Medical Consequences of Long-term Treatment of Acromegaly

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Abstract

This article discusses the impact of long-term treatment of acromegaly on cardiovascular, metabolic, respiratory and articular complications as well as on malignancies. The main goals of treatment of acromegaly include normalisation of biochemical markers of disease activity, improvement in signs and symptoms of the disease, removal or reduction of tumour mass and preservation of pituitary function, together with prevention of complications. Cardiovascular and respiratory complications are the main causes of morbidity and mortality, whereas neoplasms are a minor cause of increased risk of death. Other associated diseases are arthropathy, carpal tunnel syndrome and reproductive disorders. The prolonged elevation of growth hormone (GH) and insulin-like growth factor (IGF)-I levels results in premature death, whereas strong biochemical control improves wellbeing and restores life expectancy to normal.

Keywords

Acromegaly, growth hormone (GH), insulin-like growth factor I (IGF-I), biochemical control, systemic complications

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Acromegaly is a severe endocrine disease resulting from growth hormone (GH) and insulin-like growth factor (IGF)-I excess, usually due to a somatotroph pituitary adenoma. Prolonged exposure to hormonal excess induces a progressive somatic disfigurement and many systemic complications (see *Table 1*) that develop insidiously and slowly, generally delaying the diagnosis by more than 10 years.[1]

The therapeutic goal in acromegaly is to reduce morbidity and mortality by removing tumour mass and restoring GH and IGF-I levels to the normal range. According to Giustina et al.,[2] the biochemical control of acromegalic disease is achieved if:

- random GH is <0.4µg/l or mean integrated 24-hour GH is <2.5µg/l;
- GH nadir is <1.0µg/l after a 75g oral glucose tolerance test (OGTT); and
- IGF-I is in the normal range adjusted for age and sex.

Currently available treatments for acromegaly include neurosurgery, radiotherapy and medical therapy with dopamine agonists, somatostatin analogues and the GH receptor antagonist pegvisomant.

The first-line therapeutic approach for acromegaly is still debated.[3] Neurosurgery is indicated as the treatment of choice in GH-secreting pituitary microadenomas and in the presence of a macroadenoma with extrasellar extension to decompress mass effects on vital structures and, particularly, the optic chiasm. In experienced hands, endoscopic transsphenoidal surgery is effective in more than 80% of pituitary microadenomas and in about 50% of pituitary macroadenomas, inducing the normalisation of GH and IGF-I levels by complete tumour removal. Otherwise, in the presence of lesions invading the cavernous sinus, complete resection cannot be achieved and surgery fails to provide biochemical control of the disease. In these cases, first-line treatment with somatostatin analogues and subsequent tumour debulking is indicated in inadequately controlled patients. Petrossians et al.[4] and Colao et al.,[5] in two independent retrospective studies, showed that gross total tumour resection increases the probability of achieving and maintaining safe levels of GH and IGF-I by post-operative administration of somatostatin analogues. Radiotherapy, both conventional external-beam and stereotactic radiosurgery, is indicated for patients with recurrence or persistence of disease activity after unsuccessful surgery and in those who are resistant to or intolerant of medical treatment. However, limitations of radiotherapy include the slow attenuation of GH and IGF-I levels, requiring five to 10 years to achieve maximal hormonal control,[6] and sometimes secondary damage to near cerebral tissue or hypopituitarism.[7]

Dopamine agonists, particularly bromocriptine, have historically been used as the first-line medical approach for acromegaly, especially in GH- and prolactin-co-secreting pituitary adenomas, but have poor efficacy. More recently, cabergoline has been demonstrated to be effective in decreasing hormonal excess when used at high doses and in combination with somatostatin analogues in patients resistant to somatostatin analogues as monotherapy.[8]

Somatostatin analogues are the cornerstone of the treatment of acromegaly. Used as first-line therapy and administered every 14–28

days, depot formulations (octreotide long-acting release [LAR] and lanreotide slow release [SR] or aqueous–gel formulation) are very effective in decreasing GH and IGF-I to normal values and shrinking tumour mass in a high percentage of patients. Cozzi et al.[9] showed that long-term treatment with octreotide LAR allows safe levels of GH and IGF-I to be achieved and maintained in approximately 80% of treated patients. Colao et al.[10] reported that primary therapy with somatostatin analogues induces significant tumour shrinkage in more than 75% of treated patients, emphasising that IGF-I is the best predictor of tumour shrinkage and that control of GH and IGF-I levels is important to obtain a significant reduction of tumour mass in newly diagnosed acromegalic patients. Somatostatin analogues are also indicated after unsuccessful surgery or radiotherapy when these modalities have failed to obtain biochemical control of the acromegalic disease and hormone levels remain elevated. A novel somatostatin analogue, pasireotide (SOM 230), which binds not only the subtype 2 somatostatin receptor but four of the five somatostatin receptor subtypes, has recently been reported[11,12] to suppress hormonal levels, thus improving wellbeing in patients resistant to octreotide LAR.

Pegvisomant is a new genetically engineered pegylated analogue of human GH that functions as a highly selective GH receptor antagonist. It was demonstrated to normalise IGF-I serum levels in up to 97% of patients with active acromegaly and proven resistance to long-term and high-dose treatment with somatostatin analogues,[13] and also induced a significant improvement in symptoms and signs of hormonal excess, as well as in glucose homeostasis, insulin sensitivity and lipid profile, known to be severe risk factors for acromegalic cardiovascular disease.[14] When used in association with somatostatin analogues, pegvisomant has been demonstrated[15,16] to increase patient compliance and to greatly reduce the costs of medical treatment for acromegaly.

Effect on Cardiovascular Complications

Biventricular hypertrophy, rhythm disturbances, cardiac valve disease, hypertension and atherosclerotic risk are very common in acromegaly, and define typical acromegalic cardiomyopathy.

Patient age and disease duration are the main determinants of cardiac derangement, with a prevalence of cardiac hypertrophy >90% in patients with long disease duration.[17,18] Especially in middle-aged patients and/or those with an estimated disease duration of over 10 years, acromegalic cardiomyopathy may progress to overt cardiac hypertrophy with signs of diastolic dysfunction and/or insufficient systolic performance on effort. However, an increase in cardiac size associated with high heart rate and increased systolic output, which indicate hyperkinetic syndrome, can also be observed in patients with a disease duration of less than five years.[19] In these patients, as well as in those under 40 years of age, overt systolic dysfunction at rest and heart failure may rarely occur.[20]

Correction of GH and IGF-I excess may arrest the progression of cardiac disorders and reduce mortality from cardiovascular complications.[21] Only limited data are available about the impact of surgery on acromegalic cardiomyopathy, but it has been recognised to improve diastolic and systolic performance.[22,23] Somatostatin analogues have been reported to dramatically improve cardiovascular parameters, inducing reduction of cardiac mass and enhancement of diastolic filling,[24–29] particularly in patients achieving disease control.[30] Systolic function seems to improve to a greater extent in patients treated with somatostatin analogues than in those treated by surgery.[31] In a previous study on 22 patients adequately controlled after treatment with octreotide LAR, we observed[32] the disappearance of left ventricular (LV) hypertrophy and the normalisation of LV ejection fraction (EF) response at peak exercise in, respectively, 100 and 80% of patients below 40 years of age and in only 50% of those over 40 years of age, suggesting that in young patients with short disease duration who are controlled by medical therapy, the acromegalic cardiomyopathy can be reversed. The achievement of biochemical control also results in better control of hypertension and cardiac function, reducing the use of antihypertensive drugs.[33] Furthermore, we recently observed[34] that somatostatin analogues did not significantly modify the incidence and severity of valve regurgitation. Treatment with the GH-receptor antagonist has also been reported to improve cardiac structure and performance in acromegalic patients resistant to somatostatin analogues. In a recent study on 12 acromegalic patients resistant to somatostatin analogues, we[35] reported that 18-month pegvisomant treatment resulted in a significant decrease of cardiac size, particularly LV mass (LVM) and LVM index (LVMi), suggesting the reversibility of cardiac hypertrophy. Moreover, EF and early (E) to late or atrial (A) peak velocities ratio (E/A) were found to increase, whereas isovolumic relaxation time (IVRT) decreased after therapy with pegvisomant, indicating the enhancement of systolic and diastolic performance and the possibility of preventing the development or the progression of cardiac insufficiency.

Table 1: Signs and Symptoms of Acromegaly

Tumour Mass Effects	Visceromegaly
Pituitary enlargement	Tongue
Visual field effects	Thyroid
Cranial nerve palsy	Liver
Headache	Spleen
	Kidney
	Prostate
Skeletal Effects	**Cardiovascular Effects**
Gigantism	Left ventricular hypertrophy
Prognatism	Septal hypertrophy
Jaw malocclusion	Cardiomyopathy
Carpal tunnel syndrome	Arterial hypertension
Paresthesia	Congestive heart failure
Proximal myopathy	
Frontal bone hypertrophy	
Arthralgias	
Respiratory Effects	**Digestive Tract Effects**
Sleep apnoea	Colon polyps
Sleep disturbances	
Increase of residual volume	
Metabolic Effects	**Endocrine Effects**
Impaired glucose tolerance	Menstrual abnormalities
Insulin resistance and hyperinsulinaemia	Galactorrhoea
Diabetes	Decreased libido and impotence
Hypertriglyceridaemia	Low renin levels
Hypercalciuria	Increased aldosterone levels
Increased urinary hydroxyproline	Low thyroid-binding globulin

Effect on Metabolic Complications

Impaired glucose tolerance (IGT) and overt diabetes, associated with hyperinsulinaemia and insulin resistance, are common in acromegalic patients, with an estimated prevalence of 19–56% for diabetes and 16–46% for IGT.[36–38]

Table 2: Respiratory Disorders in Acromegaly

Craniofacial Region	Neck and Thoracic Cage
Impaired airflow	Impaired airflow transit
Obstructive sleep apnoea	Stiffened rib cage
Nocturnal snoring	Impaired breathing movements
Daytime somnolence	Respiratory muscle impairment
Morning sleepiness	Short inspiratory time
Morning headache	Emphysema
	Bronchiectasis

The incidence of hypercholesterolaemia in the acromegalic population is similar to that in the general population, whereas the incidence of type IV hypertriglyceridaemia is almost three times higher than in controls and occurs principally in acromegalic patients with a higher insulin response.[39] Furthermore, GH stimulates apolipoprotein E (Apo-E) and apolipoprotein A-I (Apo A-I) secretion.[40] Moreover, elevated levels of serum lipoprotein-α concentrations have been found in both active patients and those with controlled disease.[41]

Disease control improves glucose tolerance and diabetes. Somatostatin analogues alter, albeit modestly, glucose tolerance and insulin resistance. Ronchi et al.[42] observed that after treatment with octreotide LAR, fasting glucose was increased and fasting insulin was decreased compared with baseline, but the homeostasis model assessment of insulin resistance (HOMA-IR) significantly decreased and became similar to that recorded in control subjects. We observed that the negative effect of somatostatin analogues on insulin levels seems to be more evident at the beginning of treatment, whereas glucose tolerance usually improves during long-term treatment with these drugs.[43,44] We also found[45] that patients with normal glucose tolerance at the beginning of therapy did not develop impaired glucose tolerance after long-term treatment with high doses of octreotide LAR doses (up to 40mg every 28 days); therefore, it is more important to consider individual predisposition to diabetes than somatostatin analogue dose in the development of glucose intolerance during treatment with these drugs. The GH antagonist pegvisomant is effective in improving insulin sensitivity and glucose metabolism, inducing a significant decrease in fasting glucose to normal levels[46–48] even in patients with diagnosed diabetes and IGT, and improving insulin resistance by the reduction of HOMA-index and the increase of pancreatic β-cell secretory function (HOMA-β).

A general improvement in lipid profile has been observed in patients treated with octreotide, although no impact on small and/or dense low-density lipoprotein (LDL) particles has been obtained.[49] In our series, lipid profile abnormalities were generally improved by treatment with somatostatin analogues.[50] The GH receptor antagonist has been found to increase total cholesterol levels and total/HDL-cholesterol ratio and to decrease serum lipoprotein-α concentrations.[51]

Effect on Respiratory Complications

In acromegaly, respiratory disorders (see *Table 2*) cause illness and impaired physical performance, contributing to 25% of all deaths recorded in this condition, where respiratory mortality appears to be at least three-fold higher than in normal subjects.[52] Patients with acromegaly develop several anatomical changes affecting cranio-facial bones and soft tissues, respiratory mucosa/cartilage, lung volumes, rib-cage geometry and activity of respiratory muscles, resulting in two main respiratory dysfunctions: sleep apnoea and impaired respiratory function. Sleep apnoea induces recurrent cessation or decrease of airflow to the lungs during sleep, and commonly causes snoring and daytime sleepiness in acromegaly. It may occur in about 60–90% of acromegalic patients and generally is due to anatomical narrowing of the upper respiratory airways causing obstructive sleep apnoea.[53] Impaired respiratory function is generally due to multiple alterations involving the bone and muscle structure of the chest, as well as lung elasticity, inducing subclinical hypoxaemia and an increase of lung volume.[54] No ventilation or perfusion mismatching has been found in patients with acromegaly.[55]

Respiratory disorders may be improved by biochemical control of acromegaly. Long-term therapy is expected to produce beneficial effects on both sleep apnoea and ventilatory dysfunction, improving the ventilatory response to effort and the personal sense of weakness. Many authors have reported a significant improvement of respiratory complications after the achievement of normal and safe values of GH and IGF-I by both surgical and medical therapy, emphasising the role of somatostatin analogues in reducing the frequency of apnoeic and hypopnoeic episodes by 50% of baseline values, improving the severity of obstructive apnoeas and increasing ventilation threshold and vigour score without any significant increase in the maximal oxygen uptake.[56–59]

Effect on Arthropathy

Articular joint disorders, including articular involvement and enthesopathy, occur in the great majority of patients with acromegaly, causing morbidity and functional disability in these patients. Acromegalic arthropathy affects both axial and peripheral sites, involving the appendicular skeleton in up to 74% of patients. The knee is the most commonly involved peripheral joint, followed by the shoulder, hip, ankle, elbow and joints of the hand. Joint stiffness and swelling are also common. Acromegalic arthropathy is generally non-inflammatory, although features of osteoarthritis frequently develop in later stages of the disease. Sinovial aspirates showed that effusions are degenerative without evidence of inflammation or crystal deposition.[60] Disease duration[61] influences clinical manifestation, such as hypermobility (15–30% of cases) and limitation of joint movement (16–27% of cases). Scarpa et al.[62] found that spinal mobility was reduced in 55.6% of patients and in 18.5% of controls, while 72.2% of patients and 29.6% of controls complained of articular symptoms attributable to spinal involvement. Ossification of the anterior surface of the vertebral bodies has been commonly described, contributing to an increase in the apparent antero-posterior diameter and, in more severe cases, determining the disc space resembling diffuse idiopathic skeletal hyperostosis (DISH) syndrome. Another common condition in acromegaly is symptomatic carpal tunnel syndrome, with a prevalence of 20–64% at presentation. It occurs due to increased oedema of the median nerve in the carpal tunnel, rather than extrinsic compression due to increased volume of the carpal tunnel contents.[63]

Whether acromegalic arthropathy can be reversed by controlling GH and IGF-I levels is still questioned. However, the biochemical control achieved by long-term treatment has been found to improve symptoms and signs of acromegalic arthropathy.[50] Octreotide has been demonstrated to induce a mild to moderate improvement in pain, crepitus and range of motion. Similarly, we have observed that after lanreotide[64] or octreotide LAR treatment,[65]

cartilage thickness measured by ultrasonography at the shoulder, wrist and left knee was significantly reduced, suggesting that the suppression of circulating serum GH and IGF-I levels is associated with a significant decrease in joint thickness and the improvement of carpal tunnel syndrome.

Effect on Neoplasia Development

Malignancies constitute the third cause of mortality in acromegaly. The relative risk of cancer differs from that in the general population and is still debated. In the study by Orme et al.,[66] no significant increase of cancer mortality was found in a cohort of 1,362 patients, suggesting that the incidence of cancer was lower than in the general population but the rate of death from colon cancer was higher than expected. Digestive tumours (particularly colon adenomatous polyps and tubular, villous or tubulo-villous adenomas) constitute the most frequent malignancies recorded in acromegaly, representing nearly 27% of all malignancies developing in acromegaly.

The mechanism responsible for the enhanced epithelial cell proliferation of sigmoid crypts seems to be related to IGF-I excess,[67,68] whereas IGF-binding protein (IGFBP)-3 plays a pro-apoptotic and antiproliferative role, and its serum levels are negatively correlated with cancer risk,[69] displaying a possible mechanism compensating for these growth-promoting effects of IGF-I on colon mucosa. Other possible mechanisms are related to the decrease in the number of B-lymphocytes and natural killers and the increase in T-lymphocytes in the colon mucosa,[70] and to bile acid secretion.[71] Hyperinsulinaemia has been described as a further possible mechanism associated with colon adenomas and carcinomas, especially in acromegalic patients with IGT or overt diabetes.[72] Disease activity, GH and IGF-I levels, disease duration and a family history of colon cancer are related to colon adenomas, but do not predict their occurrence.[73]

Thyroid cancers constitute 3.1% of neplasms in acromegaly: thyroid tumours are predominantly papillary and occasionally aggressive, rarely occurring multifocal tumours,[74] with a low mortality rate.

No increase in breast or lung cancer incidence has been previously reported in acromegaly.[75] On the other hand, acromegaly predisposes to benign prostate hypertrophy, occurring in 80% of active patients and in 30% of cured acromegalic patients.[76] Only limited data are available about the impact of long-term treatment of acromegaly on malignancies. However, a decrease of GH, IGF-I and IGFBP-3 levels has been reported to induce the reduction of prostate volume in patients achieving disease control only if their age was less than 50 years,[77] indicating that chronic elevation of GH and IGF-I levels constitutes a proliferative stimulus for prostatic stromal cells independent of androgen status.

Conclusions

Long-term treatment of acromegaly allows safe levels of GH and IGF-I to be attained and maintained in approximately 80% of treated patients, inducing tumour shrinkage and improving quality of life in the great majority of patients. Serum concentrations of GH and IGF-I suppression improve all the systemic complications of acromegalic disease; in particular, cardiomyopathy can be reversed, mainly in young patients with short disease duration. Successful treatment of acromegaly dramatically improves sleep breathing disorders, as well as glucose and lipid metabolism, although somatostatin analogues may induce impairment of insulin secretion at the beginning of therapy. More aggressive treatment is required if a neoplasm is found because elevated IGF-I levels could be growth stimulators for malignancy. Some early signs of arthropathy, such as joint thickness, can be reversed by suppressing GH and IGF-I, whereas later bone complications, such as osteoarthritis and bone deformities, should be considered definitive features of the disease. ■

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