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Objective: The Acromegaly Consensus Group met in April 2009 to revisit the guidelines on criteria for cure as defined in 2000.

Participants: Participants included 74 neurosurgeons and endocrinologists with extensive experience of treating acromegaly.

Evidence/Consensus Process: Relevant assays, biochemical measures, clinical outcomes, and definition of disease control were discussed, based on the available published evidence, and the strength of consensus statements was rated.

Conclusions: Criteria to define active acromegaly and disease control were agreed, and several significant changes were made to the 2000 guidelines. Appropriate methods of measuring and achieving disease control were summarized. **(*J Clin Endocrinol Metab* 95: 3141–3148, 2010)**

Guidelines published in 2009 summarized the latest consensus on the management of acromegaly (1). Several other consensus documents have been published on various aspects of acromegaly management since 2000 (2–6), and in 2000, the criteria for cure of acromegaly were defined (2). In April 2009, the Acromegaly Consensus Group that had produced these previous documents met to reevaluate and update the guidelines on criteria for cure. The meeting was sponsored by the Pituitary Society and the European Neuroendocrine Association and included endocrinologists and neurosurgeons skilled in the management of acromegaly.

Recommendations were graded, based on the GRADE system (7, 8), depending on the quality of evidence as very low quality (VLQ; expert opinion with one or a small number of small uncontrolled studies in support), low quality (LQ; large series of small uncontrolled studies), moderate quality (MQ; one or a small number of large uncontrolled studies or metaanalyses), or high quality (HQ; controlled studies or large series of large uncontrolled studies with sufficiently long follow-up). Recommendations were classed as discretionary recommendations (DR) if based on VLQ or LQ evidence and as strong recommendations (SR) if based in MQ and HQ evidence.

Assays

The most important assays used for the diagnosis, management, and monitoring of acromegaly are GH and IGF-I measurements. The lack of reliable assays, assay standard-

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Abbreviations: DR, Discretionary recommendation; HQ, high quality; LQ, low quality; MQ, moderate quality; OGTT, oral glucose tolerance test; SR, strong recommendation; SRL, somatostatin receptor ligand; VLQ, very low quality.

ization, and adequate normative data are major issues in the interpretation of these biochemical measures (9–12). These factors can lead to major discrepancies in the values obtained in different laboratories.

The reasons for heterogeneity among GH immunoassay results include variable calibration, epitope specificity of the chosen antibody, and differences in the specificity of antibody recognition of different GH isoforms circulating in the serum (10). Furthermore, there is a lack of standardization between the use of mass units (micrograms per liter) and international units (milli-international units per liter), and several different conversion factors are used (for example, see Refs. 13–15). Problems with IGF-I assays include the variable quality of the assay performance (16), differences and deficiencies in reference ranges and age-stratified normative data, and the uncertain purity of the International Reference Reagent.

As a first step to improving the interpretation of GH assays, it is strongly recommended that the World Health Organization (WHO) international standard (WHO IS 98/574) be used and results be expressed in mass units (micrograms per liter) (SR) (17). Assays should also be standardized to measure the 22-kDa isoform of GH or, as a second-choice, standardized to multiple isoforms of GH (DR) (17). Additionally, there is a need to increase awareness of the potential problems with GH assays by engaging stakeholders, including academic and regulatory organizations, journal editors, diagnostic kit manufacturers, the International Federation of Clinical Chemistry (IFCC), and other professional endocrine societies (SR).

To improve IGF-I measurement, the highly purified recombinant IGF-I WHO first international standard (WHO IS 02/254) should be adopted (SR) (18). Other measures that will improve the quality of IGF-I measurement include the use of highly specific antibodies and the elimination of the confounding effects of binding proteins (DR) (19). Importantly, normative data must be drawn from a statistically valid control population (at least 1000 subjects) stratified by decade (20). An algorithm should be constructed to allow reporting in SD scores. The influence of gender and body mass index are modest and do not justify adjustment of normalized values.

The issues with GH and IGF-I measurements highlighted here reflect the inherent limitations of immunoassays. It is anticipated that the development of mass-spectroscopy-based technology may overcome these limitations.

The measurement of acid-labile subunit, other binding proteins (*e.g.* IGF-binding protein-3), or ghrelin offers no advantage over IGF-I measurement in the diagnosis and management of acromegaly (MQ) (19, 21–25).

GH and IGF-I Regulation

The measurement of GH and age-matched IGF-I concentrations are the most important biochemical variables for the diagnosis of acromegaly and for monitoring progression or treatment response (HQ) (11, 14, 21, 26).

The measurement of total IGF-I levels reflects GH secretory status in acromegaly (at baseline for diagnosis, after neurosurgery or radiotherapy, or during medical treatment) (HQ) (26–28). The measurement of free IGF-I and/or IGF-binding proteins does not provide additional clinical information (MQ) (19, 22, 26, 27).

In the investigation of suspected acromegaly, an elevated IGF-I level and a failure to suppress GH during an oral glucose tolerance test (OGTT) confirm the diagnosis (HQ) (29). In some cases, when the IGF-I and GH levels are clearly elevated, an OGTT may not be required (LQ) (21). During follow-up after neurosurgery or radiotherapy, controlled GH status can be defined as GH suppression during an OGTT (for patients not receiving medical therapy) and a normal IGF-I level (after 3–6 months for those that have undergone neurosurgery) (HQ) (29). When there is discrepancy between GH and IGF-I values, multiple GH sampling (three to five times over 2 h) is helpful (MQ) (14) (see below). For patients receiving medical treatment with a somatostatin receptor ligand (SRL) or dopamine agonist, IGF-I and random GH measurements are sufficient for assessment. In fact, an OGTT may not be helpful for monitoring response in patients receiving any medical treatment (MQ) (11, 29). In patients receiving a GH receptor antagonist, only IGF-I should be measured (HQ) (30).

Oral but not transdermal estrogens reduce IGF-I concentrations; results of IGF-I measurements in women receiving oral estrogens should therefore be interpreted with caution (MQ) (31–34).

Discrepant Biochemical Results

GH and IGF-I levels are closely correlated in patients with acromegaly and healthy individuals (HQ) (35, 36); however, discordance between GH and IGF-I levels has been noted in up to 30% of patients with acromegaly after treatment (MQ) (29, 32). Most discordance involves the measurement of normal GH levels and elevated IGF-I levels, but some cases exhibit elevated GH levels and normal IGF-I levels (MQ) (32, 34).

Apparent discrepant results may stem from inaccurate estimates of GH status, either from limited sampling (often a single or small number of GH measurements are obtained randomly or during dynamic testing, which may not accurately measure 24-h GH output) or from the lack

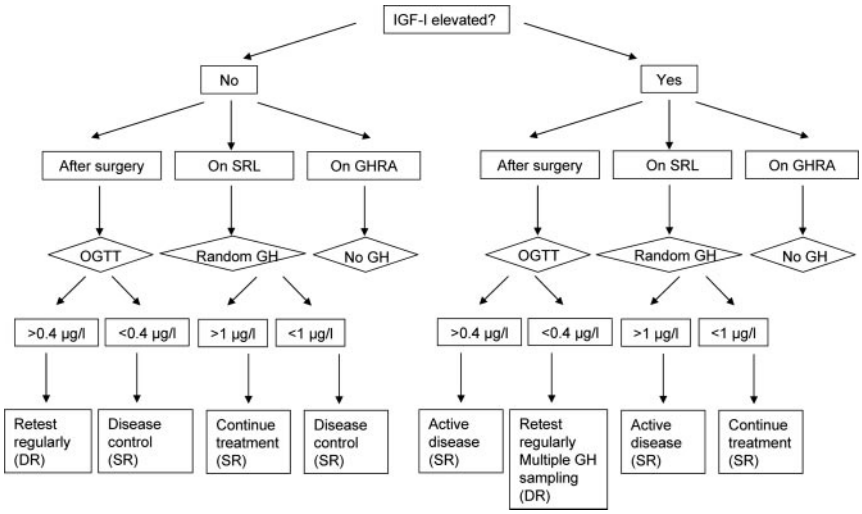

FIG. 1. Interpretation of GH and IGF-I levels in acromegaly. GHRA, GH receptor antagonist.

of assay standardization (MQ) (11). However, there are a number of other factors that can lead to discrepancies in GH/IGF-I levels, including hormone half-life, pulsatility, age, comorbidities, and genetic differences (LQ) (34, 37–42).

The combination of an elevated IGF-I level and a normal GH level is sometimes seen after radiation therapy because radiotherapy causes a flat GH secretory pattern (VLQ) (43). In contrast, a number of factors have been identified that can result in lower IGF-I levels relative to GH levels (either by reducing IGF-I levels or raising GH levels); these include nutritional or gastrointestinal disorders such as chronic inflammatory bowel disorder and anorexia nervosa (which can impair IGF-I production by the liver), hepatic or renal failure, oral estrogens, hypothyroidism, and poorly controlled type 1 diabetes (MQ) (11). In addition, patients with acromegaly in long-term remission may have discrete signs of mild GH excess (such as mild hypertension, relative glucose intolerance, and arthralgia) (LQ) (44, 45), and the chronicity of the acromegaly is an important factor when interpreting discordant results.

It should be noted that the timing of postoperative testing may affect apparent discrepancies. Because of the long IGF-I half-life and other factors regulating IGF-I, it can take several months after surgery for levels to be accurate (MQ) (46). If biochemical measurements 3–6 months after surgery show an elevated IGF-I level, further testing of GH with an OGTT, multiple GH sampling (three to five times over 2 h), or isolated GH measurement should be performed (SR) (14, 21, 35, 42, 43). If there is a significant discrepancy, further testing may be needed over time, and therapeutic decisions should be made according to the clinical context. Assessment of GH receptor polymorphisms may sometimes be helpful in this setting (DR) (47) (Fig.1).

Clinical Outcomes

Morbidity and mortality rates in uncontrolled acromegaly are increased due to the deleterious effect of raised GH and IGF-I, and sustained long-term treatment is needed to normalize these rates (HQ) (45, 48–51).

Comorbidities

The major comorbidities associated with acromegaly are cardiovascular disease, diabetes, hypertension, sleep apnea, arthritis, and metabolic bone disorders (osteoporosis). Effective biochemical control does not always result in effective control of comorbidities (MQ) (44, 52–58).

Optimal control of comorbidities should be achieved with the most effective treatments for both acromegaly and the specific comorbidities (SR) (45, 59–61). Cardiovascular disease, hypertension, diabetes, sleep apnea, and arthralgia are all improved, although only partial regression may occur, in patients with normalized GH levels (MQ) (59, 62). Cardiovascular risk factors should be actively identified and treated (SR) (52). Obstructive sleep apnea is a comorbidity that may occur in 25–60% of patients. Sleep quality and disturbances in patients with acromegaly require detailed assessment and appropriate referral for management (SR) (63). Patients with colonic polyps should be followed according to the international guidelines for colon cancer (SR) (64–67). When visual impairment is a symptom of acromegaly in the setting of chiasmal compression with macroadenomas, surgery is the primary treatment, but SRLs may decompress mass effects. Where surgery is not an option, SRLs could be used in specific cases under close ophthalmological monitoring (DR).

Tumor shrinkage with SRLs

Control of tumor mass is a major goal of acromegaly therapy, and surgery achieves this in many patients (HQ) (14, 68–72). The role of medical therapy in achieving tumor shrinkage is less well defined. In patients receiving SRL therapy, a detectable degree of shrinkage is seen in up to 80% of *de novo* patients in some treatment series (MQ) (73–82). The degree of tumor shrinkage after 3 months of SRL therapy may predict long-term (12 months) shrinkage (LQ) (81). Tumor shrinkage is not necessarily associated with biochemical remission (MQ) (83, 84).

The presurgical use of SRLs may improve surgical outcome, but this requires more data to confirm initial reports (SRL therapy has improved surgical outcome in some studies but not in others) (LQ) (85–90) and to define the

TABLE 1. Acromegaly treatment outcomes

Outcome	Criteria[a]	Management
Active disease	Random GH >1 μg/liter and nadir GH after OGTT ≥0.4 μg/liter	Periodic MRI
	Elevated IGF-I	Monitor and actively treat comorbidities
	Clinically active	Actively treat or change treatment
Controlled disease	Random GH <1 μg/liter or nadir GH after OGTT <0.4 μg/liter	Periodic but less frequent MRI[b]
	Age-sex normalized IGF-I	No change to current treatment; consider reducing SRL dose

MRI, Magnetic resonance imaging.

[a] Strong recommendations: assessment of GH during an OGTT and total IGF-I after surgery; random GH for patients on SRLs; if discrepant biochemical results, GH sampling three to five times over 2 h; always use reliable standardized assays and ultrasensitive assay for IGF-I and GH measurement.

[b] For example, every 2–3 yr.

patients that are most likely to benefit from pretreatment. There is no evidence that presurgical treatment with SRLs reduces the efficacy of surgery (MQ) (85, 87, 88).

Evidence is stronger for improvements in response to SRL therapy after surgical debulking (MQ) (91–94).

Mortality

Comorbidities and delays in diagnosis are the main factors influencing the prognosis of acromegaly (HQ) (49–51, 95). Both GH and IGF-I levels correlate with mortality, and mortality is close to levels expected in the general population when GH and serum IGF-I are controlled (MQ) (50).

In patients with discordant GH and IGF-I levels, the mortality risk does not appear to be elevated, but data are still insufficient (VLQ) (51).

Definition of Disease Control

Most of the case series (32, 34, 96) published in the last decade have suggested that use of the Cortina criteria (2) for defining disease control could have two main drawbacks: first, they were not sufficiently flexible to be applied to different treatment modalities; and second, cutoff limits for GH did not reflect the now widespread availability of ultrasensitive GH assays.

Therefore, optimal disease control (*i.e.* posttreatment remission of acromegaly) is now defined as IGF-I level (determined by a reliable standardized assay) in the age-adjusted normal range and a GH level less than 1.0 μg/liter from a random GH measurement (using an ultrasensitive assay) (MQ) (97). However, assays do not consistently report these values as reflective of biochemical control. Normalization of IGF-I is the only reliable marker of disease control under pegvisomant (HQ) (30).

In patients with acromegaly undergoing surgical management of GH-secreting tumors, OGTT can be used to assess the outcome (SR) (29, 42). There is substantial evidence to suggest that nadir GH levels less than 0.4 μg/liter (with ultrasensitive assays) may define control in these circumstances (MQ) (11, 34, 96, 98). In the case of discrepant biochemical results, multiple GH sampling may be useful (MQ) (14, 35, 43) (Table 1 and Fig. 1).

At present, there is no longer justification for staging the outcome of treatment in acromegaly, except to define active disease and controlled disease (SR) (2) (Table 1).

Summary

In the 10 yr since the criteria for cure of acromegaly were defined by the Acromegaly Consensus Group (2), significant progress has been made in the management of acromegaly. If managed appropriately by a multimodality team with specific experience of managing pituitary tumors, there is little justification for patients to have reduced life expectancy, frequent morbidity, or uncontrolled disease. Challenges related to criteria of cure include the need to standardize GH and IGF-I assays, how to interpret discrepant biochemical results, and how to refine treatment with SRLs to optimize tumor shrinkage.

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