consideration of joint replacement surgery **(334 [EL 3], 335 [EL 3])**, as indicated **(Grade C)**. BMD may be reduced in the setting of hypogonadism **(43 [EL 3], 337 [EL 3], 338 [EL 4])**. Hypercalciuria and, rarely, hypercalcemia can occur with GH excess **(339 [EL 3])** and are due to altered vitamin D metabolism **(45 [EL 3])**; they reverse with cure of acromegaly **(340 [EL 3], 341 [EL 3], 342 [EL 3])**. In patients with persistent hypercalcemia after biochemical control, the presence of hyperparathyroidism and MEN 1 should be considered **(Grade B)**. Patients should be screened with bone densitometry and determination of serum calcium levels for coexisting metabolic bone disease **(Grade C)**. If osteoporosis is present and bone densitometry findings do not improve after correction of any associated

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hypogonadism or hypercalciuria, antiresorptive therapy should be considered **(Grade C)**.

13.2. Hypopituitarism

In patients with acromegaly, the time frame and the probability for developing hypopituitarism depend on the treatment used. Pituitary insufficiency that manifests preoperatively from tumor compression of the normal gland may diminish after successful surgical debulking, as with nonfunctioning macroadenomas **(343 [EL 3])** **(Grade C)**. Alternatively, new hormonal deficits may occur as a result of the surgical procedure. Patients who have received RT need lifelong monitoring of pituitary function **(Grade C)** because new deficits can occur up to 15 years or more after irradiation **(259 [EL 3])**. GH deficiency may develop after definitive therapy for acromegaly with irradiation, surgery, or both in 30% to 70% of patients **(262 [EL 3], 344-346 [EL 3])** and is associated with a diminished quality of life in comparison with patients who have GH sufficiency **(347 [EL 2])**. It has not been established whether such patients will benefit from GH replacement therapy. A recent randomized, placebo-controlled 6-month study in patients with acromegaly and GH deficiency showed that GH replacement improved quality of life and body composition, with few side effects **(348 [EL 2])**. In contrast, 2 small open-label trials demonstrated little, if any, clinical improvement, and in one of these, several patients experienced serious vascular events early in the trial **(349 [EL 3], 350 [EL 3])**. Further studies are needed to determine whether GH replacement is effective and safe and should be recommended for this patient population **(Grade C)**.

13.3. Respiratory Disorders

Successful treatment of acromegaly results in reduction in the size of soft tissues of the upper airway and reversal of the central component of sleep apnea, leading to improvement or elimination of sleep apnea **(351-356 [EL 3])**. Persistence of sleep apnea after treatment of acromegaly, however, is common **(357 [EL 3], 358 [EL 3])**. In patients who undergo GH-lowering therapy, such as surgical or medical treatment, assessment for sleep apnea should be performed once results of these interventions have been achieved, to determine whether biochemical control leads to resolution of signs and symptoms **(Grade B)**. Formal overnight polysomnography or home overnight oximetry (as a screening test for sleep apnea), followed by formal overnight polysomnography if the screening test shows abnormal results, should be performed in patients with active acromegaly and in patients with persistent symptoms despite biochemical control **(352 [EL 3])** **(Grade C)**. Appropriate management of sleep apnea should be provided if sleep apnea is present **(Grade C)**.

An increased mortality from respiratory causes in patients with acromegaly has been demonstrated in several retrospective studies **(4 [EL 3], 72 [EL 2], 256 [EL 3], 359 [EL 3])**, although the specific causes of death are not entirely clear. Some studies have shown a higher-than-normal risk for pulmonary infections as one cause of death in patients with acromegaly **(9 [EL 3], 72 [EL 2])**. Therefore, vaccinations for influenza and pneumococcal pneumonia should be given, as recommended by the Centers for Disease Control and Prevention, for patients with medical indications **(Grade C)**. For those patients who use tobacco, aggressive intervention for cessation of tobacco use should also be initiated **(Grade C)**.

13.4. Cardiovascular Disease and Cardiovascular Risk Factors

Standard therapy should be used for patients with left ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease, or ischemic heart disease **(Grade C)**. Limited information is available about the role of screening cardiac stress tests or echocardiography in patients with acromegaly or whether there is a role for serial echocardiographic monitoring. With lowering of GH concentrations, left ventricular hypertrophy and function may improve **(187 [EL 3], 360-366 [EL 3])**, dilated cardiomyopathy may reverse **(367 [EL 3])**, and endothelial dysfunction may improve **(368 [EL 3])**. In a 5-year prospective study, a significant decrease in resting heart rate and increase in left ventricular ejection fraction at peak exercise were observed in patients achieving biochemical control of acromegaly, whereas worsening was demonstrated in those patients with uncontrolled disease **(188 [EL 3])**. In this study, no difference in cardiac function changes was found between patients controlled by surgical treatment alone or by surgery plus octreotide therapy. Cardiac performance, however, normalizes in only about 50% of patients beyond 40 years of age **(369 [EL 3])**. Therefore, routine echocardiography should be considered in patients who have evidence of left ventricular hypertrophy by electrocardiography or who are symptomatic with shortness of breath, particularly in older patients **(Grade C)**. Hypertension may or may not improve with treatment of acromegaly **(363 [EL 3], 365 [EL 3], 370 [EL 3], 371 [EL 3])** and should be monitored **(Grade C)**. Impaired glucose tolerance and type 2 diabetes mellitus are common in patients with acromegaly **(53 [EL 3], 54 [EL 2], 372 [EL 3])**. Therefore, all patients should be tested for glucose intolerance or overt type 2 diabetes mellitus and treated as indicated for these conditions **(Grade C)**. Diabetes mellitus, if present, may improve with lowering of GH and IGF-I levels **(373 [EL 3], 374 [EL 3])**. In some patients, however, SSA therapy can worsen glucose control by inhibiting insulin secretion **(375 [EL 3], 376 [EL 3])**, in which case alternative therapies, such as pegvisomant, should be considered **(Grade C)**.

Aggressive management of cardiovascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia, when present, is important because patients with

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acromegaly have an increased prevalence of cardiovascular risk factors, including dyslipidemia **(377-381 [EL 3])**, and, on average, a higher Framingham risk score than men and women of comparable age without acromegaly **(377 [EL 3])**. In the absence of definitive interventional studies in this patient population, it seems prudent to attempt to achieve the goals for high-risk cardiac patients, including blood pressure less than 130/80 mm Hg **(382 [EL 4])** and hemoglobin A_{1c} less than 6.5% **(383 [EL 3]) (Grade C)**. The effect of medical therapy on cardiovascular hard end points including myocardial ischemia and infarction remains to be substantiated **(Grade C)**.

13.5. Neoplasms

Colon cancer develops from malignant transformation of benign colon polyps—a process believed to take from 5 to 10 years. Early detection and treatment of colon cancer improve survival, and the removal of premalignant polyps will prevent the development of colon cancer. Although data regarding the risk of benign or malignant colon lesions in patients with acromegaly are conflicting, the risk of death from colon cancer is increased in patients with acromegaly in whom colon cancer develops and possibly in patients with acromegaly who have other cancers, including premenopausal women with breast cancer **(72 [EL 2])**. The onset of GH hypersecretion is difficult to ascertain; it usually precedes the diagnosis of acromegaly by many years. Therefore, it is prudent to screen patients for colorectal cancer and polyps with colonoscopy at the time of diagnosis of acromegaly, with follow-up appropriate for patients at higher-than-average risk for colon cancer as well as consistent with the findings at the time of the original screening **(384 [EL 3]) (Grade C)**. In addition, follow-up colonoscopy should be performed in patients with polyps found at the time of baseline colonoscopy and those with persistently elevated IGF-I levels because such patients may be at higher risk of recurrent colon neoplasms **(75 [EL 3], 385 [EL 3]) (Grade C)**.

Rigorous adherence to standard screening guidelines for other cancers established by national organizations **(386 [EL 3])** is important **(Grade B)**. Because patients with acromegaly may receive treatments that, in themselves, may alter cancer risk (such as hormone replacement therapy and breast cancer, testosterone replacement therapy and prostate cancer, and cranial irradiation and intracranial neoplasms), the screening guidelines should be adjusted accordingly **(Grade C)**.

13.6. Psychosocial Complications

Acromegaly is associated with impaired quality of life **(387 [EL 3])**, and biochemical control of the disease is accompanied by improvements in many aspects of psychosocial function **(388 [EL 3])**. Recovery to normal, however, does not always occur with biochemical remission **(389 [EL 3], 390 [EL 3])**. In a recent study of 68 patients with acromegaly who had biochemical remission for a mean of 13 years, there was a higher prevalence of psychopathologic conditions and maladaptive personality traits in patients with prolonged remission in comparison with matched control subjects and patients with clinically nonfunctioning pituitary adenomas **(391 [EL 3])**. These data raise the possibility of an irreversible effect of previous GH hypersecretion on mood and behavior. The extent to which residual impairments in psychosocial function are attributable to the development of GH deficiency in a subset of patients, residual effects of acromegaly, or other unrecognized factors is unknown. In patients with active acromegaly and those in remission, attention to quality-of-life issues is recommended **(Grade C)**.

DISCLOSURE

Chair

Dr. Laurence Katznelson reports that he has received speakers' bureau honoraria from IPSEN and advisory board honoraria and research grant support from Novartis AG.

Task Force Members

Dr. John L. D. Atkinson reports that he does not have any relevant financial relationships with any commercial interests.

Dr. David M. Cook reports that he has received speaker honoraria from Pfizer Inc., research grant support from Indevus Pharmaceuticals, and speaker honoraria and research grant support from Eli Lilly and Company.

Dr. Shereen Z. Ezzat reports that he has received speaker honoraria from Novartis AG.

Dr. Amir H. Hamrahian reports that he has received speaker honoraria from Pfizer Inc. and speaker and consultant honoraria from IPSEN and Novartis AG.

Dr. Karen K. Miller reports that she does not have any relevant financial relationships with any commercial interests.

Reviewers

Dr. William H. Ludlam reports that he has received speaker honoraria from IPSEN, Novartis AG, Pfizer Inc., and Tercica, Inc. and advisory group honoraria from Endo Pharmaceuticals, IPSEN, Novartis AG, and Tercica, Inc.

Dr. Susan L. Samson reports that she has received speaker honoraria from IPSEN and Novartis AG.

Dr. Steven G. Waguespack reports that he does not have any relevant financial relationships with any commercial interests.

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Note: Reference sources are followed by an evidence level ***[EL]*** *rating of 1, 2, 3, or 4. The strongest evidence levels (****EL 1*** *and* ***EL 2****) appear in red for easier recognition.*

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