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CONSENSUS STATEMENT

Biochemical Assessment and Long-Term Monitoring in Patients with Acromegaly: Statement from a Joint Consensus Conference of The Growth Hormone Research Society and The Pituitary Society

Acromegaly is associated with significantly increased morbidity and mortality. As a consequence, treatment of the disease is indicated in almost all cases once the diagnosis is established. Studies published between 1970 and 1988 reported standardized mortality rates in patients with acromegaly to be 1.6–3.3; more recent studies, published in the past 3 yr, reported the rate to be lower, ranging from 1.3–1.8. However, when disease activity is controlled in patients with acromegaly, the relative mortality risk is reduced toward normal. Changes brought about by improvements in assay methodology for GH and IGF-I mean that hormone levels reported from these retrospective analyses cannot be simply converted by formula to draw conclusions about the outcome of acromegaly assessed biochemically using current assays.

For these reasons The Growth Hormone Research Society and The Pituitary Society formed a joint program committee and invited international experts to address the current status of both biochemical assessment and long-term monitoring in patients with acromegaly at a consensus conference held in Feldafing, Germany, in April 2003.

Biochemical assessment of the patient with acromegaly

Biochemical evaluation of the patient with possible acromegaly status includes measurements of serum concentrations of IGF-I and GH and study of the neurosecretory regulation of GH secretion through dynamic testing (1). The analysis of serum GH and IGF-I concentrations is limited by the lack of standardization and diverse technical problems with current and previous assays.

GH assays

Previous epidemiological studies have shown that GH levels in acromegaly are a prognostic indicator of mortality. Since the early 1960s, GH measurement has been the cornerstone of the biochemical evaluation of acromegaly. The measurement of GH has evolved from polyclonal RIAs of limited sensitivity to today's two-site monoclonal antibody, nonisotopic assays with enhanced sensitivity, allowing accurate quantification of previously undetectable levels, including nadir and glucose-suppressed GH levels. These assays are of value in diagnosis and follow-up treatment because they allow better definition of the neurosecretory properties of GH, particularly in characterizing the lower limit of spontaneous and suppressed GH secretion. They have permitted diagnosis of mild and subtle manifestations of acromegaly and improved critical evaluation of therapeutic outcomes.

The epidemiological studies linking GH levels measured by RIA to mortality need to be interpreted in the context of the new and more sensitive assays. These studies had identified that treatment to target GH thresholds varying between 2 and 5 μg/liter was associated with improvement in the mortality rate to nearer that of the general population. Comparative studies have demonstrated that GH levels quantified by current assays are lower than those measured by RIAs. There is no simple conversion factor between the two types of assays, but it would appear that the target threshold may be lowered severalfold.

Regardless of methodology, an optimal assay should present information on precision and sensitivity across the expected physiological and pathological ranges. The sensitivity limit of the assay should be less than 0.1 μg/liter, with an interassay coefficient of variation less than 15%. Under ideal conditions any assay should be validated with a normal range for suppressed GH levels after an oral glucose load.

The pituitary somatotrophs as well as somatotroph pituitary adenomas secrete various isoforms of GH, with the monomeric 22-kDa isoform being the most abundant (~50%) in the circulation. As biological activity is not confined to the 22-kDa form of GH, but is also mediated by other isoforms, *e.g.* the 20-kDa form, assays developed to specifically measure 22-kDa GH isoform are not necessarily advantageous to other GH assays. For any GH assay, information on which GH isoforms are recognized by its antibodies is desirable.

The absence of adequate standardization of GH assays limits comparisons of results between different laboratories. Discordance between laboratories should be minimized by adoption of a common recombinant reference preparation, the use of appropriate matrix conditions, and participation in external quality control programs. To interpret the results of GH measurement, treating physicians must have knowledge of relevant assay characteristics (*e.g.* specificity and GH-binding protein interference). The availability of highly purified

Abbreviations: MRI, Magnetic resonance imaging; OGTT, oral glucose tolerance test.

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recombinant human GH in the standards used facilitates the adoption of mass units.

IGF assays

The availability of IGF-I assays has improved the diagnosis and management of acromegaly. The serum IGF-I level is a reliable indicator of GH status in acromegaly and is the best biochemical marker of clinical disease activity. The physiology of the regulation of IGF-I and its binding proteins is complex. The biochemical diagnosis of acromegaly is difficult in states of physiologically high GH production, such as puberty and pregnancy.

Some of the factors that contribute to the shortcomings of GH measurement also apply to IGF-I assays. Problems include inadequate age-adjusted normative data, lack of standardization, susceptibility to interference from binding proteins, and the lack of a pure international reference preparation. A robust IGF-I assay should address these problems. The laboratory should participate in an external quality control program and provide adequate age-adjusted normative data that will also allow presentation of individual IGF-I results as an SD score. IGF assays should be standardized to improve patient management. This includes the use of a common recombinant IGF-I standard. Until an appropriate international reference preparation is universally applied, it is essential that comprehensive reference ranges be defined for each assay. Harmony between assays is desirable, for example, for epidemiological studies, but for the individual patient it is not necessary as long as the analytical technique is not changed over time.

The emerging use of the GH receptor antagonist for the treatment of acromegaly highlights the need for a rigorous IGF-I assay system, because GH measurements cannot be used to evaluate treatment efficacy. The majority of IGF-I circulates as a ternary complex bound to acid-labile subunit and IGF-binding protein 3, both of which are GH dependent. Measurement of these peptides offers no advantage to IGF-I in the assessment of disease activity, except in unusual circumstances.

Dynamic tests

Before the availability of IGF-I assays, numerous dynamic tests, such as the GH response to an oral glucose tolerance test (OGTT), GnRH, and TRH, were used in the diagnosis and follow-up of acromegaly. Of all of these dynamic tests, the OGTT has stood the test of time. Despite its utility, the lack of GH suppression in response to oral glucose is not specific for acromegaly, because other conditions, such as puberty, pregnancy, hepatic and renal disease, anorexia nervosa, and diabetes mellitus, also cause inadequate GH suppression. In patients with overt diabetes mellitus the OGTT should not be performed to diagnose acromegaly.

OGTT does not add diagnostic value when the IGF-I level is clearly elevated, but serves for the assessment of carbohydrate intolerance. Comparing glucose-suppressed GH levels pre- and posttherapy may, however, add to the assessment of therapeutic outcome in individual patients. Independently of IGF-I normalization after treatment, failure of GH to fall into the normal post-OGTT GH range, which has to be defined for the specific GH assay used, indicates persisting impaired neuroregulation of GH secretion. This has been found to be associated with a higher risk of recurrence of active disease.

Early postoperative assessment of treatment outcome

Biochemical evaluation is necessary for the critical assessment of therapeutic outcome. Clinical benefits of surgery may be seen rapidly (within days). Postoperative timing of the evaluation of the GH and IGF-I status is influenced by the patient's clinical response to surgery and by local practice. This is usually undertaken in conjunction with the evaluation of pituitary function. Early assessment may provide limited information on operative outcome, but formal evaluation should be performed 3 months postoperatively. Stabilization of serum IGF-I levels usually occurs within 3 months after surgery, but may, on rare occasions, be delayed until 12 months. Preoperative medical treatment with long-acting somatostatin analogs may influence the timing of postoperative evaluation because of the prolonged suppressive effect on GH of up to 3 months. Subsequent to the postoperative assessment, further life-long evaluation is mandatory.

Long-term monitoring

Biochemical assessment. Measurement of both serum GH and IGF-I levels should be undertaken. Currently, data linking IGF-I and mortality are scarce. Good data exist linking random GH levels to mortality (2). Serum GH concentrations of 2.0 μg/liter, determined by a traditional RIA, have been associated with reversal of the increased mortality of the disease. The equivalent level in modern two-site assays is likely to be considerably lower.

For each GH assay, normative data for glucose-suppressed GH concentrations are necessary for conclusions about adequate control in individual patients. To define restoration of normal neuroregulation of GH secretion, glucose suppression of GH should be measured. This may correspond to levels as low as 0.3 μg/liter in a two-site assay with monoclonal antibodies. In addition, the plasma IGF-I level should be within the age-adjusted normal range. Normal neurosecretory dynamics, as assessed by an OGTT, may not be essential for reduction of mortality risk.

Discordant values for random GH and IGF-I may be encountered in up to 30% of the patients. In such cases an OGTT should be performed to properly assess a nadir GH level. In the presence of discordant GH and IGF-I levels, therapy may be indicated depending on the clinical symptoms of active acromegaly and the presence of comorbidities, such as glucose intolerance, sleep apnea, hypertension, or cardiac dysfunction.

Cardiovascular and metabolic risk factors. Disease-specific metabolic and cardiovascular risk factors include hypertension, glucose intolerance, hypopituitarism, and sleep apnea. These risk factors should routinely be assessed at the time of diagnosis and during follow-up. The measurements include blood pressure, glucose metabolism (fasting blood glucose and hemoglobin A_{1c} at a minimum), evaluation of residual pituitary function, and evaluation of sleep apnea.

Cardiac abnormalities are prevalent in acromegaly. There

is a poor correlation of cardiac dysfunction with GH status. For this reason even patients with mild disease may be at risk. Appropriate cardiac evaluation is warranted when clinically indicated. Awareness of additional established and modifiable risk factors, such as dyslipidemia, smoking, and obesity, also applies in acromegaly. Active management of persisting, modifiable cardiovascular and metabolic risk factors should be included as a therapeutic goal.

Follow-up recommendations in treated acromegaly. Surgery is usually the first-line treatment for acromegaly. If surgery does not achieve satisfactory disease control, further therapy is mandatory.

Postsurgery. After surgery, GH and IGF-I should be measured as described above. If found to be normal, GH and IGF-I should continue to be monitored at least at annual intervals lifelong. Recurrences may occur at any time and have been documented in up to 10% of patients within the first 15 yr. Biochemical or clinical evidence of recurrence necessitates magnetic resonance imaging (MRI) evaluation of the pituitary.

Medical therapy

Dopamine agonists. These include cabergoline, bromocriptine, pergolide, or quinagolide. They provide adequate biochemical control in a minority of patients with acromegaly. It may take 3 months to achieve maximal suppression of GH and IGF-I. If treatment is successful measurements should be repeated annually. Side-effects may include nausea, occasional vomiting, orthostatic hypotension (particularly at initiation of therapy), constipation, a Raynaud-like phenomenon, and, rarely, psychosis.

Somatostatin analogs. These include formulations of octreotide and lanreotide. The achievement of satisfactory GH and IGF-I levels occurs in up to 60% of patients, but is inversely related to pretreatment GH levels. Dose titration is indicated. Once stable control is achieved, measurements can be repeated annually. The inhibition of insulin secretion by somatostatin analogs may cause temporary and reversible deterioration in glucose tolerance, so fasting blood glucose and hemoglobin A_{1c} should be measured annually, and if doubt persists, an OGTT for the assessment of glucose tolerance can be performed. Gall stones occur on somatostatin analogs because of loss of gall bladder motility and other mechanisms, but only rarely does their development cause symptoms, so routine gall bladder ultrasonography is not indicated.

GH receptor antagonist. This drug suppresses IGF-I to normal in over 90% of patients, whereas circulating GH values may rise over the first few weeks, but then plateau. For patients taking GH receptor antagonists, only IGF-I is measured for assessment of disease activity, because measurement of endogenous GH levels by conventional assays is not possible. After dose titration, IGF-I should be measured every 6 months. Abnormalities of liver function have occasionally been described, so monthly monitoring of liver enzymes over the initial 6 months of therapy is required and less frequently thereafter. Occasional patients have been described whose tumors have enlarged during GH receptor antagonist therapy. For this reason, at the present time it is recommended that pituitary tumor size is closely monitored with MRI every 6 months during the first year of therapy and annually thereafter.

Postradiotherapy

Concerns about possible increased mortality from cerebrovascular disease in patients who have been treated with external pituitary irradiation as well as the introduction of new medical therapies have narrowed the indication for radiotherapy in acromegaly.

Conventional multiple dose radiotherapy induces hypopituitarism frequently, so pituitary function should be assessed annually. The effects of single dose radiosurgery are more rapid in onset and therefore should be evaluated at 6-month intervals. Pituitary hormone replacement therapy is commenced according to good endocrine practice. In the patient with cured acromegaly, GH replacement may be considered if symptoms of GH deficiency occur, and IGF-I is below the normal age-adjusted normal range. However, data demonstrating the long-term benefit and safety of GH replacement in such patients are scarce. In this context the use of IGF-I is recommended in the diagnosis of GH deficiency because stimulation tests may not be reliable in the diagnosis of GH deficiency in such patients.

The decline in GH is exponential after conventional radiotherapy but fairly slow, so efficacy should be assessed at 2 yr and annually thereafter. After single dose radiosurgery, on the other hand, the effects on GH and IGF-I can be assessed after 1 yr. If the patient is receiving concomitant medical therapy, the assessment of residual disease activity can be achieved either by dose reduction or discontinuation for at least 3 months. For patients taking dopamine agonists, 1 month off treatment is sufficient for assessing residual activity. Evaluation of tumor size by MRI is recommended in patients with persistent disease after radiotherapy.

Assessment of comorbidities

Controversy exists over the development of colonic polyps and subsequent progression to colonic cancer in acromegaly. Most studies do not support these concerns. Therefore, colonoscopy should be performed according to conventional guidelines for screening colonic cancer. This should mean that colonoscopy is undertaken in patients with acromegaly at the age of 50 yr. Other cancers are not known to have an increased incidence in acromegaly, so screening for breast and prostate cancer should be undertaken as in the normal population.

Summary and perspectives

A number of important issues have been assessed by this consensus conference. The epidemiology discussion highlighted the difficulty of defining target GH and IGF-I levels because of changing assay methodology. As the field moves forward, results for IGF-I should be reported as both absolute concentrations and SD scores defined against a well validated, age-adjusted, normal range. As a consequence, future studies would not be confined by changes in assay method-

ology. The pulsatile nature of GH secretion hinders the establishment of meaningful reference ranges for random GH levels. Standardization of normal response to glucose tolerance tests, however, is achievable and remains a worthy goal for every GH assay. The use of recombinant reference preparations now allows the use of mass units for reporting of GH and IGF-I values, which is strongly endorsed.

In the future, we believe that studies will clarify whether a normal IGF-I level in treated acromegalic patients will be reflected in restoration of normal standardized mortality rates. The remaining question is whether the lack of adequate suppression of GH in response to glucose in the face of a normal IGF-I level will presage recurrence or a worse prognosis.

General population mortality rates have fallen, and therefore the reference rate is changing against which the acromegaly mortality rate is compared. Furthermore, the risk of death from cancer in patients with acromegaly is now acknowledged not to be increased. It is possible that the apparent reduction in premature death from acromegaly may be methodological or may result from earlier diagnosis and improved treatment. The complications of acromegaly give rise to significant morbidity. The relationship between GH status and these complications and the mechanisms by which they arise remain to be elucidated through timely, well controlled, research studies.

Acknowledgments

Participants in the Joint Workshop by The Growth Hormone Research Society and The Pituitary Society on Biochemical Assessment and Long-Term Monitoring in Patients with Acromegaly, held in Feldafing, Germany, April 30 to May 3, 2003, were invited by a joint program committee with equal representation of council members from both Societies. The attendees were: Dr. Bengt-Ake Bengtsson (Sahlgrenska University Hospital, Goteborg, Sweden), Dr. Lena Carlsson (Sahlgrenska Academy, Goteborg, Sweden), Dr. Jens Sandahl Christianssen (Aarhus Kommunehospital, Aarhus, Denmark), Dr. David Clemmons (University of North Carolina, Chapel Hill, NC), Dr. Lawrence Frohman (University of Illinois, Chicago, IL), Dr. Ken Ho (Garvan Institute of Medical Research, Sydney, Australia), Dr. Primus E. Mullis (Inselspital, Bern, Switzerland), Dr. Iain Robinson (National Institute for Medical Research, London, UK), Dr. Christian J. Strasburger (Charité Humboldt University, Berlin, Germany), Dr. Michael O. Thorner (University of Virginia Health Sciences Center, Charlottesville, VA), Dr. Mary Lee Vance (University of Virginia Health Sciences Center, Charlottesville, VA), Dr. Klaus von Werder (Schlosspark Klinik, Berlin, Germany), Dr. Pamela U. Freda (Columbia University, New York, NY), Dr. Ian Holdaway (Auckland Hospital, Auckland, New Zealand), Dr. Gudmundur Johansson (Sahlgrenska University Hospital, Goteborg, Sweden), Dr. Jens Otto L. Jorgensen (Aarhus Kommunehospital, Aarhus, Denmark), Dr. John Wass (Churchill Hospital, Oxford, UK), Dr. Ariel Barkan (University of Michigan, Ann Arbor, MI), Dr. Thierry C. Brue (Hopital de la Timone, Marseilles, France), Dr. Kazuo Chihara (Kobe University School of Medicine, Kobe, Japan), Dr. Annamaria Colao (Federico II University, Naples, Italy), Dr. Wouter W. de Herder (Erasmus Medical Center, Rotterdam, The Netherlands), Dr. Saul Malozowski (NIDDK, NIH, Bethesda, MD), Dr. Mark E. Molitch (Northwestern University Medical School, Chicago, IL), Dr. Hans Orskov (Aarhus Kommunehospital, Aarhus, Denmark), Dr. Jochen Schopohl (Medizinische Klinik Innenstadt, Munich, Germany), Dr. Stephen M. Shalet (Christie Hospital, Manchester, UK), Dr. Paul M. Stewart (Queen Elizabeth Hospital, Birmingham, UK), Dr. Brooke Swearingen (Massachusetts General Hospital, Boston, MA), Dr. Peter J. Trainer (Christie Hospital, Manchester, UK), Dr. Bengt Anderberg (Ferring Pharmaceuticals A/S, Copenhagen, Denmark), Mrs. Liz Baister (Novartis Pharmaceuticals UK, Camberley, UK), Dr. Keith E. Friend (Pharmacia Corp., Bedminster, NJ), Dr. Philip E. Harris (Pfizer Ltd., High Wycombe, UK), Dr. Mark L. Hartman (Eli Lilly & Co., Indianapolis, IN), Dr. Simona Ispas-Jouron (Lilly France, Suresne, France), Dr. Anne-Marie Kappelgaard (Novo Nordisk A/S, Bagsvaerd, Denmark), Dr. Kira Weirum Knudsen (Ferring Laegemidler A/S, Copenhagen, Denmark), Dr. Tomoicho Konno (Sumitomo Pharmaceuticals, Tokyo, Japan), Dr. Ernest Loumaye (Beaufor Ipsen International, Paris, France), Dr. David Musgrave (Ipsen Scandinavia A/S, Brondb, Denmark), Dr. Clément Olivier (Serono International SA, Geneva, Switzerland), Dr. Alberto Pedroncelli (Ospedali Riuniti, Bergamo, Italy), and Dr. Akira Shimatsu (Kyoto National Hospital, Kyoto, Japan).

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