Feature Review

CellPress

Growth hormone deficiency in treated acromegaly

Gherardo Mazziotti[1], Paolo Marzullo[2,3], Mauro Doga[1], Gianluca Aimaretti[2], and Andrea Giustina[1]

[1] Endocrinology, University of Brescia, Brescia, Italy
[2] Endocrinology, Department of Translational Medicine, Università del Piemonte Orientale 'A. Avogadro', Novara, Italy
[3] Division of General Medicine, Ospedale S. Giuseppe, Istituto Auxologico Italiano, Verbania, Italy

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

Corresponding author: Giustina, A. (a.giustina@libero.it).
Keywords: growth hormone deficiency; IGF-1; acromegaly; neurosurgery; radiotherapy; mortality.

1043-2760/
 http://dx.doi.org/10.1016/j.tem.2014.10.005

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

patients, hypopituitarism may persist in the long-term with potential consequences on the QoL and survival of the patient [8,42]. In published surgical series, the incidence of hypopituitarism after removal of GH-secreting tumor was variable, but only few studies investigated the GH reserve in acromegaly patients undergoing neurosurgery (Table 1). In some studies the prevalence of post-surgical GHD was less than 10% [17,20], whereas others reported greater frequencies of GHD exceeding 50% of acromegaly patients who were defined as cured from the disease after neurosurgery [15]. Differences in the reported rates of severe GHD may be attributable to differences in selection criteria for dynamic testing, tumor size, methods used to evaluate GH secretory function, interval after surgical procedure, metabolic background, and manipulation of the pituitary gland during surgery. It was argued that the incidence of severe GHD in surgically cured acromegalics was lower than that observed in patients with nonfunctioning pituitary adenomas, likely in relationship to the growth direction of somatotropinomas that often grow inferiorly, without dislocation or compression of the pituitary gland. In fact, when the tumor was shown to involve bilaterally the pituitary gland, the risk of GHD tended to be significantly higher [20]. The risk of GHD was also shown to correlate with the dimension of the somatotropinoma and serum GH levels before and soon after neurosurgery [15,20].

The introduction of the endoscope to transsphenoidal pituitary surgery could offer the surgeon better visualization as well as an improved range of motion compared to the operating microscope, although it is still unclear whether the incidence of post-surgical hypopituitarism may be reduced by using this new procedure [25,43].

GHD post-irradiation

Hypopituitarism is a well-recognized sequela of radiotherapy for pituitary tumors, and GH is usually the first hormone affected [44]. It was shown that 30–69% of acromegaly patients developed GHD after conventional fractioned radiotherapy [10,15]. GH status evolves with time after cranial radiotherapy and depends on dose, and the likelihood of GHD is greater than 50% if the biological effective dose is greater than 40 Gy [45]. The younger the patient, the longer the interval after radiotherapy, and the higher the dose, the greater is the chance of developing GHD after irradiation. The risk of hypopituitarism was shown to be lower in patients treated by stereotactic radiosurgery compared to conventional fractioned radiotherapy [13,46], although in some cases the incidence of hypopituitarism induced by stereotactic radiosurgery was not low, and appeared to be in close relationship with the radiation dose to the tumor margin and the way hormonal deficiencies were ascertained [16,19].

Diagnosis of GHD in (over)treated acromegaly (acroGHD)

Assuming that no clinical feature can be relied on as a guide, as for auxological criteria in children, the approach to diagnosing GHD in adults must include a high index of suspicion. The diagnosis is often not easy, especially in clinical conditions, such as acromegaly, in which there are persistent qualitative abnormalities in GH secretion especially following irradiation [47,48] (Table 1).

As in the general hypopituitary population, having normal age-adjusted levels of IGF-I does not exclude a diagnosis of GHD also in patients with treated acromegaly [39,49]. However, a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is good evidence for significant GHD, and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing [39]. When expressed as standard deviation score, serum IGF-I levels less than two standard deviations below the age-matched mean are highly suggestive of GHD [50]. Analysis of the Pfizer International Metabolic Database (KIMS) suggests that, in the clinical practice, serum IGF-I values have been often used by clinicians to guide the selection of acromegaly patients to be investigated for GHD [24]. In fact, low IGF-I values were found to be more frequent in patients with post-acromegaly GHD compared to those with a history of non-functioning adenoma [24]. Mean IGF-I

Table 1. Results of studies investigating the risk of growth hormone deficiency (GHD) in patients with acromegaly undergoing surgery and/or radiotherapy (RT) and/or radiosurgery (RS)[a]

Ref.	Median/mean follow-up (months)	Patients (*n*)	Sex (M/F)	Median/mean age (years)	Treatments	Stimulating tests for diagnosis of GHD	Frequency of severe GHD	Median/mean serum IGF-I in GHD
[11]	131	90	44/46	61	Surgery	GH day profile	22%	
[15]	60	56	23/33	54	Surgery/RT	GHRH+arginine	61%	−1.1 SDS
[17]		186	81/105	NS	Surgery	GHRP-2/Arginine	9.1%	−1.180 SDS
[18]	NS	72	25/47	51	Surgery	ITT	12.5%	0.38 SDS
[20]	49	123	60/63	44	Surgery	ITT	9.8%	176 ng/ml
[10]	180	36	23/13	44	Surgery+RT	ITT	36%	NS
[12]	108	33	11/22	49	Surgery+RT/RS	Ghrelin	27.3%	146.2 ng/ml
[13]	66	61	32/29	47	RS	ITT	5.7%	NS
[14]	167	57	38/19	38	Sugery+RT	NS	5.8%	NS
[16]	114	35	17/18	45	Surgery+RS	GHRH+arginine	13%	NS
[19]	61	136	62/74	44	Surgery+RS	ITT	NS	NS

[a]Abbreviations: F, female; GHRH, growth hormone releasing hormone; GHRP-2, growth hormone releasing peptide 2; IGF-I, insulin like growth-factor-1; ITT, insulin-tolerance test; M, male; *n*: number; NS, not specified; SDS, standard deviation score.

levels and z-scores in cured acromegalic patients with GHD are also significantly decreased compared to those measured in cured patients with GH sufficiency [17,42]. Also relevant is the finding of a longer duration of GHD in some patients with previous history of acromegaly, which likely reflects low clinician awareness of the risk of GHD in patients in remission [21,24]. By contrast, some authors based their diagnostic assumption of GHD exclusively on IGF-I levels when three or more pituitary hormone deficiencies were present [50–53].

In other cases, stimulation testing is mandatory for diagnosis of GHD in acromegaly patients, as well as in those with other pituitary diseases. GH production is largely under hypothalamic control including GH releasing hormone (GHRH) and somatostatin, which stimulate and inhibit secretion, respectively [47]. In the early 1980s a class of synthetic peptidyl compounds, collectively termed GH secretagogs, were shown to stimulate GH release both *in vivo* and *in vitro* [54]. Ghrelin, which is the natural ligand of GH secretagog receptor, mediates the release of GH by increasing GHRH and decreasing somatostatin neuronal activity within the hypothalamus [54]. It also directly stimulates GH release from pituitary somatotropes. In addition to classic and 'non-classic' hypothalamic peptides, many other neuropeptides (galanin), neurotransmitters (acetylcholine), metabolic signals (fasting, hypoglycemia, aminoacids) and peripheral hormones (thyroid and sex hormones) are involved in the modulation of GH secretion [47,55–60].

The insulin-tolerance test (ITT) is the gold standard in establishing the diagnosis of GHD in adults and the GHRH in conjunction with arginine (GHRH+arginine) test was shown to give comparable results [52,53,61,62]. Notwithstanding possible variability related to individual factors (age, body composition, etc.) and different GH assays, 3 μg/L is traditionally considered the cut-off for diagnosis of severe GHD in adults as assessed by ITT [52,53], whereas different cut-offs have been proposed for the GHRH+arginine test in relationship to body mass index (BMI). Corneli *et al.* [63] showed that the appropriate GH cut-off points for diagnosing GHD were 11.5 μg/L for patients with a BMI less than 25 kg/m^2, 8.0 μg/L for a BMI within 25–30 kg/m^2, and 4.2 μg/L for those with a BMI greater than 30 kg/m^2. Both ITT and GHRH+arginine tests have been used to investigate GH secretion in patients with treated acromegaly, with positive correlation between the peak GH responses to the two tests [64]. As an alternative to ITT and GHRH+arginine, some authors proposed to use GHRH alone or ghrelin-mimetic GH secretagogs to stimulate GH secretion in patients with acromegaly [12,65]. These tests were shown to be reliable in patients previously treated by surgery, whereas the results could be misleading in patients treated with conventional radiotherapy who could show abnormal response to ITT and arginine, but can retain a normal or low-normal response to GHRH and ghrelin-mimetic GH secretagogs [65]. In fact, the response to ITT and arginine requires an intact somatostatin axis, which indeed is more vulnerable to radiation-induced damage than the GHRH axis and pituitary parenchyma [66]. As a matter of fact, GHRH+arginine test was shown to be unreliable for diagnosis of GHD when performed in the first 5 years after conventional radiotherapy [67], whereas data in patients treated with γKnife are still lacking. Evolution of spontaneous GH secretion may be of help in patients with equivocal GH response to stimulating tests [68,69]. In fact, patients developing GHD after acromegaly show abnormalities of spontaneous GH secretion, with specific attenuation of the size of GH bursts and a highly irregular pattern, but with retained circadian properties [70], which are comparable to those occurring in patients developing GHD after radiotherapy for other pituitary adenomas [64]. By contrast, some cranially irradiated adult patients with isolated abnormal response to stimulating tests may transiently show near-normal spontaneous GH secretion likely reflecting an initial compensatory increase in hypothalamic stimulatory input within a partially damaged hypothalamic–pituitary axis [71].

Clinical features of GHD in (over)treated acromegaly (acroGHD)

The clinical significance of GHD in overtreated acromegalic patients is explained by the pleiotropic effects of GH and IGF-I on lipolysis, gluconeogenesis, bone formation, muscle anabolism, and psychological well-being. Patients with acromegaly have a considerable burden of complications and coexisting illnesses, such as cardiomyopathy, hypertension, diabetes mellitus, sleep apnea, osteoarthropathy, and fragility vertebral fractures, which lead to different extents to an impairment of QoL and shortened life expectancy [9,72–74]. On the other side, adult GHD is associated with high cardiometabolic risk due alterations in body composition, lipoprotein profile, fibrinolytic activity, and endothelial function [75–77]. Moreover, GHD is associated with feelings of social isolation, fatigue, and poorer QoL [78], and high risk of fragility fractures [79]. If GHD is left untreated, mortality rates double compared to the reference population [80]. Nonetheless, controversial opinions exist on beneficial effects of long-term GH therapy on mortality rates in GHD [81].

GHD in patients treated for acromegaly (acroGHD): pathophysiological aspects

GH excess and defects share some clinical features (Figure 1). Thus, it is conceivable that the transition from active acromegaly to GHD may have severe impact on several targets, such as the cardiovascular system and the skeleton, with consequent progression of some clinical complications already caused by GH excess.

Hypertension and insulin resistance may be persistent in several patients with acromegaly even after adequate biochemical control of GH hypersecretion [82,83]. In this specific clinical context, it is expected that the occurrence of GHD, with consequent negative effects on body composition and endothelial function, may favor hypertension and insulin resistance, with further increase of cardiovascular risk and mortality. It is worth mentioning that GHD also favors accelerated atherosclerosis and coronary artery disease [75].

GH exerts direct effects on myocardial growth [84], and the occurrence of GHD is expected to decrease ventricular mass in patients with persistent acromegalic cardiomiopathy. Although GH may also exert positive effects on

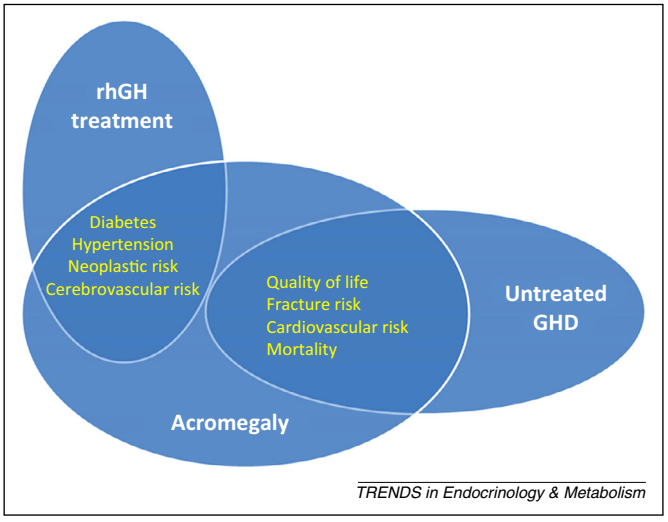

Figure 1. Clinical domains shared by acromegaly, untreated, and replaced growth hormone deficiency (GHD). Untreated GHD and acromegaly share impaired quality of life and high fracture, cardiovascular, and mortality risk. The replacement of GHD by human recombinant growth hormone (rhGH) may cause complications (i.e., hypertension, diabetes, high neoplastic, and cardiovascular risk) which are similar to those occurring in acromegaly.

myocardial function [84,85], the development of GHD may theoretically lead to heart failure in predisposed patients with pre-existing cardiac abnormalities [69,86], such as those with acromegalic cardiomyopathy [87].

GH excess and deficiency have opposite effects on bone turnover, but both lead to skeletal fragility and high risk of vertebral fractures [88]. Interestingly, although appropriate and effective treatment of acromegaly improves skeletal health [89–91], the risk of vertebral fractures may persist high in some patients with well-controlled or cured acromegaly, in close relationship with pre-existing vertebral fractures and untreated hypogonadism [91,92]. In this specific clinical context, the development of hypopituitarism and GHD may further increase the fracture risk [93–95].

GHD in patients treated for acromegaly (acroGHD): clinical/epidemiological studies

Notwithstanding these pathophysiological premises, the clinical consequences of naïve GHD in previously acromegalic subjects have been analyzed only in terms of body composition and QoL outcomes in a so far limited number of studies with small population samples. Race, personal and family history, age, duration of acromegaly, degree of GH/IGF-I excess exposure, treatment strategies, and duration of GHD may be specific relevant confounding factors. Current studies suggest that BMI may be slightly increased [12,96,97] or similar [17,23,98,99], in acroGHD patients as compared to reference GHD and acromegalic populations. Body composition analysis by dual-energy X-ray absorptiometry (DXA) produced conflicting results. A study on 10 acroGHD patients (nine of whom were women) found no difference in body fat and lean mass, while quadriceps muscle endurance was reduced in comparison to 10 reference GHD patients [22]. It is worth noting, however, that acroGHD patients included in the study were more hypertensive, dyslipidemic, and diabetic than their counterparts [22]. In a larger study, analysis by abdominal computed tomography and DXA of 31 acroGHD patients found an increase in percent body fat, visceral adipose tissue, and high-sensitivity C-reactive protein concentrations compared both to cured and active acromegalic patients [98]. This may explain the increase in leptin levels, a fat-derived hormone, seen in males with GHD compared with non-GHD cured acromegalic subjects [12]. Conversely, the prevalence of glucose abnormalities and dyslipidemia was found to be comparable between acroGHD and reference GHD groups [12,15], a circumstance which suggests that these populations may be metabolically similar.

There is, at present, very limited data on cardiac function, with one study documenting slight alterations in diastolic function investigated by tissue Doppler imaging in acroGHD patients as compared to healthy subjects [96].

Despite the additional burden of GHD in this subset of patients, it remains to be convincingly demonstrated whether GHD can further aggravate the mortality risk beyond that originating from previous acromegaly [100].

Results on QoL are more uniform, and support the concept that low GH levels may contribute to an impaired QoL in previously acromegalic patients. Analysis of KIMS data documented that QoL assessed on the QoL-AGHDA (QoL Assessment of Growth Hormone Deficiency in Adults) scale was decreased in women with acroGHD compared to those with GHD from other pituitary causes [21]. Wexler *et al.* [42] found a strong correlation between QoL and GH peak after GHRH+arginine test using QoL-AGHDA (36 in-depth interviews), the symptom questionnaire (92 item questionnaire), and the short-term health survey (SF-36, 36 items on physical and psychological well-being). In this cohort of 45 acromegaly subjects, 26 GHD and 19 GH sufficient, QoL was significantly poorer in subjects with GHD by all scales and subscales (except the anxiety and anger/hostility subscales of the symptom questionnaire) also after controlling for potentially confounding factors such as gender, BMI, radiation therapy, or other hormone deficiencies [42].

Replacement therapy of GHD in (over)treated acromegaly (acroGHD): pros and cons

In non-acromegalic adult populations with hypopituitarism, replacement therapy with recombinant human GH (rhGH) has been shown to reverse many systemic abnormalities associated with GHD. Body composition and QoL can improve within a few months after starting rhGH therapy [101], while increases in bone mineral density (BMD) are usually achieved in longer time-periods [102,103]. Reductions in total body fat and visceral adipose tissue have been observed in hypopituitary patients treated with rhGH [104], and are usually paralleled by improvements in serum lipoproteins [105], also when rhGH therapy is added on top of maintenance statin therapy [106]. Conversely, if GHD is left untreated, or if rhGH treatment is suspended, deterioration of QoL, cardiovascular risk factors, and cardiac performance is observed [105,107]. Importantly, insulin-resistance and raised blood glucose levels may develop at the beginning of rhGH therapy, particularly in patients exhibiting an adverse risk profile at baseline such as high BMI [108].

When GHD subjects with previous acromegaly are taken into consideration, studies on the effects of short- or long-term rhGH therapy have generated conflicting results (Table 2). In a sub-analysis of the KIMS database, 6 month rhGH therapy determined no statistically significant improvement of QoL, BMI, waist circumference, or blood pressure in acroGHD patients, although a positive trend was registered for these clinical end-points [21]. In a subsequent 6 month prospective study on 15 patients randomized to rhGH compared to 15 patients randomized to placebo, the authors reported about 10% reduction (treatment vs placebo) in body fat mass, 14% and 7.8% decrease in visceral and subcutaneous abdominal adipose tissue, respectively, and an increase in fat-free mass of 1.4 kg [51]. In the same study, QoL measured by the AGHDA improved with rhGH, as did five of eight SF-36 subscales (physical health, vitality, mental health, social functioning, and general health) and one of four symptom questionnaire subscales (somatic symptoms). In the rhGH-treated arm, improvements in body composition and abdominal adipose tissue were greater in patients with lower baseline GH peak after the GHRH+arginine test and higher final rhGH dosing [51]. The same researchers obtained similar favorable effects of rhGH therapy on QoL in a group of GHD women with prior acromegaly [107]. Conversely, a 2 year rhGH replacement therapy study failed to document significant changes in body composition, while isometric knee flexor strength significantly improved and a trend towards reduction was seen for total and LDL cholesterol levels [22]. In line with these latter data, a 1 year open-label prospective study found that replacement with rhGH therapy was able to increase IGF-I concentrations to the age- and gender-adjusted normal range, while neither echocardiographic parameters nor any of the cardiovascular risk factors or QoL parameters changed significantly during rhGH treatment in this clinical setting [109]. As expected, longer-term studies found more remarkable effects of rhGH therapy [97]. In a 3 year prospective controlled study, Giavoli *et al.* observed a progressive improvement of QoL, total and LDL cholesterol levels, and percent body fat in rhGH-treated subjects, while a further deterioration of the lipid profile

Table 2. Results of studies investigating the effects of recombinant human growth hormone (rhGH) treatment in patients with growth hormone deficiency (GHD) caused by overtreatment of acromegaly[a,b]

Refs	*n*	Sex (M/F)	Median/mean age (years)	Starting daily dose of rhGH	Duration (months)	Results	Undesired effects
[21]	40	14/26	49.3	0.006 mg/kg	6	↑ (QoL) ↓ (Waist, diastolic BP)	NS
[22]	10	1/9	57.6	0.36 mg	24	↑↑ (BCM, knee flexion 60°) ↓ (BF, waist, BMI, HbA1c, LDL-C) ↑ (HDL-C, TBN) ↔ (LBM, ECW, BP, TG)	MI (10%)** CI (20%)**
[23]	10	4/6	46	0.2-0.3 mg	36	↓↓ (BF, LDL-C, Total-C) ↑↑ (QoL) ↓ (HDL-C) ↑ (TG, BP, 2 h glucose) ↔ (BMI, waist, HbA1c)	None
[24]	115	44/71	49.8	0.2 mg	60	↓↓ (Total-C, LDL-C) ↑↑ (QoL, HDL-C, HbA1c) ↑ (Waist, BF) ↔ (BMI, BP, TG)	Neoplasms (8.7%)* Cardiovascular disease (8.7%)* Cerebrovascular disease (6%)* Diabetes (16.5%) Cardiovascular mortality (6%)**
[51]	15	6/9		0.003–0.006 mg/kg	6	↓↓ (BF, VAT) ↑↑ (FFM, REE, QoL) ↓ (hsCRP) ↑ (TBW) ↔ (BMI, CIMT, total-C, BP, HDL-C, LDL-C)	Arthralgia (33%)* Edema (33%)* Carpal tunnel symptoms (6.7%)*
[97]	65	27/38	53	0.28 mg	37	↔ (BMI, waist, HDL-C, TG) ↓↓ (BP, total-C, LDL-C) ↑↑ (HbA1c)	Cardiovascular disease (3.8%)* Stroke (1.7%)*
[107]	9	0/9	44	0.003–0.006 mg/kg	6	↑↑ (QoL)	NS
[109]	16	8/8	56	0.2 mg	12	↑↑ (PINP, CTX) ↓↓ (FN-BMD) ↓ (Total-C, LDL-C, BF, LVM) ↑ (TG, glucose, LBM, LVEF) ↔ (HDL-C, BP, Waist, LS-BMD, QoL)	NS

[a]Symbols: ↑↑, statistically significant increase; ↓↓, statistically significant decrease; ↑, trend towards increase; ↓, trend towards decrease; ↔, unchanged; *, non-significant difference with respect to the control group; **, significantly difference compared to the control group.

[b]Abbreviations: BCM, body cell mass; BF, body fat; BMI, body mass index; BP, blood pressure; CI, cerebral infarction; CIMT, carotid intimal-media thickness; CTX, β-crosslaps; PECW, extracellular water; F, female; FFM, fat-free mass; FN-BMD, femoral neck-bone mineral density; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; PINP, N-terminal propeptides of type I collagen; LBM, lean body mass; LDL-C, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LS-BMD, lumbar spine-bone mineral density; M, male; *n*, number of patients treated with rhGH; NS, not specified; MI, myocardial infarction; QoL, quality of life; REE, resting energy expenditure; TBN, total body nitrogen; TBW, total body water; TG, triglyceride; total-C, total cholesterol; VAT, visceral adipose tissue.

was noted in the rhGH-untreated GHD group [23]. Similar effects of rhGH treatment were observed after 3 years of follow-up in acroGHD compared to patients with GHD post-(over)-treatment of non-functioning adenomas [97]. rhGH was also shown to stimulate circulating markers of bone turnover without changes in BMD at the lumbar spine and hip after 1 [109] and 2 years of therapy [22]. In a recent analysis of data extracted from the KIMS database on 115 acroGHD patients treated for up to 5 years with rhGH, significant reduction of total and LDL cholesterol levels, as well as a significant increase of HDL cholesterol levels, were reported during rhGH therapy [24]. In this analysis the change in lipids was not associated with changes in BMI or body adiposity, a circumstance that supports the beneficial role of rhGH therapy on lipoprotein kinetics. In a subanalysis on fasting blood glucose and glycated hemoglobin levels, rhGH therapy was found to impair glucose levels in relation to attained BMI values, thus substantiating the BMI-dependent risk of incident diabetes in GHD treated with rhGH [24]. Collectively, current data seem to suggest that long-term (≥3 years) rhGH treatment might be needed to achieve significant improvements in body composition and lipid profile in acroGHD subjects. QoL status may motivate patients and clinicians to start rhGH therapy and can be a useful index of therapy effectiveness even in the short term.

Side effects in acroGHD patients are infrequent, mild, and comparable between the rhGH-treated and placebo groups or other reference groups [21,23,51,64,107] (Table 2). These may include musculoskeletal pain, carpal tunnel symptoms, or aggravation of hypertension [110]. Nonetheless, safety issues have been recently raised in prospective and long-term retrospective intervention studies on rhGH therapy. In 10 acroGHD and their reference controls, Norrman *et al.* [22] witnessed a case of myocardial infarction in one acroGHD woman 5 months after initiation of rhGH, and cerebrovascular accidents in one woman and one man (both previously irradiated) after 2 and 6 weeks of starting rhGH therapy, respectively. In an analysis of the KIMS database, Feldt-Rasmussen *et al.* [21] recognized a higher risk of stroke in acroGHD patients before starting rhGH therapy, suggesting the potential impact of previous GH excess and/or cranial irradiation on this event. In a recent scrutiny of long-term KIMS data, Tritos *et al.* [24] identified higher standard mortality rates (SMR) for all-cause mortality in patients with acroGHD treated with rhGH than in the reference GHD population (SMR = 1.88, $P < 0.05$), with women showing a slightly increased risk over men (SMR = 1.51, $P = 0.04$). Compared to the general population, rhGH treatment did not increase the risk of all-cause mortality, nor the prevalence of cerebrovascular accidents, malignant and benign brain tumors, or the incidence of diabetes mellitus [24]. Cardiovascular mortality appeared to be increased in acroGHD on rhGH compared to both the general population (observed/expected = 2.89) and the reference GHD population (SMR = 4.23, $P = 0.004$), with female gender acting as the second-best predictor of cardiovascular mortality. Based on these data, it seems reasonable to suggest a prudent approach in considering rhGH therapy in acroGHD patients with older age, elevated cardiovascular risk, resistant hypertension, uncontrolled diabetes mellitus, and a long-term history of metabolic diseases or previous cranial irradiation. Because the neoplastic risk is intrinsically increased in acromegaly [110], while fatal and nonfatal malignancies are as prevalent in GH-treated adults as in the general population [111], a prudent approach would also suggest that the risk of neoplasia should be assessed in acroGHD patients who are candidates for replacement therapy. In fact, some clinicians have started rhGH therapy in patients with negative colonoscopy and in women aged 40 years and older with negative mammograms within 1 year before baseline visit [51]. However, extensive interventional studies are required to definitively clarify the benefit/risk ratio of rhGH treatment in this setting.

Recommendations for management of GHD in (over)treated acromegaly (acroGHD)

There are no specific guidelines for the diagnosis and treatment of GHD in patients with history of acromegaly. However, several recommendations provided for the general population of adults with pituitary diseases [52,53,112,113] may be translated also to patients with acroGHD, taking into account some peculiar aspects inherent to this latter clinical condition.

Based on the available data, we should test all patients who meet the biochemical criteria of cure of acromegaly after surgery and/or radiotherapy and radiosurgery, and who have clinical features suggestive of GHD, such as poor exercise capacity, impaired QoL, heart failure, adverse lipid profiles, and low bone mass and/or fractures. An IGF-I value below the reference range for age is highly suggestive for severe GHD, particularly if other pituitary deficiencies are already known [39,50]. However, the absence of other pituitary deficiencies and normal IGF-I values do not exclude the diagnosis of GHD.

ITT is the gold standard for diagnosis especially in irradiated patients (Box 1). In patients treated by surgery, GHRH+arginine may be used as valuable alternative to ITT (Box 1), especially in patients at risk for undesired effects of hypoglycemia (i.e., high cardiovascular risk). Patients should be tested 6 months after neurosurgery. In patients treated with conventional radiotherapy, the

Box 1. Protocols of clinical interest

Protocol of insulin-tolerance test

Regular insulin is intravenously injected in a dose of 0.10 IU/kg. Thereafter blood samples for GH and glucose are drawn every 15 minutes for 1 h and then every 30 min for the second hour. The pharmacological stimulus is considered appropriate if plasma glucose decline to values below 2.2 mmol/L and/or patients show symptoms of hypoglycemia. Severe GHD is defined when GH peak is below 3 μg/L.

Protocol of GHRH+arginine test

Arginine hydrochloride is intravenously administered at the dose of 0.5 g/kg (i.v., up to a maximum of 30 g) over 30 min from 0 to 30 min. Thereafter, GHRH is intravenously administered at dosage of 1 μg/kg. Blood samples for GH evaluation are taken at 0, 30, 45, 60, 90, and 120 min. Severe GHD is defined by a GH peak below 11.5 ng/ml for patients with a BMI less than 25 kg/m^2, below 8.0 ng/ml for a BMI of 25–30 kg/m^2, and below 4.2 ng/ml for those with a BMI greater than 30 kg/m^2.

GHRH+arginine test becomes reliable after a 5 year interval since treatment [67]. Before testing GH reserve, all other possible pituitary deficiencies should be corrected because functional GHD may be caused by hypoadrenalism (Giustina effect), hypogonadism, and hypothyroidism [47,57,58]. Irradiated patients should be evaluated at regular intervals given that hypopituitarism and GHD may develop as late as 10–15 years after treatment.

rhGH has been licensed for use in adult patients with GHD for over 15 years. Early weight- and surface area-based dosing regimens, derived from pediatric practice, resulted in supraphysiological levels of IGF-I and increased incidence of side effects, such as arthralgia and peripheral edema [112,114]. These symptoms are also common in active acromegaly, and subside after cure of the disease. A 'low-dose' approach (0.7–3.5 mg/week) is in line with current guidelines [52,112,113] and is also advisable in the context of acroGHD patients. This approach is based on a tailored dose-titration strategy, which accounts for inter-individual differences in GH sensitivity related to age, gender, and various baseline characteristics. Because dose requirements are greater in younger than older individuals, in women than in men, and in obese compared to lean individuals [52,112], the starting dose is higher in young (0.2 and 0.3 mg/day in men and women, respectively) than older subjects (0.1 mg/day) [115], and is titrated according to individual IGF-I levels and clinical responsiveness. At present, there is no consensus on the optimal dose titration, final replacement dose, or ideal IGF-I values to achieve on rhGH therapy in GHD patients with prior acromegaly. Interventional studies have used weight-based [21,109] or fixed-dose regimens of rhGH therapy [22–24,51]. The achieved IGF-I levels were variable and comprised between –1.1 and +1.7 IGF-I standard deviation scores. The likelihood of reaching target IGF-I levels recommended by current guidelines was greater in mid- and long-term interventional studies [24,64] than in short-term ones [51,107]. As in treating GHD from other causes, dose titration of rhGH in patients with acroGHD should be based on age, gender, and use of oral estrogens. At the Massachusetts General Hospital [51,107] the starting doses were reported to be as follows: 3 μg/kg daily in men ≥50 years and women ≥50 years not on oral estrogens; 5 μg/kg daily and 6 μg/kg daily, respectively, in women <50 years not on oral estrogens and in women <50 years on oral estrogens; and 4 μg/kg daily in men <50 years.

Treatment goals of rhGH therapy in acroGHD are (not different from those of GHD from other causes): (i) correcting the clinical alterations associated with GHD, (ii) achieving IGF-I in the normal range, and (iii) avoiding overtreatment, as reflected in side effects and high IGF-I levels. Replacement therapy with rhGH is expected to yield clinical benefits in acroGHD patients, and positive outcomes such as decreased body fat, increased lean mass, improvement in C-reactive protein levels and QoL have been documented to occur as soon as after 6 months of therapy [51,107]. After at least 1 year of therapy, significant improvements in total as well as LDL and HDL cholesterol become measurable [23,24], while after the same interval the effect of rhGH on BMD, echocardiographic parameters, and carotid IMT is modest [96]. Objective parameters used to monitor responsiveness to rhGH therapy, once maintenance rhGH dose is achieved, should include body composition and fasting lipid levels after 6 months and then yearly, in conjunction with evaluation of arterial blood pressure and electrocardiogram. Particular caution is warranted in patients with severe cardiometabolic impairment. Fasting glucose levels should be carefully monitored during the initial titration phase of GH replacement therapy and then yearly during the long-term to identify the development of hyperglycemia and/or diabetes mellitus. Indeed, GH replacement was shown to affect insulin sensitivity in GHD patients, especially those with high starting BMI and metabolic syndrome [112,116]. A specific questionnaire for QoL should be used before treatment, at 6 months, and then annually after starting treatment. QoL may improve to a lesser extent in patients suffering from musculoskeletal disabilities caused by long-term exposure to GH excess. If the initial bone DXA scan is abnormal, repeated scans are recommended every 18–24 months to assess the need for additional bone-treatment modalities. An independent assessment of vertebral fractures by a radiological and morphometric approach [117] also could be useful because BMD is not a good predictor of fractures in GHD [91,118]. In fact, early diagnosis of vertebral fractures is important to assess the future risk of clinical osteoporotic fractures [92,119]. Because acromegaly is associated with high risk of colon tumors [9] and rhGH could favor their development and growth, colonoscopy should be regularly performed during long-term treatment of acroGHD.

Concluding remarks

Current guidelines recommend GH treatment in GHD adult patients in an appropriate clinical context, in other words, documented pituitary disease. The first question that now needs to be addressed is: are the acromegaly patients made GHD by (over) treatment an appropriate clinical context? Obviously, the story is slightly different compared to other somewhat similar conditions, such as thyroid hormone supplementation in hypothyroid thyroidectomized patients or even in hypoadrenal ex-Cushing patients, because no doubt exists in the scientific community concerning the necessity of thyroxine/cortisol replacement, whereas no definitive consensus exists on the risk–cost/benefit ratio of rhGH treatment in the general GHD population [120]. However, the patient with acromegaly could be thought to be even a more appropriate candidate for rhGH treatment than the other GHD patients because, paradoxically, excess and deficiency of GH share many clinical characteristics which may make the acromegaly patient more clinically vulnerable than the other patients to the onset of GHD.

Having said this, two other questions may arise: is there enough clinical evidence on the positive effects of GH replacement to recommend universal screening for GHD in 'cured' acromegaly patients? Has the issue of the dose of GH, already largely debated in the general GHD population, in combination with what IGF-1 level to target, been adequately addressed in acroGHD? These questions are legitimate considering the risk of double overtreatment bringing the patient back to a status of 'subtle acromegaly'. Outstanding questions are summarized in Box 2. We know from epidemiological data that acroGHD is not marginal,

Box 2. Outstanding questions

- Who are the acromegaly patients to be tested for GHD?
- Who are the patients with post-acromegaly GHD who should be treated with recombinant GH?
- Which is the dose of recombinant GH to be used in patients with post-acromegaly GHD?
- Which is the biochemical target of GH replacement in patients with post-acromegaly GHD?

if we proactively look for it. Acromegaly patients with features likely to be complicated by GHD (osteoporosis, heart failure, impaired QoL, and adverse lipid profile) are probably the best candidates to be biochemically tested for GHD. However, literature data on the positive effects of GH substitution in this clinical setting are preliminary at best and cannot sustain the recommendation for testing all these acroGHD patients. Decisions should be made on an individual basis, taking into account the risk profile of GH substitution in these patients, because it is also true that some acromegaly features could be worsened by rhGH (oncologic and diabetogenic risk). In this context, a non evidence-based decision – but a suggestion based on good clinical sense – is to use starting doses lower than in other GHD patients, targeting initially the low IGF-I range for age. Finally, biochemical and clinical monitoring of the rhGH-treated acroGHD patient should be strict to allow careful assessment of short and long-term positive results versus possible side effects.

References

1 Melmed, S. (2006) Medical progress: acromegaly. *N. Engl. J. Med.* 355, 2558–2573
2 Holdaway, I.M. and Rajasoorya, C. (1999) Epidemiology of acromegaly. *Pituitary* 2, 29–41
3 Daly, A.F. *et al.* (2006) High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J. Clin. Endocrinol. Metab.* 91, 4769–4775
4 Rajasoorya, C. *et al.* (1994) Determinants of clinical outcome and survival in acromegaly. *Clin. Endocrinol.* 41, 95–102
5 Holdaway, I.M. *et al.* (2004) Factors influencing mortality in acromegaly. *J. Clin. Endocrinol. Metab.* 89, 667–674
6 Melmed, S. *et al.* (2009) Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J. Clin. Endocrinol. Metab.* 94, 1509–1517
7 Giustina, A. *et al.* (2014) Investigational drugs targeting somatostatin receptors for treatment of acromegaly and neuroendocrine tumors. *Exp. Opin. Invest. Drugs* 23, 1619–1635
8 Schneider, H.J. *et al.* (2007) Hypopituitarism. *Lancet* 369, 1461–1470
9 Melmed, S. *et al.* (2013) A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary* 16, 294–302
10 Biermasz, N.R. *et al.* (2000) Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. *J. Clin. Endocrinol. Metab.* 85, 2476–2482
11 De, P. *et al.* (2003) Transsphenoidal surgery for acromegaly in Wales: results based on stringent criteria of remission. *J. Clin. Endocrinol. Metab.* 88, 3567–3572
12 Pekic, S. *et al.* (2006) Ghrelin test for the assessment of GH status in successfully treated patients with acromegaly. *Eur. J. Endocrinol.* 154, 659–666
13 Vik-Mo, E.O. *et al.* (2006) Gamma knife stereotactic radiosurgery for acromegaly. *Eur. J. Endocrinol.* 157, 255–263
14 Mullan, K. *et al.* (2009) Long term effect of external pituitary irradiation on IGF1 levels in patients with acromegaly free of adjunctive treatment. *Eur. J. Endocrinol.* 161, 547–551
15 Ronchi, C.L. *et al.* (2009) Prevalence of GH deficiency in cured acromegalic patients: impact of different previous treatments. *Eur. J. Endocrinol.* 161, 37–42
16 Ronchi, C.L. *et al.* (2009) Efficacy and tolerability of gamma knife radiosurgery in acromegaly: a 10-year follow-up study. *Clin. Endocrinol.* 71, 846–852
17 Yamada, S. *et al.* (2011) GH deficiency in patients after cure of acromegaly by surgery alone. *Eur. J. Endocrinol.* 165, 873–879
18 Fujio, S. *et al.* (2013) Severe growth hormone deficiency is rare in surgically-cured acromegalics. *Pituitary* 16, 326–332
19 Lee, C.C. *et al.* (2014) Stereotactic radiosurgery for acromegaly. *J. Clin. Endocrinol. Metab.* 99, 1273–1281
20 Ku, C.R. *et al.* (2014) Clinical predictors of growth hormone deficiency in surgically cured acromegalic patients. *Eur. J. Endocrinol.* 171, 379–387
21 Feldt-Rasmussen, U. *et al.* (2002) KIMS International Study Board of KIMS Study Group. Growth hormone deficiency and replacement in hypopituitary patients previously treated for acromegaly or Cushing's disease. *Eur. J. Endocrinol.* 146, 67–74
22 Norrman, L.L. *et al.* (2008) Baseline characteristics and the effects of two years of growth hormone (GH) replacement therapy in adults with GH deficiency previously treated for acromegaly. *J. Clin. Endocrinol. Metab.* 93, 2531–2538
23 Giavoli, C. *et al.* (2012) GH replacement improves quality of life and metabolic parameters in cured acromegalic patients with growth hormone deficiency. *J. Clin. Endocrinol. Metab.* 97, 3983–3988
24 Tritos, N.A. *et al.* (2014) Effects of long-term growth hormone replacement in adults with growth hormone deficiency following cure of acromegaly: a KIMS analysis. *J. Clin. Endocrinol. Metab.* 99, 2018–2029
25 Mamelak, A.N. (2014) Pro: endoscopic endonasal transsphenoidal pituitary surgery is superior to microscope-based transsphenoidal surgery. *Endocrine* 47, 409–414
26 Mortini, P. (2014) Cons: endoscopic endonasal transsphenoidal pituitary surgery is not superior to microscopic transsphenoidal surgery for pituitary adenomas. *Endocrine* 47, 415–420
27 Giustina, A. *et al.* (2014) Expert consensus document: a consensus on the medical treatment of acromegaly. *Nat. Rev. Endocrinol.* 10, 243–248
28 Giustina, A. *et al.* (2011) Current management practices for acromegaly: an international survey. *Pituitary* 14, 125–133
29 Giustina, A. *et al.* (2012) Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS ONE* 7, e36411
30 Giustina, A. *et al.* (2013) Octreotide for acromegaly treatment: a reappraisal. *Expert Opin. Pharmacother.* 14, 2433–2447
31 Carmichael, J.D. *et al.* (2014) Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments – a meta-analysis. *J. Clin. Endocrinol. Metab.* 99, 1825–1833
32 Marazuela, M. *et al.* (2014) Cabergoline treatment in acromegaly: pros. *Endocrine* 46, 215–219
33 Kasuki, L. *et al.* (2014) Cabergoline treatment in acromegaly: cons. *Endocrine* 46, 220–225
34 Giustina, A. *et al.* (2014) Use of Pegvisomant in acromegaly. An Italian Society of Endocrinology guideline. *J. Endocrinol. Invest.* 37, 1017–1030
35 Giustina, A. (2014) Optimal use of pegvisomant in acromegaly: are we getting there? *Endocrine* Published online October 28, 2014, http://dx.doi.org/10.1007/s12020-014-0462-0
36 Giustina, A. *et al.* (2000) Criteria for cure of acromegaly: a consensus statement. *J. Clin. Endocrinol. Metab.* 85, 526–529
37 Giustina, A. *et al.* (2010) Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. *J. Clin. Endocrinol. Metab.* 95, 3141–3148
38 Giustina, A. *et al.* (2013) Commentary: post-surgical monitoring of acromegaly. *Neurosurgery* 73, E746–E748
39 Aimaretti, G. *et al.* (2003) Diagnostic reliability of a single IGF-I measurement in 237 adults with total anterior hypopituitarism and severe GH deficiency. *Clin. Endocrinol. (Oxf.)* 59, 56–61
40 Arafah, B.M. *et al.* (1994) Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas. *J. Clin. Endocrinol. Metab.* 79, 348–354
41 Arafah, B.M. (1986) Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. *J. Clin. Endocrinol. Metab.* 62, 1173–1179
42 Wexler, T. *et al.* (2009) Growth hormone deficiency is associated with decreased quality of life in patients with prior acromegaly. *J. Clin. Endocrinol. Metab.* 94, 2471–2477

43 Goudakos, J.K. *et al.* (2011) Endoscopic versus microscopic transsphenoidal pituitary surgery: a systematic review and meta-analysis. *Clin. Otolaryngol.* 36, 212–220
44 Littley, M.D. *et al.* (1989) Hypopituitarism following external radiotherapy for pituitary tumours in adults. *Q. J. Med.* 70, 145–160
45 Gleeson, H.K. *et al.* (2004) Reassessment of growth hormone status is required at final height in children treated with growth hormone replacement after radiation therapy. *J. Clin. Endocrinol. Metab.* 89, 662–666
46 Losa, M. *et al.* (2008) The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma. *J. Clin. Endocrinol. Metab.* 93, 2546–2552
47 Giustina, A. and Veldhuis, J.D. (1998) Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr. Rev.* 19, 717–797
48 Peacey, S.R. *et al.* (1998) Hypothalamic dysfunction in 'cured' acromegaly is treatment modality dependent. *J. Clin. Endocrinol. Metab.* 83, 1682–1686
49 Marzullo, P. *et al.* (2001) Usefulness of different biochemical markers of the insulin-like growth factor (IGF) family in diagnosing growth hormone excess and deficiency in adults. *J. Clin. Endocrinol. Metab.* 86, 3001–3008
50 Hartman, M.L. *et al.* (2002) Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J. Clin. Endocrinol. Metab.* 87, 477–485
51 Miller, K.K. *et al.* (2010) Growth hormone deficiency after treatment of acromegaly: a randomized, placebo-controlled study of growth hormone replacement. *J. Clin. Endocrinol. Metab.* 95, 567–577
52 Molitch, M.E. *et al.* (2011) Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 96, 1587–1609
53 Giustina, A. *et al.* (2008) Guidelines for the treatment of growth hormone excess and growth hormone deficiency in adults. *J. Endocrinol. Invest.* 31, 820–838
54 Ghigo, E. (2001) Biologic activities of growth hormone secretagogues in humans. *Endocrine* 14, 87–93
55 Giustina, A. and Wehrenberg, W.B. (1995) Influence of thyroid hormones on the regulation of growth hormone secretion. *Eur. J. Endocrinol.* 133, 646–653
56 Giustina, A. *et al.* (1993) Effects of sex and age on the growth hormone response to galanin in healthy human subjects. *J. Clin. Endocrinol. Metab.* 76, 1369–1372
57 Mazziotti, G. and Giustina, A. (2013) Glucocorticoids and the regulation of growth hormone secretion. *Nat. Rev. Endocrinol.* 9, 265–276
58 Giustina, A. and Mazziotti, G. (2014) Impaired growth hormone secretion associated with low glucocorticoid levels: an experimental model for the Giustina effect. *Endocrine* 47, 354–356
59 Brogan, R.S. *et al.* (1997) Effects of food deprivation on the GH axis: immunocytochemical and molecular analysis. *Neuroendocrinology* 65, 129–135
60 Giustina, A. *et al.* (1992) Arginine normalizes the growth hormone (GH) response to GH-releasing hormone in adult patients receiving chronic daily immunosuppressive glucocorticoid therapy. *J. Clin. Endocrinol. Metab.* 74, 1301–1305
61 Aimaretti, G. *et al.* (1998) Comparison between insulin-induced hypoglycemia and growth hormone (GH)-releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. *J. Clin. Endocrinol. Metab.* 83, 1615–1618
62 Ghigo, E. *et al.* (2001) Growth hormone-releasing hormone combined with arginine or growth hormone secretagogues for the diagnosis of growth hormone deficiency in adults. *Endocrine* 15, 29–38
63 Corneli, G. *et al.* (2005) The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. *Eur. J. Endocrinol.* 153, 257–264
64 van der Klaauw, A.A. *et al.* (2006) GH deficiency in patients irradiated for acromegaly: significance of GH stimulatory tests in relation to the 24 h GH secretion. *Eur. J. Endocrinol.* 154, 851–858
65 Murray, R.D. *et al.* (2001) The diagnosis of growth hormone deficiency (GHD) in successfully treated acromegalic patients. *Clin. Endocrinol. (Oxf.)* 54, 37–44
66 Toogood, A.A. (2014) Endocrine consequences of brain irradiation. *Growth Horm. IGF Res.* 14 (Suppl.), 118–124
67 Darzy, K.H. *et al.* (2003) The usefulness of the combined growth hormone (GH)-releasing hormone and arginine stimulation test in the diagnosis of radiation-induced GH deficiency is dependent on the post-irradiation time interval. *J. Clin. Endocrinol. Metab.* 88, 95–102
68 Giustina, A. *et al.* (1991) Effects of pyridostigmine on spontaneous and growth hormone-releasing hormone stimulated growth hormone secretion in children on daily glucocorticoid therapy after liver transplantation. *Clin. Endocrinol. (Oxf.)* 35, 491–498
69 Giustina, A. *et al.* (1996) Impaired spontaneous growth hormone secretion in severe dilated cardiomyopathy. *Am. Heart J.* 131, 620–622
70 van der Klaauw, A.A. *et al.* (2007) Attenuated pulse size, disorderly growth hormone and prolactin secretion with preserved nyctohemeral rhythm distinguish irradiated from surgically treated acromegaly patients. *Clin. Endocrinol. (Oxf.)* 66, 489–498
71 Darzy, K.H. *et al.* (2009) Cranially irradiated adult cancer survivors may have normal spontaneous GH secretion in the presence of discordant peak GH responses to stimulation tests (compensated GH deficiency). *Clin. Endocrinol. (Oxf.)* 70, 287–293
72 Yedinak, C.G. and Fleseriu, M. (2014) Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: a pilot study. *Endocrine* 46, 585–593
73 Anagnostis, P. *et al.* (2014) Psychological profile and quality of life in patients with acromegaly in Greece. Is there any difference with other chronic diseases? *Endocrine* 47, 564–571
74 Arosio, M. *et al.* (2012) Italian Study G-roup of Acromegaly. Predictors of morbidity and mortality in acromegaly: an Italian survey. *Eur. J. Endocrinol.* 167, 189–198
75 Doga, M. *et al.* (2006) Growth hormone deficiency in the adult. *Pituitary* 9, 305–311
76 Gola, M. *et al.* (2005) Growth hormone and cardiovascular risk factors. *J. Clin. Endocrinol. Metab.* 90, 1864–1870
77 Gazzaruso, C. *et al.* (2014) Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH – an update. *J. Clin. Endocrinol. Metab.* 99, 18–29
78 Rosén, T. *et al.* (1994) Decreased psychological well-being in adult patients with growth hormone deficiency. *Clin. Endocrinol. (Oxf.)* 40, 111–116
79 Mazziotti, G. *et al.* (2006) Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. *J. Bone Miner. Res.* 21, 520–528
80 Sherlock, M. *et al.* (2010) Mortality in patients with pituitary disease. *Endocr. Rev.* 31, 301–342
81 van Bunderen, C.C. *et al.* (2011) Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. *J. Clin. Endocrinol. Metab.* 96, 3151–3159
82 Maison, P. *et al.* (2007) Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *J. Clin. Endocrinol. Metab.* 92, 1743–1747
83 Mazziotti, G. *et al.* (2009) Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. *J. Clin. Endocrinol. Metab.* 94, 1500–1508
84 Saccà, L. *et al.* (1994) Growth hormone and the heart. *Endocr. Rev.* 15, 555–573
85 Volterrani, M. *et al.* (1997) Haemodynamic effects of intravenous growth hormone in congestive heart failure. *Lancet* 349, 1067–1068
86 Giustina, A. *et al.* (1999) Endocrine predictors of acute hemodynamic effects of growth hormone in congestive heart failure. *Am. Heart J.* 137, 1035–1043
87 Bihan, H. *et al.* (2004) Long-term outcome of patients with acromegaly and congestive heart failure. *J. Clin. Endocrinol. Metab.* 89, 5308–5313
88 Giustina, A. *et al.* (2008) Growth hormone, insulin-like growth factors, and the skeleton. *Endocr. Rev.* 29, 535–559
89 Bonadonna, S. *et al.* (2005) Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. *J. Bone Miner. Res.* 20, 1837–1844
90 Mazziotti, G. *et al.* (2008) Prevalence of vertebral fractures in men with acromegaly. *J. Clin. Endocrinol. Metab.* 93, 4649–4655
91 Mazziotti, G. *et al.* (2014) Bone turnover, bone mineral density and fracture risk in acromegaly: a meta-analysis. *J. Clin. Endocrinol. Metab.* Published online November 3, 2014, http://dx.doi.org/10.1210/jc.2014-2359

92 Mazziotti, G. *et al.* (2013) Vertebral fractures in patients with acromegaly: a 3-year prospective study. *J. Clin. Endocrinol. Metab.* 98, 3402–3410
93 Mazziotti, G. *et al.* (2008) Effect of gonadal status on bone mineral density and radiological spinal deformities in adult patients with growth hormone deficiency. *Pituitary* 11, 55–61
94 Mazziotti, G. *et al.* (2010) Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. *Eur. J. Endocrinol.* 163, 15–20
95 Mazziotti, G. *et al.* (2014) Association between l-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism. *Eur. J. Endocrinol.* 170, 893–899
96 van der Klaauw, A.A. *et al.* (2008) Cardiac manifestations of GH deficiency after treatment for acromegaly: a comparison to patients with biochemical remission and controls. *Eur. J. Endocrinol.* 159, 705–712
97 van Bunderen, C.C. (2014) Effect of long-term growth hormone replacement therapy on cardiovascular outcomes in growth hormone deficient patients previously treated for acromegaly - a sub-analysis from the Dutch national registry of growth hormone treatment in adults. *Eur. J. Endocrinol.* Published online September 16, 2014, http://dx.doi.org/10.1530/EJE-14-0515
98 Lin, E. *et al.* (2012) Effects of growth hormone deficiency on body composition and biomarkers of cardiovascular risk after definitive therapy for acromegaly. *Clin. Endocrinol. (Oxf.)* 77, 430–438
99 Wexler, T.L. *et al.* (2010) Growth hormone status predicts left ventricular mass in patients after cure of acromegaly. *Growth Horm. IGF Res.* 20, 333–337
100 Bex, M. *et al.* (2007) AcroBel – the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. *Eur. J. Endocrinol.* 157, 399–409
101 Woodhouse, L.J. *et al.* (2006) The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. *Endocr. Rev.* 27, 287–317
102 Götherström, G. *et al.* (2007) Ten-year GH replacement increases bone mineral density in hypopituitary patients with adult onset GH deficiency. *Eur. J. Endocrinol.* 156, 55–64
103 Barake, M. *et al.* (2014) Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J. Clin. Endocrinol. Metab.* 99, 852–860
104 Beauregard, C. *et al.* (2008) Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab.* 93, 2063–2071
105 Colao, A. *et al.* (2002) The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study. *J. Clin. Endocrinol. Metab.* 87, 1088–1093
106 Monson, J.P. *et al.* (2007) Growth hormone (GH) replacement decreases serum total and LDL-cholesterol in hypopituitary patients on maintenance HMG CoA reductase inhibitor (statin) therapy. *Clin. Endocrinol. (Oxf.)* 67, 623–628
107 Valassi, E. *et al.* (2012) Effect of growth hormone replacement therapy on the quality of life in women with growth hormone deficiency who have a history of acromegaly versus other disorders. *Endocr. Pract.* 18, 209–218
108 Luger, A. *et al.* (2012) Incidence of diabetes mellitus and evolution of glucose parameters in growth hormone-deficient subjects during growth hormone replacement therapy: a long-term observational study. *Diabetes Care* 35, 57–62
109 van der Klaauw, A.A. *et al.* (2009) Limited effects of growth hormone replacement in patients with GH deficiency during long-term cure of acromegaly. *Pituitary* 12, 339–346
110 Giustina, A. *et al.* (2003) Diagnosis and treatment of acromegaly complications. *J. Endocrinol. Invest.* 26, 1242–1247
111 van Bunderen, C.C. *et al.* (2014) Efficacy and safety of growth hormone treatment in adults with growth hormone deficiency: a systematic review of studies on morbidity. *Clin. Endocrinol. (Oxf.)* 81, 1–14
112 Ho, K.K. *et al.* (2007) Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur. J. Endocrinol.* 157, 695–700
113 Doga, M. *et al.* (2005) Current guidelines for adult GH replacement. *Rev. Endocr. Metab. Disord.* 6, 63–70
114 Cuneo, R.C. *et al.* (1998) The Australian multicenter trial of growth hormone (GH) treatment in GH-deficient adults. *J. Clin. Endocrinol. Metab.* 83, 107–116
115 Cook, D.M. *et al.* (2009) Medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients – 2009 update. *Endocr. Pract.* 15 (Suppl. 2), 1–29
116 Attanasio, A.F. *et al.* (2010) International Hypopituitary Control Complications Study Advisory Board. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. *J. Clin. Endocrinol. Metab.* 95, 74–81
117 Griffith, J.F. and Genant, H.K. (2012) New advances in imaging osteoporosis and its complications. *Endocrine* 42, 39–51
118 Mazziotti, G. *et al.* (2012) New understanding and treatments for osteoporosis. *Endocrine* 41, 58–69
119 Cauley, J.A. *et al.* (2007) Long-term risk of incident vertebral fractures. *JAMA* 19, 2761–2767
120 Giustina, A. (2007) Does growth hormone replacement therapy improve cardiac function? *Nat. Clin. Pract. Endocrinol. Metab.* 3, 614–615