

Growth Hormone in Musculoskeletal Pain States

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Growth hormone is essential for normal linear growth and the attainment of an adult mature height. It also plays an important role in cartilage growth and the attainment of normal bone mass. There is only one rheumatic disorder, namely acromegaly, in which abnormalities of growth hormone production play a major etiologic role. However, there is increasing appreciation that suboptimal growth hormone secretion, leading to a state of adult growth hormone deficiency, may occur in the setting of chronic inflammatory disease, chronic corticosteroid use, and fibromyalgia. Therefore, the evaluation and effective management of growth hormone oversecretion and undersecretion is relevant to practicing rheumatologists.

Introduction

Growth hormone (GH) secretion is pulsatile because of a tonic inhibition by the hypothalamic secretion of somatostatin in conjunction with a pulsatile secretion of GH releasing hormone (GHRH) [1•]. Serum GH levels are usually undetectable between pulses. There are approximately 10 pulses of GH secretion per day, lasting approximately 90 minutes, and separated by approximately 128 minutes. Peak GH secretory activity occurs within an hour after the onset of deep sleep. Exercise, physical activity, and sepsis are associated with increased GH secretion. In general, women have an increased daily integrated growth hormone secretions compared with men. However, men have an increased pulsatility compared with women. This is thought to be an important determinant to linear growth, as the tissue response to GH appears to be determined by the pulsatility of GH secretion rather than the absolute amount of GH that is secreted. Peak serum GH concentrations are 4.3 ± 0.7 ng/mL at night and 2.7 ± 0.5 ng/mL during the day. The critical actions of GHRH and somatostatin in controlling GH and its secretion are also influenced by several other factors. For instance, serotonin, dopamine, enhanced α_2 -adrenergic tone, and gamma-

aminobutyric acid (GABA) receptor stimulation all lead to an increase in GH secretion. Whereas GH itself, insulin-like growth factor 1 (IGF-1), enhanced β -adrenergic tone and IGF-1, and cortisol all inhibit GH secretion. Furthermore, several drugs, fasting, estrogen levels, and exercise, all modulate GH production. GH secretion is lower in elderly, postmenopausal, and obese patients, and estrogen replacement improves GH secretion.

In 1996, this classical view of GH secretion was complicated by the identification and cloning of an endogenous GH secretagogue receptor. This is structurally different from the receptor for GHRH and its ligand, ghrelin was discovered in 1999. Ghrelin is a 28 amino acid peptide produced by endocrine cells within the stomach that increases appetite and stimulates GH secretion. Ghrelin secreting cells have also been reported in the intestine, pancreas, hypothalamus, and testis. There is an inverse relationship between body weight and plasma ghrelin levels. However, its precise role in modulating the pulsatile release of GH is not yet fully elucidated. It is increasingly evident that ghrelin has other actions, which include increased gastric motility and acid secretion, stimulation of endocrine and exocrine pancreatic function, modulation of the pituitary gonadal axis, and stimulation of slow wave sleep. Ghrelin levels are reduced by approximately 80% after total gastrectomy and to a lesser extent by gastric bypass surgery. So far the only rheumatic disorder that has been studied, in regards to ghrelin, is fibromyalgia. In a report on 19 patients with fibromyalgia and 14 healthy controls there was no significant difference in plasma ghrelin levels [2].

Physiology and Actions of Growth Hormone and Insulin-like Growth Factor 1

Growth hormone has multiple actions, which serve to promote linear growth, increase muscle mass, and reduce fat stores. These actions are due in part to direct effects of GH, but most are mediated through the effects of IGF-1 (Table 1). With increased availability of supplemental GH therapy it has become increasingly apparent that GH has subtle but important effects on the general sense of well-being.

Growth hormone acts by binding to a specific receptor in the liver leading to the production and secretion of IGF-1 (Fig. 1). The GH receptor is a 70 kd protein which is dimer-

Table 1. Actions of growth hormone and insulin-like growth factor 1

Stimulation of protein synthesis
Mobilization of stored fat
Retention of sodium, phosphate, and water
Maintains blood glucose by suppressing insulin
Inhibits proteolysis
Inhibits apoptosis
Enhances the effects of stimulating hormones such as TSH and ACTH
Stimulates differentiation and proliferation of chondrocytes
Stimulates the differentiation and proliferation of muscle cells
Increases glomerular filtration rate
Decreases blood glucose
Stimulates wound healing

TSH—thyroid-stimulating hormone; ACTH—adrenocorticotropic hormone.

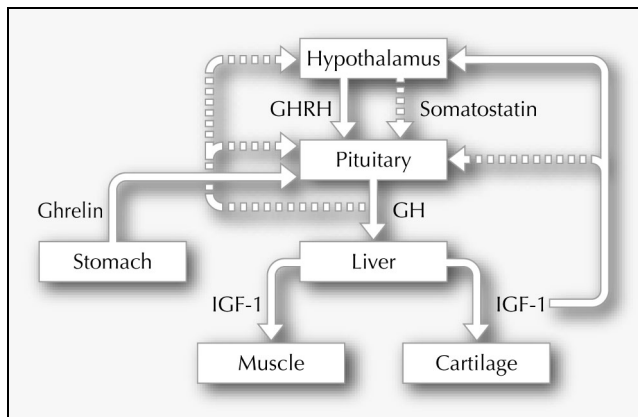


Figure 1. Pathways of growth hormone and insulin-like growth factor 1 secretion. Solid lines are stimulatory pathways and dashed lines are inhibitory pathways. GH—growth hormone; GHRH—growth hormone releasing hormone; IGF-1—insulin-like growth factor 1.

ized by interaction with GH. Then a complex second signaling cascade that involves phosphorylation through various protein kinases follows. Mutations of the GH receptor are associated with partial or complete GH insensitivity and growth failure (*eg*, Laron dwarfism).

Insulin-like growth factor 1 is a small protein of molecular weight 7647 kd that is secreted into the blood under the control of GH. Some 75% of IGF-1 is secreted by the liver, the other 25% is synthesized into peripheral tissues resulting in autocrine and paracrine responses. It is 99% protein-bound to one of six IGF binding proteins (IGFBPs). These function to transport IGF and control access to extra-vascular spaces. IGFBP-3 has the highest affinity for IGF-1 and is the most abundant of the binding proteins, however, it is usually fully saturated. The second most abundant binding protein, IGFBP-2 accounts for the greatest changes in the levels of free IGF-1. The levels of IGF binding proteins are positively influenced by the magnitude of GH secretion and

reduced by deficiency states of testosterone, estrogen, and thyroxine.

The blood levels of IGF-1 vary greatly over the lifespan. Peak values are reached in early puberty (300–500 ng/mL) and fall rapidly to approximately 40% of the peak value by age 20 and decline after age 20 by approximately 3 ng/mL per year. Twin studies have indicated that approximately 40% of an individual's IGF-1 is related to undefined genetic factors. Nutritional status significantly affects blood IGF-1 levels. For instance, a 7-day fast decreases the IGF-1 level by approximately 50%. Disorders associated with malnutrition such as renal failure, severe liver dysfunction, and chronic inflammatory disorders such as Crohn's disease also result in reduced IGF-1 levels. There is a strong inverse correlation between GH secretion and obesity, especially intra-abdominal fat deposits. However, there is often a paradoxical effect of obesity on IGF-1 levels, as in some obese patients the IGF-1 level is normal whereas in others it may be elevated or depressed. This discrepancy between GH secretion and IGF-1 levels is probably because of increased levels of IGFB-3 in obese patients.

Oversecretion of Growth Hormone

Oversecretion of GH in children leads to gigantism and acromegaly in adults. This is not a common condition, its prevalence is approximately 40 per million. Acromegaly (from the Greek *akron* = extremity and *megale* = great) becomes clinically evident when there is an increasingly disproportional enlargement of distal skeletal structures such as the jaw, hands, feet, nose, and ears.

Articular disorders

The prevalence of joint problems in untreated acromegalic patients is nearly 100%. However, with earlier recognition and more effective treatment these figures have decreased to less than 50%.

Before the typical clinical picture of acromegaly emerges, some patients present to rheumatologists with a poorly defined joint pain and morning stiffness, which may be mistaken for an early inflammatory arthritis (Table 2). This joint discomfort is because of a disproportionate expansion of cartilage—causing "tight joints." Over the course of time the joint capsule enlarges with a resulting hypermobility, which causes joint instability [3]. The thickened cartilage in acromegaly is mechanically dysfunctional and becomes fissured and ulcerated leading to a secondary osteoarthritis that is often enhanced by joint laxity [4••]. Joint effusions are uncommon and when present in the synovial fluid it is typified by a low leukocyte count, as in osteoarthritis. In some patients synovial hypertrophy is prominent, but this is because of increased amounts of fibrous tissue and fat in the synovium rather than synovocyte hyperplasia. The most commonly involved joints are hands, hips, knees, and shoulders. Axial involvement is common with symptoms of neck and

Table 2. Clinical features of growth hormone excess

Joint involvement
Cartilage hyperplasia
Synovial proliferation
Secondary osteoarthritis
Joint hypermobility
Capsular thickening
Bursal enlargement
Muscle involvement
Muscle enlargement
Proximal weakness
Myalgias
Muscle cramping
Nerve involvement
Carpal tunnel syndrome
Palpable peripheral nerves
Peripheral neuropathy
Other problems
Raynaud's phenomena
Dorsal kyphosis
Neck and back pain

back pain [5]. Diffuse idiopathic skeletal hyperostosis has been reported to occur in 20% of acromegalic patients [6]. Temporomandibular pain, usually because of malocclusion, occurs in approximately one-third of patients. An important clue in differentiating acromegalic arthritis from classical osteoarthritis is the clinical finding of pronounced joint crepitus and hypermobility in acromegalic patients. Another clue, which occurs in most cases of advanced acromegaly, is the finding of a visible enlargement of the costochondral junctions. This is sometimes referred to as the "acromegalic rosary."

Soft tissue overgrowth is a prominent feature of acromegaly and results in thickened digits, bursal enlargement, and hypertrophy of joint capsules. Bony thickening of the distal ungula tufts, seen in approximately 60% of patients, can produce an appearance of pseudo clubbing. Other common symptoms are excessive sweating, peripheral neuropathy, impotence, headaches, and visual field defects. Acromegaly is often complicated by other endocrine disorders such as hypothyroidism and diabetes mellitus.

Elevated levels of GH and IGF-1 have been reported in patients with hypermobility syndrome without any other features of acromegaly [7]. It has also been reported that the course of knee osteoarthritis is influenced by IGF-1 levels, in that higher levels are associated with more osteophytes [8]. However, another study failed to find any significant relationship between age-adjusted IGF-1 levels and radiologic progression of knee osteoarthritis [9].

Carpal tunnel syndrome, which is frequently bilateral, occurs in approximately 30% of patients with acromegaly. This is because of hyperplasia of the flexor tendons and synovial edema. Medical or surgical reduction of the IGF-1 level leads to a rapid resolution of median nerve compression symptoms.

Peripheral neuropathy occurs in approximately 50% of patients with acromegaly [10]. Its cause is complex but in some cases appears to be a result of segmental demyelination without obvious axonal degeneration [11]. Histologically an irreversible hypertrophy of Schwann cells is seen in advanced cases. In some acromegalic patients this is a major cause of morbidity which is not benefited by normalization of GH levels. In some patients an associated diabetes mellitus contributes to the neuropathy.

A distinctive "acromegalic myopathy" has been described in a small number of patients [12]. This might seem paradoxical in view of the anabolic actions of GH on muscle. Muscle biopsies have shown a hypertrophy of type 1 fibers with an atrophy of type 2 fibers. Electron microscopy has revealed abnormal looking mitochondria, inclusion bodies, and infiltration of glycogen granules [13]. The molecular basis of acromegalic myopathy is now thought to be related to an upper regulation of a muscle wasting factor called myostatin [14]. This molecule is a member of the transforming growth factor-beta (TGF-beta) superfamily.

Bone metabolism is influenced directly and indirectly by GH/IGF-1 with a resulting increased rate of bone turnover. Depending upon the severity and duration of acromegaly, this increased bone turnover is not always associated with structurally sound bone formation and this can result in widely varying problems. For example, some studies have reported osteoporosis and increased vertebral fractures and other studies have reported increased bone density in acromegalic patients. Furthermore, hypogonadism is a common accompaniment of severe acromegaly, and probably contributes to reduced bone mineral density (BMD) in that subset of patients.

Diagnosing acromegaly

The diagnosis of acromegaly is based on the typical clinical features in conjunction with a consistently elevated IGF-1 level [15•] (Fig. 2). The levels of GH itself are also elevated, but this is a less reliable screening test as the measurement of GH is subject to more variation because of pulsatile secretion. It is important to remember that IGF-1 levels vary significantly with age, with the highest levels being seen in early puberty. Thus, an IGF-1 level that would be normal in puberty could be indicative of a GH secreting pituitary adenoma in a 70-year-old.

As in other functional tumors, there is no feedback inhibition of GH secretion from pituitary adenomas and this forms the basis for the confirmatory glucose load test. In normal individuals, the serum GH concentrations fall to 2 ng/mL or less within 2 hours after ingestion of 50 to 100 g glucose. In patients with acromegaly the post-glucose levels of GH are greater than 2 ng/mL.

Management of acromegaly

As there are many subtle variables influencing the treatment algorithm for acromegaly, a close working relationship

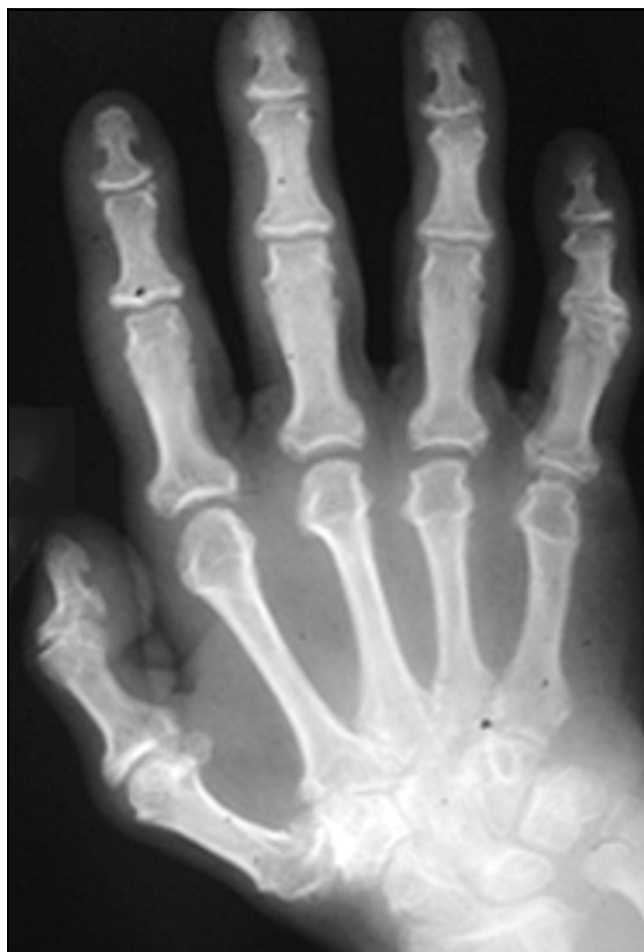


Figure 2. Radiograph of a hand in moderately advanced acromegaly showing a mixture of joint space enlargement and degenerative changes.

between an endocrinologist and an experienced neurosurgeon is essential. There are several therapeutic options in managing patients with acromegaly, with the overriding aim of reducing the serum level of IGF-1 to normal range for the patient's age and sex.

In general, small adenomas (< 10 mm in diameter) can be excised through the transsphenoidal route without significantly compromising the secretion of other pituitary hormones. Large adenomas can seldom be removed entirely, and the goal of surgery is to remove enough tissue to maximize the results of nonsurgical therapy. Potential complications of surgery include meningitis, cerebrospinal fluid rhinorrhea, central diabetes insipidus, and other pituitary hormone deficiencies.

There are several drugs that inhibit GH secretion or its action that have proven to be useful in managing symptoms of acromegaly that cannot be totally cured by surgery. The most widely used medications are the somatostatin analogues octreotide and lanreotide which are given by intramuscular injection. Because they have a long half-life (2 hours versus 2 minutes) they are more effective than naturally occurring somatostatin. In general somatostatin analogues are well tolerated but approxi-

mately one-third of patients have nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption. These problems become less severe with ongoing therapy. In some acromegalic patients a reduction of the IGF-1 level may be achieved by the use of dopamine agonists such as cabergoline. The advantage of these is that they can be given orally.

Undersecretion of Growth Hormone

Undersecretion of GH gives rise to pituitary dwarfism in children and the syndrome of adult GH deficiency (AGHD) in adults. This latter problem is of relevance to rheumatologists as there are several scenarios in which they may encounter AGHD. The experience of rheumatologists in this respect is very different from that of an endocrinologist in that the cause of deficient GH secretion is usually because of a disordered pituitary or its adjacent structures. Thus, the common causes of AGHD in an endocrinology practice are a pituitary tumor, surgical resection of the tumor, or pituitary radiation (approximately 75% of cases), an adjacent tumor (*eg*, craniopharyngioma—approximately 15% of cases), infiltrative disorders (*eg*, sarcoidosis, hemochromatosis—approximately 1% of cases), and Sheehan's syndrome (approximately 0.5% of cases). In a rheumatology practice the cause of AGHD deficiency is seldom because of pituitary disease itself, but results from a dysregulation of the hypothalamic hormones controlling the pituitary secretion of GH or a peripheral insensitivity to GH.

The syndrome of adult growth hormone deficiency

There has been increasing realization over the past 10 years that the secretion of GH is not only important in promoting normal linear growth and an adult stature, but is also important in the attainment of an optimal hormone milieu in adults. Deficiency of GH in adults is now well accepted to cause a distinctive syndrome known as AGHD [16••,17]. In large part, this burgeoning awareness of AGHD has been because of the increasing availability of GH supplementation, from the use of DNA recombination technology, and its beneficial effects in GH deficiency in adults.

As might be predicted from the actions of GH (Table 1), the most obvious clinical features of AGHD are changes in body composition resulting in a decreased muscle mass and increased total body fat (Table 3). The fat accumulation is preferentially intraabdominal, a distribution that has been associated with dyslipidemia, insulin intolerance, hypertension, and some malignancies (breast and colon). It has been hypothesized that the predilection for intraabdominal fat deposition in AGHD is because of relative hypercortisolism—as a result of increased activity of 11-hydroxysteroid dehydrogenase (the enzyme that converts inactive cortisone to active cortisol).

A major factor contributing to reduced life expectancy in AGHD is the additive effect of several consequences

Table 3. Clinical features of adult growth hormone deficiency

Clinical features of adult GH deficiency	Improved by GH replacement
Increased abdominal fat	Yes
Reduced muscle mass and strength	Yes
Reduced cardiac capacity	Yes
Reduced blood volume	Yes
Cold intolerance	Probably
Impaired exercise capacity	Yes
Thin, dry skin	Yes
Reduced sweating	Yes
Reduced bone mineral density	Yes (delayed effect after 1 year)
Psychosocial dysfunction	Yes
Atherogenic lipid profile	Probably
Increased atherosclerosis	Not known
Reduced life expectancy	Not known

GH—growth hormone.

deleterious to cardiac function [18]. These include a reduced left ventricular ejection fraction, stroke volume and cardiac index (a result of reduced left ventricular wall thickness), and the atherogenic lipid profile. Therefore it is not surprising that patients with AGHD, from whatever cause, have a twofold increase in cardiovascular related mortality and a threefold increase in cerebrovascular related mortality [17].

Rheumatologists are used to hearing their patients complain of increase fatigability. In inflammatory rheumatic disorders there is an increasing awareness that, in part, the fatigue results from increased levels of proinflammatory cytokines. Nowhere is this more evident than in the dramatic improvements in fatigue that patients experience when placed on anti-tumor necrosis factor (anti-TNF). Other causes of fatigue that rheumatologists often consider, are depressive illness, anemia of chronic inflammation, deconditioning, and drug side effects. To this list should be added the syndrome of AGHD.

The cause of fatigue in AGHD probably results from an accumulation of several factors, such as a reduced cardiac index, a reduction in maximal oxygen uptake, reduced muscle strength, reduced red cell blood volume, reduced plasma volume, and an array of psychosocial difficulties. These latter include a significantly reduced overall quality of life, low self-esteem, poor socioeconomic achievement, dysthymia, and reduced vitality [16••].

Diagnosis of adult growth hormone deficiency

Because GH has a very short half-life and is secreted in a pulsatile manner, mainly at night and after vigorous exercise, the measurement of a single GH level is a useless exercise. The most stringent test for GH deficiency is to measure GH levels every 10 to 20 minutes to obtain an integrated 24-hour GH profile. As this is impractical outside the research setting,

the recommended screening test for AGHD is the measurement of an IGF-1 level. The levels of IGF-1 (which have a half-life of approximately 22 hours) are stable throughout the day with minimal diurnal variation and thus measurement of an IGF-1 level does not require the subject to be in fasting state. A low IGF-1 level, age-adjusted, is a very specific indicator of AGHD. However its sensitivity is poor, especially in the setting of pituitary disease. In this situation there are often coexistent endocrine deficiencies as part of a syndrome of panhypopituitarism, which provides initial diagnostic clues. The sensitivity of IGF-1 levels for diagnosing AGHD in the setting that most rheumatologists are likely to encounter (*ie*, hypothalamic dysregulation or peripheral insensitivity to GH) has not been rigorously studied. Unfortunately, nonpituitary AGHD is not recognized by most insurance companies in the United States as they require "confirmation" of GH deficiency with a GH stimulation test. These tests were initially developed in the pediatric population and basically assess the pituitary's ability to secrete GH under conditions of maximal stimulation. Currently the most widely used GH stimulation test involves the oral administration of arginine (an amino acid that inhibits hypothalamic somatostatin tone) concurrently with intravenous GH releasing hormone (GHRH) at a dose of 1 ng/kg. GH levels are measured every 30 minutes over the next 2 hours. A single GH level greater than or equal to 5 ng/mL is considered indicative of normal pituitary function. As the problem in rheumatologic causes of AGHD is not at the level of the pituitary, most patients with conditions such as rheumatoid arthritis, chronic corticosteroids usage, and fibromyalgia will be shown to have a normal pituitary secretion of GH in response to this test and are thus ineligible for supplemental GH therapy through most insurers.

Corticosteroid induced growth hormone deficiency

Rheumatologists are very familiar with the stunting of linear growth that occurs in children on chronic corticosteroid therapy [19]. The reasons for this stunting are complex and still not fully worked out. To date, two major abnormalities have been reported: 1) a suppression of the transcription of GH receptor messenger RNA (mRNA) with a resultant down regulation of GH stimulated synthesis of GH receptor and IGF-1 receptor, and 2) a reduced production of local IGF-1 (*ie*, inhibited paracrine secretion), a key determinant of chondrocyte proliferation and endochondral ossification. There are several persuasive studies, regarding children on chronic corticosteroid therapy, that have reported a normalization of linear growth after treatment with recombinant human GH [20]. Therefore, GH therapy should be considered a potentially important adjunctive therapy in children with steroid responsive rheumatic disorders that cannot be weaned off their medication. However, supplemental GH should be used with caution in patients with systemic lupus erythematosus as there are two case reports of significant disease flares.

Inflammation induced growth hormone deficiency

Inflammatory cytokines, in general, acutely stimulate the secretion of GH. Paradoxically, chronic inflammation is often associated with stunted growth. Reduced linear growth has been well described in juvenile rheumatoid arthritis and inflammatory bowel disease. The reasons for this are not entirely clear, but ongoing research indicates that chronic inflammation reduced the expression of GH responsive genes [21]. For instance, TNF-alpha, and IL-6 down regulate the expression of mRNA for the GH receptor on hepatocytes, thus causing a state of GH insensitivity. Clinically GH unresponsiveness should be suspected in patients with normal elevated GH levels who have low or normal IGF-1 levels. Evaluation of the GH/IGF-1 axis in patients with adult onset rheumatoid arthritis has not been extensively studied, but two studies have reported a sub-optimal GH response to GHRH [22] and insulin-induced hypoglycemia in rheumatoid patients [23], whereas another study reported a normal GH/IGF-1 axis [24]. There are no good studies to indicate a beneficial effect of supplemental GH in inflammation induced GH deficiency. This might be expected if the problem is mainly a GH insensitivity state.

Bone mass and growth hormone deficiency

Growth hormone and IGF-1 are essential for linear growth and the achievement of an adult bone mass. Bone mass increases steadily through childhood, peaking in the mid-20s and subsequently declines throughout life. Linear growth results from a proliferation and differentiation of chondrocytes at the epiphyseal growth plates through the effects of GH directly and indirectly through IGF-1, which directly stimulates proteoglycan synthesis [25]. The accumulation of bone mass results from the iterative process of bone remodeling with bone resorption by osteoclasts and new bone formation by osteoblasts. GH and IGF-1 stimulate osteoclasts differentiation and activity thus promoting bone resorption. They also stimulate osteoclast proliferation and activity to promote bone resorption. This results in an overall increase of bone remodeling leading resultant reduction in BMD [26] which can be improved with supplemental GH therapy [27]. There has naturally been an interest as to the potential role of the GH/IGF-1 axis in postmenopausal osteoporosis. In one placebo-controlled study in postmenopausal women, GH supplementation on top of hormone replacement therapy and calcium/vitamin D, increased bone mineral content by 14% [28]. Considering the current cost of supplemental GH therapy (\$600–\$1200 per month) and the ready availability of effective alternatives, there is little enthusiasm for using GH in the management of postmenopausal osteoporosis. This situation may change as oral GH secretagogues become available. A recent study evaluated the individual and combined effects of MK-677 (an experimental oral GH secretagogue) and alendronate

on BMD and biochemical markers of bone formation [29]. MK-677 plus alendronate increased BMD at the femoral neck 4.2% versus 2.5% for alendronate alone. However, a similar additive, enhancement of BMD was not seen at the lumbar spine or total body.

Fibromyalgia and growth hormone deficiency

A possible link between AGHD in fibromyalgia was reported in 1992, based on the theory that fibromyalgia patients may have impaired GH production because of the alpha-delta sleep anomaly [30]—stages three and four of nonREM sleep are a prime time for GH secretion [31]. Several subsequent studies have supported a disordered GH/IGF-1 axis in fibromyalgia [32–37] and some other studies have not [38–41]. Most of the negative studies have been underpowered. When IGF-1 levels were measured in a cohort of 500 fibromyalgia patients, there was a very significant reduction compared with healthy controls ($P = 0.0000001$) [42•]. A subsequent 9-month placebo-controlled therapeutic trial in fibromyalgia patients, with low IGF-1 levels, reported a significant clinical benefit [43]. Paiva *et al.* [44] has reported an impaired GH response to the stress of exercise to volitional exhaustion, the GH response was normalized after the patients had taken pyridostigmine (an acetyl cholinesterase inhibitor that reduces hypothalamic somatostatin tone by stimulation of cholinergic pathways). McCall-Hosenfeld *et al.* [41] have reported a similar impairment of GH secretion to the stress of hypoglycemia. The latter article found a correlation of increasing body mass index with an impaired GH response to hypoglycemia, whether this is the cause of the impairment or a result of GH deficient patients having increased fat stores is not known. The current hypothesis is that a subset of fibromyalgia patients (approximately 30%) developed AGHD because of a stress induced increase in corticotropin releasing factor, which in turn stimulates hypothalamic somatostatin tone [45–47].

Conclusions

In the early stages of oversecretion of GH, before the obvious appearance of acromegaly, symptoms of diffuse polyarticular pain may mimic the early stages of an inflammatory arthritis. In a subset of patients there are myopathic and neuropathic presentations. As the course of acromegaly progresses, joint laxity and dysregulated chondrocyte proliferation production results in osteoarthritic changes. The syndrome of AGHD is increasingly recognized as a cause of fatigue, dysthymia, and increased mortality as a result of dyslipidemia. Rheumatologists will encounter this syndrome in some patients on chronic corticosteroids with long-standing inflammatory arthritis and fibromyalgia. There is an increasing experience with using GH to minimize growth retardation in children on corticosteroids for management of inflammatory rheumatic disorders.

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