

Acromegaly

Massimo Scacchi · Francesco Cavagnini

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Abstract Acromegaly is a slowly progressive disease characterized by 30% increase of mortality rate for cardiovascular disease, respiratory complications and malignancies. The estimated prevalence of the disease is 40 cases/1000000 population with 3–4 new cases/1000000 population per year. The biochemical diagnosis is based upon the demonstration of high circulating levels of GH and IGF-I. A random GH level lower than 0.4 $\mu\text{g/l}$ and an IGF-I value in the age- and sex-matched normal range makes the diagnosis of acromegaly unlikely. In doubtful cases, the lack of GH suppressibility below 1 $\mu\text{g/l}$ (0.3 $\mu\text{g/l}$ according to recent reports) after an oral glucose load will confirm the diagnosis. A pituitary adenoma is demonstrated in most cases by CT scan or MRI. A negative X-ray finding or the presence of empty sella do not exclude the diagnosis. Cardiovascular complications (acromegalic cardiomyopathy and arterial hypertension) should be looked for and, if present, followed-up by echocardiography and 24h-electrocardiogram. Sleep apnoea, when clinically suspicious, should be confirmed by polysomnography. At the moment of diagnosis all patients should undergo colonoscopy. Lipid profile should be obtained and glucose tolerance evaluated. Surgery, radiotherapy and medical treatment represent the therapeutic options for acromegaly. The outcome of transsphenoidal surgery is far better for microadenomas (80–90%) than for macroadenomas (less than 50%), which unluckily represent more than 70% of all GH-secreting pituitary tumours. Therefore, pituitary surgery is the first line treatment for microadenomas. Medical therapy is based on GH-lowering drugs (somatostatin receptor agonists and, in

some cases, dopaminergic agents) and GH receptor antagonists (pegvisomant). The former are traditionally indicated after unsuccessful surgery and while awaiting the effectiveness of radiation therapy. However, GH-lowering drugs are also used as primary therapy when surgery is contraindicated or in the case of large GH-secreting macroadenomas which are not likely to be completely removed by surgery. These compounds may also be indicated in the preoperative management of some acromegalic patients in order to lower the risk of surgical and anaesthetic complications. For the moment pegvisomant is indicated for patients resistant to the GH-lowering drugs and there is no evidence for drug-induced enlargement of the pituitary tumour. In order to avoid this possibility, however, a combination of pegvisomant and GH-lowering compound can also be conceived. With pegvisomant, IGF-I plasma levels are the marker of therapeutic efficacy and normalize in 97% of patients. Radiotherapy is employed sparingly due to the number of side effects (80% of hypopituitarism). It is indicated after unsuccessful surgical and/or medical treatment and allows the control of hormonal secretion and tumour growth in approx. 40% and 100% of cases, respectively. Acromegaly is defined as controlled when, in the absence of clinical activity, IGF-I levels are in the age- and sex-matched normal range and GH is normally suppressible by the oral glucose load.

Keywords Acromegaly · GH · IGF-I · Diagnosis · Treatment

Demographic and clinical findings

Acromegaly is a progressively disfiguring disease characterized by a wide range of systemic complications, some of which are responsible for the increased mortality of

M. Scacchi · F. Cavagnini (✉)
Chair of Endocrinology, University of Milan, Ospedale San Luca,
Istituto Auxologico Italiano,
Milan, Italy
e-mail: francesco.cavagnini@unimi.it

untreated patients. The estimated annual incidence is 3–4 cases/1000000 population, while the estimated prevalence is 40 cases/1000000 population. Due to the indolence of this clinical condition, 4–10 years of active disease may precede diagnosis. Patients generally exhibit coarsened facial features, acral enlargement, increased skin thickness and soft tissue hyperplasia. Other manifestations include increased sweating, goiter, joint involvement, carpal tunnel syndrome, visual abnormalities, headache, colon polyps, sleep apnoea, reproductive disorders, metabolic disturbances (hypertriglyceridemia, reduced insulin sensitivity), and cardiovascular disease (cardiac hypertrophy, hypertension, arrhythmias). Patients with acromegaly display about 30% enhanced mortality rate: in particular, cardiovascular disease represents the cause of death in 60%, respiratory disease in 25% and malignancies in 15% of cases. High GH levels, high blood pressure and heart disease represent the major negative survival determinants in acromegaly, whereas symptom duration, diabetes mellitus and cancer play a minor role in determining mortality. Considering that control of GH/IGF-I hypersecretion makes mortality rates similar to those observed in the non-acromegalic population, this target, together with the control of hypertension and heart disease, is pivotal to improve the survival of these patients.

Diagnosis

Biochemical diagnosis

Baseline biochemical parameters for the diagnosis of acromegaly include the measurement of fasting or random GH and of IGF-I. According to the criteria proposed by the consensus developed during the workshop held in Cortina, Italy, in February 1999 and published the following year in the *Journal of Clinical Endocrinology and Metabolism* [1], a random GH level lower than 0.4 $\mu\text{g/l}$ and an IGF-I value in the age- and sex-matched normal range exclude the diagnosis of acromegaly. When these two criteria are discordant, a 75 g oral glucose test (OGTT) should be performed: a fall of serum GH to 1 $\mu\text{g/l}$ or less within two hours will exclude acromegaly. This latter is also ruled out by mean integrated 24-h GH levels of less than 2.5 $\mu\text{g/l}$: however, this test is expensive and correlates tightly with the results of OGTT, and therefore it cannot be recommended for use in clinical practice.

Although the quoted criteria are currently widely used in clinical practice for the diagnosis of acromegaly, the refinement of GH assay techniques will certainly require a redefinition of cut-off values. Bearing in mind that this diagnosis should be allowed using criteria applicable by worldwide clinical laboratories, the changes so far suggested can be

summarized as follows: acromegaly should be excluded by normal IGF-I and random GH levels less than 0.3 $\mu\text{g/l}$; when OGTT is made necessary by discordance of these two parameters, the diagnosis should be ruled out in case of GH suppression below 0.3 $\mu\text{g/l}$ [2].

Stimulatory tests (TRH, GnRH) offer no advantage over OGTT and their use is not recommended for diagnosis. Measurement of circulating GHRH is the preferred test for the differential diagnosis between GH-secreting pituitary adenoma and ectopic GHRH secretion.

Pituitary imaging

In more than 98% of all patients, acromegaly is caused by an adenoma of the pituitary gland. The size of the tumour and its expansion must be documented by MRI. Gadolinium-enhanced coronal and sagittal views in 2 mm slices will give optimal results. If the tumour extends into the suprasellar space and/or laterally beyond the cavernous sinus, an ophthalmological examination is recommended to determine possible impairment of the visual field and function of oculomotor nerves.

Search for complications [3, 4]

Cardiovascular complications

The most common feature of acromegalic cardiomyopathy is concentric biventricular hypertrophy (20% of young normotensive patients and 90% of patients with long disease duration). The cardiac hypertrophy of acromegaly mainly occurs in the absence of hypertension, but it can be aggravated by hypertension itself and by abnormalities of glucose metabolism. The initial cardiac hypertrophy, associated with increased systolic output, is followed by diastolic dysfunction and insufficient systolic function on effort; in the final stage of untreated disease systolic dysfunction at rest and heart failure with signs of dilative cardiomyopathy usually ensue. Furthermore, acromegalic patients display an increased prevalence of valve abnormalities. Arrhythmias are present in about 40% of acromegalic subjects: ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia and bundle branch blocks are frequently documented in these patients, chiefly at maximal exercise. There is no clear consensus regarding the prevalence of coronary artery disease in acromegaly (3 to 37% in different series); however, several risk factors for myocardial ischemia, such as elevated levels of lipoprotein-a, triglycerides, fibrinogen, plasminogen activator inhibitor and tissue plasminogen activator, are documented in acromegalic patients. Arterial hypertension, reported in 30–40% of patients, is likely due to increased plasma volume, to decreased ANP levels and to

insulin resistance (and diabetes mellitus); sleep apnoea syndrome and disease duration are coexisting factors likely to increase the risk of hypertension. This latter is very probably the most important factor aggravating cardiac hypertrophy.

At the time of the diagnosis of acromegaly, cardiac morphology and function should be investigated by echocardiography. 24 h-electrocardiogram should be recorded to exclude arrhythmias. Exercise ECG is indicated when angina pectoris is present. 24 h-blood pressure monitoring may be required because of vascular wall thickening in acromegaly.

Respiratory complications

Between 20 and 80% of acromegalic patients may suffer from sleep apnoea, which can be suspected based on the presence of snoring, fragmented sleep, daytime somnolence, morning sleepiness and morning headache. Sleep apnoea is known to predispose to ischemic heart disease, arrhythmias, arterial hypertension and cerebrovascular accidents. Approximately two-thirds of patients with sleep apnoea have obstructive type (due to increased soft tissue in the naso-and oropharynx and other upper airway passages) while the remainder have the central type (likely due to direct effects on breathing center exerted by either high GH/IGF-I levels or increased somatostatin tone) or mixed forms. The diagnosis should be suspected from the history or the results of specific sleep score questionnaires, and confirmed by polysomnography. Small airway narrowing (36% of patients), derangement of respiratory muscles, thoracic spine hyperscoliosis, lung overgrowth and increased lung volume (up to 80% of patients) lead to respiratory dysfunction often resulting in emphysema and bronchiectasis. Spirometry can confirm the clinical suspicion of respiratory dysfunction in selected patients.

Metabolic complications

Impaired glucose tolerance, due to GH-induced insulin resistance, has been reported in 16–46% of acromegalic patients, while overt diabetes mellitus seems to be present in 19–56% of cases, i.e. more frequently than in the general population. Diagnostic methods are the same used in the non-acromegalic population. The lipid abnormalities more commonly described in acromegaly are hypertriglyceridemia, due to GH-dependent inhibition of lipoprotein lipase activity, elevated lipoprotein-a levels, positively correlated with GH concentrations, and increased small dense LDL particles, possibly as a consequence of insulin resistance.

Neoplastic complications

Acromegaly increases the risk of developing colon adenomas after the age of 50 years. Polyp size is usually larger

in acromegalic patients than in subjects from the normal population. In acromegaly colon adenomas predominate in males, in patients with disease duration longer than 5 years, in those with three or more skin tags, and in the case of positive family history. The question as to whether the enhanced frequency of premalignant colon lesions implies a higher prevalence of colon cancer in acromegaly is still under debate. Recent observations in these patients seem to demonstrate an increased mortality rate from colon cancer, but not an augmented incidence rate of this neoplasm. All put together, colonoscopy should be performed in all patients at the moment of diagnosis.

Although acromegaly predisposes to benign prostate hypertrophy, there is no conclusive evidence that prostate cancer rates are increased in this clinical condition. The same holds true for breast cancer. Thus, screening procedures for these two neoplasms should be performed in acromegalic patients as recommended for the general population.

Joint and bone complications

Acromegalic arthropathy affects both axial and peripheral sites. The knee is the most frequently involved joint, followed by shoulder, hip, ankle, elbow and joints of the hand. On the whole, these abnormalities occur in around two-thirds of patients. X-ray examination shows joint space widening in the early phases, and narrowing of joint spaces, osteophytosis and other signs of osteoarthritis in long-lasting disease. Nerve conduction studies are indicated in selected cases to confirm the diagnostic suspicion of carpal tunnel syndrome, a condition described in 20–64% of acromegalic patients at presentation. Bone demineralization appears to be a feature of those acromegalic subjects who display concomitant hypogonadism; thus, assessment of bone mineral density by dual energy X-ray absorptiometry (DEXA) should be performed only in patients found to be hypogonadal.

Endocrine complications

Benign thyroid overgrowth is a common phenomenon in acromegaly. Ultrasound examination of the gland reveals goiter in 25–92% of cases; in particular, multinodular goiter is demonstrated in 65% of patients and may be toxic in about 15% of them. At the time of diagnosis of acromegaly, thyroid morphology (ultrasonography) and function (laboratory) should be assessed. Measurement of serum free thyroid hormones and TSH also allows disclosing cases of concomitant secondary hypothyroidism. Hypogonadism and gonadal dysfunction, present in about half of the patients, are usually due to concomitant hyperprolactinemia, to gonadotropin insufficiency (linked to mass effect of the tumour) and, in women, to insulin-dependent hyperandrogenism. All patients should undergo measurement of serum

prolactin; gonadotropins and testosterone should be evaluated in men, while gonadotropins and estradiol should be assayed in women with abnormal menstrual function. Measurement of morning plasma cortisol and ACTH is indicated when secondary hypoadrenalism is suspected.

Treatment

Therapeutical control of GH and IGF-I secretion is the main goal of treatment, since normalization of these two parameters is the most significant determinant of reversing the increased mortality rate of acromegalic patients. Indeed, survival in acromegaly is restored to that observed in the general population after correction of GH/IGF-I hypersecretion, while morbidity (obstructive sleep apnoea, carpal tunnel syndrome, cardiac dysfunction, diabetes mellitus) is markedly improved by IGF-I lowering. On the whole, the optimal treatment for acromegaly should restore normal GH and IGF-I secretion, remove or reduce the pituitary tumour while preserving a normal residual pituitary function, prevent recurrences, and relieve comorbid features (cardiovascular, pulmonary and metabolic abnormalities) contributing to the unfavourable long-term outcome [4]. Surgery, radiotherapy and medical treatment represent the therapeutical armamentarium for acromegaly. Pituitary surgery allows removal of the adenoma or reduction of the tumoral mass, and is considered first-line therapy. Radiation is able to reduce tumour volume and GH/IGF-I values, but the onset of action is slow and hypopituitarism typically develops. Pharmacotherapy is often used following surgery but also as first-line treatment for nonresectable tumours.

Surgical treatment

Transsphenoidal surgery remains the most cost-effective and rapid initial treatment for the majority of patients with acromegaly. Large tumour size and tumour extension, together with high preoperative circulating GH, are major determinants of surgical failure. Furthermore, successful surgical outcome depends on the ability and the specific experience of the neurosurgeon. Recent experiences, considering series of patients operated by experienced dedicated pituitary surgeons, report an overall surgical cure rate of 44–76%. The outcome is greatly better for microadenomas (80–90%) than for macroadenomas (less than 50%): when evaluating these results, it should be taken into account that the former represent only 20–30% of GH-secreting adenomas at the moment of the diagnosis of acromegaly [5]. In experienced hands, major complications of surgery (mortality, visual impairment, meningitis) occur in less than 2% of cases. Liquoral leak, permanent anterior pituitary hormone deficiency, diabetes insipidus and local nasal complications are reported in about 5% of patients [6]. Technical surgical adjuncts such

as endoscopy, neuronavigation and intraoperative hormone assay and/or MRI may improve outcome, patient satisfaction and complication rates.

Medical therapy

Pharmacological treatment of acromegaly is traditionally indicated after unsuccessful surgery and awaiting the effectiveness of radiation therapy. GH-lowering drugs can also be used as primary therapy when surgery is contraindicated (high risk related to a particular frailty of the patient due to important comorbidity) or in the case of large GH-secreting macroadenomas, which are not likely to be cured by surgery. Current options for the pharmacological treatment of acromegaly include dopamine agonists, somatostatin receptor ligands (SRLs) and the GH receptor antagonist pegvisomant.

Dopamine agonists

Bromocriptine has been used widely in the past to treat acromegaly: however, this drug allows normalization of IGF-I levels only in 10% of the treated patients. Cabergoline, a newer dopamine agonist with a prolonged duration of action, is more effective and better tolerated than bromocriptine. Cabergoline has been shown to normalize IGF-I in about 40% of acromegalic patients and to suppress GH levels to less than 2 $\mu\text{g/l}$ in 44% of patients bearing pure GH-secreting adenomas; a similar suppression of GH was demonstrated in 56% of patients with GH-prolactin cosecreting tumours. Nausea, constipation, headache and dizziness are frequent adverse effects of dopamine drugs, whose efficacy in the treatment of acromegaly has to be considered poor. Their use might be taken into account, possibly in association with SRLs, for patients with adenomas cosecreting prolactin [7].

SRLs

Octreotide and lanreotide, both available as long-acting preparations, suppress GH and IGF-I levels effectively and safely. Adequate GH suppression is reported in 49–56% of cases and IGF-I normalization is described in 48–66% of patients, when SRLs are employed as adjunctive therapy (previous surgery and/or radiation therapy). Primary therapy with SRLs yields GH suppression and IGF-I normalization in 50% and 60% of cases, respectively. About 30% of patients receiving SRLs as adjunctive treatment exhibit significant tumour shrinkage (tumour size reduction of 20–50%). A similar shrinkage is described in 48% of the patients treated with SRLs as primary therapy [8]. SRL treatment is also effective in improving most of the clinical manifestations of acromegaly: headache, fatigue, excessive

sweating, arthralgias and carpal tunnel syndrome improve or resolve in up to 75% of patients; cardiovascular function also improves and episodes of sleep apnoea diminish; hyperglycaemia and glycated haemoglobin levels may also improve with therapy if GH concentration is lowered. Future studies will establish the effectiveness of new SRLs endowed with a broader spectrum of affinity for somatostatin receptors and of new chimeric molecules able to bind both somatostatin and dopamine receptors. The most common adverse events of SRL therapy, usually mild, are represented by diarrhoea, abdominal discomfort and nausea; gallstones, usually asymptomatic, occur in 10–20% of the treated patients.

Pegvisomant

This drug acts on peripheral GH receptors to block the hormonal action. The primary biochemical goal of this treatment is normalization of serum IGF-I levels. GH concentrations increase during the first two weeks of therapy, and therefore GH cannot be a useful marker of disease activity in patients undergoing pegvisomant treatment. This compound has been shown to normalize IGF-I in 97% of patients after more than one year of administration [9], with significant improvement in soft tissue swelling, excessive perspiration, fatigue, insulin resistance and lipid abnormalities. The study with the longest period of treatment and follow-up seems to exclude tumour growth following pegvisomant administration [9]; in any case, neuroradiological monitoring of tumour volume is mandatory during this therapy, requiring also periodical control of liver function tests.

Radiation therapy

The role of radiation for the treatment of acromegaly has become more and more controversial after the improvement of surgical techniques and availability of newer effective drugs [10–12]. External beam radiotherapy induces normalization of IGF-I levels in approximately 40% of patients followed up for at least ten years, whereas the same biochemical goal is achieved in one-third of cases by stereotactic radiosurgery. This latter, delivered by the proton accelerator γ -knife or by a conventional linear accelerator, allows the administration of a very large dose of radiation to an extremely defined area in a single treatment, determining a fall in GH/IGF-I levels which is faster than that obtained by conventional radiotherapy [13]. Furthermore, radiotherapy is able to control tumour growth, although it is more effective on non-secreting pituitary adenomas. Hypopituitarism, occurring in up to 80% of patients after external beam radiotherapy, is the major long-term consequence of this treatment: other concerns are related to the possible development of optic nerve damage or ophthalmoplegia (apparently more likely after stereotactic

surgery), to the increased risk of cerebrovascular accidents and to the possible occurrence of second tumours within the brain and of neurocognitive impairments. Simultaneous administration of SRLs reduces the effectiveness of radiotherapy [14].

Treatment algorithm

Transsphenoidal surgery should be the first-line therapy in patients with GH-secreting microadenomas and borderline macroadenomas with a high likelihood of cure. Patients with symptoms requiring immediate decompression (visual loss) should also undergo surgery as the first option. Primary medical therapy should be conducted in patients bearing macroadenomas with significant lateral extension: in these cases, the role of surgery is more questionable, since subsequent life-long medical therapy is certainly necessary for the inevitable residual hypersecreting tumour tissue [3]. Some retrospective and prospective studies indicate that primary treatment with SRLs may provide long-term biochemical control equivalent to that of surgery or surgery plus subsequent medical therapy [5–17]. However, pharmacotherapy may have a role in the preoperative management of many acromegalic patients in order to lower the risk of surgical and anaesthetic complications related to sleep apnoea, impaired cardiac function, arrhythmias, hypertension, diabetes mellitus, laryngeal abnormalities caused by soft tissue swelling and determining a difficult intubation [18]. If surgery fails (a common occurrence, considering the surgical cure rate for GH-secreting macroadenomas), medical therapy should be started or reinstated. Dopaminergic drugs might be considered for a small group of patients with mildly elevated GH/IGF-I levels or harbouring GH-prolactin cosecreting adenomas. However, the majority of patients will require long-term maintenance therapy with SRLs, which are able to effectively control hormonal hypersecretion in about two-thirds of cases. The remaining patients are very likely to achieve normalization of IGF-I when treated with the GH receptor antagonist pegvisomant. This latter could be associated to SRLs in those rare cases in which intense headaches remain a major complaint. The use of radiotherapy appears to be justified as a treatment of last resort in patients with tumours progressively growing and unresponsive to SRLs, and in a small group of acromegalic patients who bear aggressive pituitary adenomas invasive of local structures including the cavernous sinus and even the temporal lobes. Regrettably, these tumours occur more frequently in younger patients, for whom the concerns about radiation-dependent hypopituitarism and second tumour formation are higher. In conclusion, several considerations must be taken into account when choosing an individualized treatment program for each patient [19].

Criteria for cure

The criteria for cure of acromegaly put forward by the consensus conference of Cortina d'Ampezzo [1] are currently widely used in clinical practice. According to these suggestions, acromegaly is defined as controlled when, in the absence of clinical activity, IGF-I levels are in the age- and sex-matched normal range and the GH nadir value following OGTT is lower than 1 $\mu\text{g/l}$. The disease is inadequately controlled when the latter biochemical profile is associated with clinical activity. However, problems of interpretation of GH suppressibility by OGTT have arisen because of assay changes allowing enhanced sensitivity [20]. Recent papers propose a revision of the remission criteria for glucose-suppressed GH, suggesting cut-off values of 0.26 $\mu\text{g/l}$ [21], 0.25 $\mu\text{g/l}$ [22] or 0.14 $\mu\text{g/l}$ [23]. In particular, nadir GH values after OGTT greater than 0.14 $\mu\text{g/l}$ may be associated, in postoperative patients with normal IGF-I, with increased risk of disease recurrence [23]. Thus, with the progressive availability of more sensitive GH assays in worldwide clinical laboratories, the criteria for cure of acromegaly will be necessarily revised in the next future.

Follow-up

As regards therapy monitoring, it has to be underlined that, although symptoms and signs represent an important parameter, they cannot be used as the sole evidence of adequate control. Indeed, a combination of clinical and biochemical assessment is essential for the follow-up of patients. As already discussed, the most reliable biochemical parameters to verify successful cure are glucose-suppressed GH values (using sensitive assays) and age- and gender-adjusted IGF-I levels. These latter represent the biological marker of choice in the follow-up of patients treated with pegvisomant. Tumour size should also be monitored by means of yearly MRIs; a more frequent neuroradiological control is required when the tumour is known to be actively growing. Computerized visual field assessment once or twice per year is recommended in patients with visual impairment before therapy and in those harbouring macroadenomas and residual extrasellar tumour tissue after surgery. From the clinical point of view, a follow-up of acromegaly complications is mandatory. As for cardiovascular complications (cardiac dysfunction, arrhythmias, hypertension), specific drugs should be administered, in association with IGF-I lowering agents, as appropriate. Echocardiography, electrocardiogram (24 h-ECG when necessary) and 24 h blood pressure monitoring should be performed yearly; exercise ECG is indicated when angina is present. If the patient presented at the moment of diagnosis sleep apnoea syndrome, he should undergo yearly polysomnography, in order to establish whether specific

treatments, in addition to IGF-I lowering drugs, are needed. As for metabolic complications, diabetes mellitus may improve during SRL treatment; if hyperglycaemia persists, it should be treated conventionally; rarely, if SRLs are ineffective in lowering GH, this therapy may induce glucose intolerance. Hypertriglyceridemia improves during SRL treatment. Glucose metabolism should be monitored through strict control of blood glucose and glycated haemoglobin; serum lipid profile should be verified annually. During the follow-up, the frequency of colonoscopy depends on findings at initial colonoscopy, age and background prevalence. Colonoscopic resection of adenomatous polyps at the moment of diagnosis should be followed by yearly endoscopic examinations; the frequency decreases to every two-three years in the case of a negative first colonoscopy. If hypogonadism is present and persists despite tumour mass reduction and GH/IGF-I lowering, patients should receive replacement therapy with gonadal steroids: in these cases regular gynaecologic and breast examinations in women and prostate and PSA evaluations in men should be periodically performed. Assessment of BMD by DEXA should be reserved to hypogonadal acromegalic patients and performed every two-three years [3].

References

- Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S (2000) Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab* 85:526–529
- Trainer PJ (2002) Editorial: Acromegaly—consensus, what consensus? *J Clin Endocrinol Metab* 87:3534–3536
- Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA, Gaillard R, Ho K, Jaquet P, Kleinberg DL, Lamberts SW, Lombardi G, Sheppard M, Strasburger CJ, Vance ML, Wass JA, Melmed S; The Pituitary Society and the European Neuroendocrine Association (2003) Diagnosis and treatment of acromegaly complications. *J Endocrinol Invest* 26:1242–1247
- Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 25:102–152
- Sheppard MC (2003) Primary medical therapy for acromegaly. *Clin Endocrinol (Oxf)* 58:387–399
- Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A; Acromegaly Treatment Consensus Workshop Participants (2002) Guidelines for acromegaly management. *J Clin Endocrinol Metab* 87:4054–4058
- Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ (2002) Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. *Endocr Rev* 23:623–646
- Freda PU (2002) Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 87:3013–3018
- Van Der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR,

- Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 358:1754–1759
10. Wass JA (2003) Radiotherapy in acromegaly: a protagonists viewpoint. *Clin Endocrinol (Oxf)* 58:128–131
 11. Barkan AL (2003) Radiotherapy in acromegaly: the argument against. *Clin Endocrinol (Oxf)* 58:132–135
 12. Thorner MO (2003) Controversy: radiotherapy for acromegaly. *Clin Endocrinol (Oxf)* 58:136–137
 13. Swords FM, Allan CA, Plowman PN, Sibtain A, Evanson J, Chew SL, Grossman AB, Besser GM, Monson JP (2003) Stereotactic radiosurgery XVI: a treatment for previously irradiated pituitary adenomas. *J Clin Endocrinol Metab* 88:5334–5340
 14. Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, Wellis G (2000) Octreotide may act as a radioprotective agent in acromegaly. *J Clin Endocrinol Metab* 85:1287–1289
 15. Newman CB, Melmed S, George A, Torigian D, Duhaney M, Snyder P, Young W, Klibanski A, Molitch ME, Gagel R, Sheeler L, Cook D, Malarkey W, Jackson I, Vance ML, Barkan A, Frohman L, Kleinberg DL (1998) Octreotide as primary therapy for acromegaly. *J Clin Endocrinol Metab* 83:3034–3040
 16. Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lancranjan I, Lombardi G (2001) Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab* 86:2779–2786
 17. Jaquet P, Cortet-Rudelli Ch, Sassolas G, Morange-Ramos I, Chanson P, Brue T, Andrieu JM, Beckers A, Bertherat J, Borson-Chazot F, Brassier G, Caron P, Cogne M, Cottier JP, Delemer B, Dufour H, Enjalbert A, Figarella-Branger D, Gaillard R, Gueydan M, Jan M, Kuhn JM, Raingard I, Regis J, Roger P, Rohmer V, Sadoul JL, Saveanu A, Tabarin A, Travers N, Trouillas J French Acromegly Registry (2003) Therapeutic strategies in somatotroph adenomas with extrasellar extension: role of the medical approach, a consensus study of the French Acromegaly Registry. *Ann Endocrinol* 64:434–441
 18. Ben-Shlomo A, Melmed S (2003) Clinical review 154: The role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab* 88:963–968
 19. Clemmons DR, Chihara K, Freda PU, Ho KK, Klibanski A, Melmed S, Shalet SM, Strasburger CJ, Trainer PJ, Thorner MO (2003) Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab* 88:4759–4767
 20. Shalet SM (2004) Biochemical monitoring of disease activity after surgery for acromegaly. *J Clin Endocrinol Metab* 89:492–494
 21. Gullu S, Keles H, Delibasi T, Tonyukuk V, Kamel N, Erdogan G (2004) Remission criteria for the follow-up of patients with acromegaly. *Eur J Endocrinol* 150:465–471
 22. Serri O, Beauregard C, Hardy J (2004) Long-term biochemical status and disease-related morbidity in 53 postoperative patients with acromegaly. *J Clin Endocrinol Metab* 89:658–661
 23. Freda PU, Nuruzzaman AT, Reyes CM, Sundeen RE, Post KD (2004) Significance of “abnormal” nadir growth hormone levels after oral glucose in postoperative patients with acromegaly in remission with normal insulin-like growth factor-I levels. *J Clin Endocrinol Metab* 89:495–500