Feature Review

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# Growth hormone deficiency in treated acromegaly

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**Growth hormone deficiency (GHD) of the adult is characterized by reduced quality of life (QoL) and physical fitness, skeletal fragility, and increased weight and cardiovascular risk. Hypopituitarism may develop in patients after definitive treatment of acromegaly, but an exact prevalence of GHD in this population is still uncertain owing to limited awareness and the scarce and conflicting data available on this topic. Because acromegaly and GHD may yield adverse consequences on similar target systems, the final outcomes of some complications of acromegaly may be further affected by the occurrence of GHD. However, it is still largely unknown whether patients with post-acromegaly GHD may benefit from GH replacement. We review the diagnostic, clinical, and therapeutic aspects of GHD in adult patients treated for acromegaly.**

## Introduction

Acromegaly is a chronic disease characterized by excess secretion of growth hormone (GH), generally caused by a pituitary macroadenoma (~70% of cases), which results in the elevation of circulating levels of GH and insulin-like growth factor (IGF)-I [1]. The estimated prevalence of acromegaly is approximately 40–70 patients per million, with an incidence of 3–4 new cases per million every year [2,3]. Although a relatively rare disease, acromegaly is associated with reduced life expectancy in strict relationship with GH hypersecretion and comorbidities such as cardiovascular, respiratory, metabolic, and neoplastic complications [4,5].

Therapies and treatment modalities for acromegaly aim to reduce or control tumor growth, inhibit GH hypersecretion, and normalize IGF-I values to improve quality of life (QoL) and reduce morbidity and mortality associated with GH and IGF-I excess [6]. As a matter of fact, the therapy should ideally be directed to the restoration of physiological GH secretion, which is achieved when the tumor is removed, such that the response of GH to dynamic stimuli and its integrated daily secretion are normalized. However, several acromegaly patients receiving treatment do not achieve complete normalization of GH secretion [7]. Some patients maintain high serum GH and IGF-I values, whereas others may develop GHD as a result of overtreatment of acromegaly.

GHD of the adult is now recognized as a well-defined clinical condition, characterized by reduced QoL and physical fitness, skeletal fragility, adiposity, and increased cardiovascular risk [8]. All these complications of GHD may be clinically relevant in patients with a history of acromegaly who have already developed cardiovascular, metabolic, and skeletal complications [9]. Although GHD has been extensively characterized in relation to its primary causes, the exact prevalence of this clinical condition in patients treated for acromegaly is still uncertain because of low awareness and scarce and conflicting data in the literature on this topic [10–20]. Moreover, it is largely unknown whether patients with post-acromegaly GHD may benefit from replacement with GH [21–24].

This review deals with the emerging clinical challenge of GHD in adult patients undergoing treatment for acromegaly, focusing on diagnostic, clinical, and therapeutic aspects of this condition.

## Current management options in acromegaly

Multimodal treatment is often necessary to control acromegaly by suppressing GH hypersecretion, reducing IGF-I levels, and controlling tumor growth, leading to symptom control and minimizing the associated clinical signs and comorbidities [6]. The three approaches to therapy are surgery, medical management, and radiotherapy. Each treatment modality has specific advantages and disadvantages, but the optimal use of these treatments should theoretically result in reducing mortality in the acromegaly patient population to that of the general population [4,5].

Transsphenoidal surgery is the treatment of choice for intrasellar microadenomas, noninvasive macroadenomas (i.e., those without cavernous sinus or bone invasion), and when the tumor is causing compression symptoms [6,25,26]. In patients with intrasellar microadenomas, surgical removal provides biochemical control with normalization of IGF-I in 75–95% of patients, whereas control rates are much lower in patients with macroadenomas [6]. Options for such latter tumors include primary medical therapy or primary surgical debulking followed by medical

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therapy for hormonal control and/or radiation therapy for treatment of residual tumor [6].

Three forms of medical therapy have been used in the treatment of acromegaly [27]. Long-acting formulations of somatostatin analogs currently approved for clinical use, in other words octreotide long-acting release and lanreotide autogel, are the primary medical treatment option if surgery is not appropriate and are the primary first-line therapy after surgery [27,28]. These drugs signal via somatostatin receptor subtype 2, and to a lesser extent by targeting receptor subtype 5, leading to a decrease in GH secretion and to tumor shrinkage [29,30]. About 50% of patients treated with these drugs achieve full biochemical control of acromegaly, although this percentage was shown to decline when data from registries of unselected patients were considered [7,31]. The dopamine agonist cabergoline, which targets type 2 dopamine receptors on pituitary adenomas, may retain some advantage in treating acromegalic patients with biochemically mild disease [32,33]. Patients unresponsive to somatostatin analog therapy are switched to pegvisomant, a drug capable of blocking GH receptor and reducing liver IGF-I production [34,35]. In initial multicenter trials, serum IGF-1 levels were normalized in more than 90% of patients treated with pegvisomant, while drug effectiveness was somewhat lower in open-label or postmarketing studies performed in clinical settings or based on retrospective analysis of disease-specific databases [34]. In some patients, who do not respond to medical monotherapy and/or require tumor mass control, combination therapies with somatostatin analogs plus cabergoline, somatostatin analogs plus pegvisomant, or pegvisomant plus cabergoline have been proposed [27,34,35].

Radiation therapy should generally be scheduled as third-line treatment, occasionally as second-line treatment, but rarely as first-line treatment [6]. Patients who do not have tumor growth control or normalization of hormone levels with surgery and/or medical therapy are possible candidates for radiation therapy. Conventional radiotherapy can lower GH levels and normalize IGF-I in over 60% of patients, but maximal response is achieved 10–15 years after radiotherapy is administered [6]. Before the generation of modern medical therapies, conventional radiotherapy was used as a second-line option when surgery failed to control GH/IGF-I hypersecretion, but this approach was burdened by variable efficacy, long time to reach complete effectiveness, high prevalence of hypopituitarism, increased cerebrovascular mortality, and increased risk of secondary brain tumors in recipient patients [6]. More recently, stereotactic radiosurgery techniques, such as γKnife, have been used in patients with acromegaly with the aim of avoiding irradiation of normal brain and minimizing the long-term consequences of radiotherapy while improving its effectiveness [6,13,16,19], but very long-term data on safety and efficacy of these newer approaches are still lacking. Moreover, stereotactic neurosurgery may cause optic neuropathy more often than conventional radiotherapy in patients with tumor remnant too close to the optic pathways [6]. In fact, choice of the technique is dependent upon the tumor characteristics: conventional radiotherapy is preferred for large tumor remnants or tumors that are too close to optic pathways, whereas γKnife is preferred when there is a smaller tumor size or when improved patient convenience is desired [6].

## Criteria for cure of acromegaly

Before 2000 there was a wide variability in the criteria arbitrarily used for defining biochemical control of acromegaly in different settings. The first historical step to define the biochemical control of acromegaly was the Cortina Consensus Conference which, for the first time, established general criteria for universal use based on the concept that both GH and IGF-I should be 'normalized' for a complete control of disease [36]. Thereafter, several subsequent studies and reappraisals did challenge the validity of the consensus criteria and called for their revision [37]. Optimal disease control (i.e., post-treatment 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/L from a random GH measurement (using an ultrasensitive assay) [37]. In patients with acromegaly undergoing surgical management of GH-secreting tumors, oral glucose-tolerance test can be used to assess the outcome and a nadir GH levels less than 0.4 μg/L (with ultrasensitive assays) may define control in these circumstances [37,38]. Normalization of IGF-I is the only reliable marker of disease control under pegvisomant [34,37].

## Risk of GHD in acromegaly with different treatments

In an effort to achieve biochemical remission in patients with acromegaly, it is predictable that a proportion of patients may be rendered GHD when subjected to proeradicative treatments. In fact, as the cure criteria for acromegaly have become stricter, the space between definitive cure on one side and subnormal GH secretion on the other has become narrower. GHD is not expected to occur in acromegaly patients undergoing medical therapies because dosing can be finely adjusted on the basis of serum GH and/or IGF-I values [27,34,39]. However, it is conceptually possible that a state of functional GHD may occur in some medically treated patients, mainly when pegvisomant is used. Nevertheless, the risk of drug-induced functional GHD in acromegaly is still unknown, whereas there has been convincing evidence that radiotherapy and to a lesser extent neurosurgery may cause GHD in this clinical context, as has been demonstrated for other pituitary diseases [8]. Overtreated acromegaly may be considered a distinct category of disease outcome, and attention should be paid to prevent it when possible and particularly during pharmacological treatment.

### *GHD post-neurosurgery*

Hypopituitarism may be present at diagnosis of acromegaly owing to the effects of compression of a macroadenoma on the portal vessels in the pituitary stalk and/or the surrounding pituitary gland [1]. Successful surgery is expected to resolve GH hypersecretion and at the same time to immediately restore normal pituitary function [40]. However, experience from patients with other histotypes of pituitary adenomas suggests that GH is less likely to recover compared to gonadotropins, corticotropin, and thyrotropin once the tumor bulk is removed [41]. In some