Insulin-like growth factor-I: marker for diagnosis of acromegaly and monitoring the efficacy of treatment

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Abstract
Acromegaly is caused by chronic excess secretion of growth hormone (GH) and resultant persistent elevation in concentrations of insulin-like growth factor-I (IGF-I), also called somatomedin-C. A number of diagnostic tests are available to support the diagnosis of acromegaly, but those that rely on measurement of serum GH concentrations have important limitations. Concentrations of serum IGF-I, which is produced principally in the liver and mediates the actions of GH, have been shown to correlate with clinical and metabolic markers of disease activity. Additionally, normalisation of IGF-I levels in acromegaly is associated with the resolution of symptoms and normal life expectancy. Thus, serum IGF-I is an important marker of disease activity and a sensitive, practical, and reliable measure of integrated GH concentrations in patients with acromegaly.

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Introduction
Acromegaly is caused by excessive secretion of growth hormone (GH; also called somatotropin) and a resultant persistent elevation of insulin-like growth factor-I (IGF-I; also called somatomedin-C) concentrations. The condition occurs after puberty (oversecretion of GH in children, before epiphyseal closure, causes gigantism) and in nearly all cases is due to a benign pituitary adenoma. Acromegaly causes distinctive and disfiguring physical changes, particularly of the extremities, due to skeletal and soft tissue growth. Importantly, acromegaly is associated with an increased rate of mortality due to cardiovascular, cerebrovascular, and respiratory disorders (1–3). Reduced survival is associated with increased GH levels, and studies in patients with acromegaly have demonstrated that normalisation of mortality rates accompanies control of GH concentrations (3–5).

The growth-promoting effects of GH are mediated by the induction of growth factors called somatomedins, one of which is IGF-I (or somatomedin-C). IGF-I is produced by cells in the liver, kidney, pituitary gland, gastrointestinal tract, muscle, and cartilage, but the primary source of circulating IGF-I is the liver. Recently published data showed that selective inhibition of IGF-I production from the liver caused an 85% reduction in circulating concentrations of IGF-I in a murine model (6). Only about 1% of circulating IGF-I is present as free, uncomplexed molecules (7) (Fig. 1); the remainder are bound to IGF-specific binding proteins (IGFBPs), six of which have been characterised (8). The most abundant of these is IGFBP-3, which forms a ternary complex with IGF-I and another protein, the acid-labile subunit (ALS). Both IGFBP-3 and ALS are also tightly regulated by GH and have been evaluated as markers for GH-deficiency disorders (9).

The relationship between IGF-I concentrations and clinical manifestations of acromegaly
It has long been known that serum IGF-I levels are correlated with disease activity in acromegaly. Clemmons et al. demonstrated that IGF-I concentrations correlated with heel pad thickness, fasting blood sugar concentrations, and response to an oral glucose tolerance test (OGTT) in patients with acromegaly (10) (Fig. 2). Furthermore, in 15 patients followed for 1 year after treatment, changes in IGF-I concentrations paralleled the degree of clinical improvement. Importantly, Swearingen and colleagues have demonstrated that treatment-induced normalisation of serum IGF-I levels correlates with normalisation of the survival rate in acromegalic patients (1) (Fig. 3).

Additional compelling evidence demonstrating a relationship between IGF-I and the clinical manifestations of acromegaly is based on the results of IGF-I therapy for genetic GH insensitivity syndrome (Laron
type dwarfism). This condition results from disruption of GH receptor function that inhibits IGF-I production. In a well-documented case study, a child treated with recombinant IGF-I achieved a desirable increase in height but also developed the manifestations of overtreatment, namely facial coarsening similar to that seen in patients with acromegaly (11).

The clinical utility of IGF-I concentrations in acromegaly

**Diagnosis**

Several biochemical tests may be used to support a diagnosis of acromegaly. These include random measurement of GH serum concentrations, mean 24-h GH serum concentrations, GH response to OGTT, and random measurement of IGF-I concentrations.

Diagnosis of acromegaly based on measurement of basal or random serum GH concentrations is uncertain because of the pulsatile secretion of GH, which occurs in normal individuals, in patients with active acromegaly, and in successfully treated patients with acromegaly (12–14). This was demonstrated by Kaltsas et al. (15), where they calculated the mean GH value from 5 random GH level determinations in patients with newly diagnosed acromegaly (n = 67). Although the mean GH values correlated overall with the
5 random GH measurements, individual GH values clearly fluctuated around the mean in individual patients (Fig. 4). Thus, single random measurements of serum GH concentrations are of limited value in the diagnosis of acromegaly. Serial GH concentrations over a 24-h period provide an overview of GH secretion and can be used in diagnosing acromegaly, but this method is impractical in an office setting (16). In contrast, oral glucose tolerance testing is useful in the clinical setting. In healthy individuals, an oral glucose load causes a reduction in serum GH concentrations to less than 1 μg/l or 2 μg/l (depending on the assay used), but GH concentrations remain above this cutoff in patients with acromegaly. Recent data using sensitive GH assays, such as immunoradiometric assay (IRMA) and enzyme-linked immunosorbent assay (ELISA) in pre- and postoperative patients with acromegaly showed that a large percentage of the patients had GH nadir concentrations >1 μg/l after OGTT (17, 18). Therefore, using GH measurement alone, the diagnosis could be missed for many patients.

In contrast, plasma concentrations of IGF-I are not pulsatile. They are usually elevated in patients with active acromegaly who have GH values that overlap the normal ranges, and they remain elevated in patients with normal GH nadir concentrations after OGTT (17, 18). Additionally, the IGF-I ternary complex has a half-life of approximately 15 h compared with the 15- to 20-min half-life of GH (19). Importantly, serum IGF-I concentrations appear to reflect mean serum GH concentration over a 24-h period. Close correlation is observed when plasma IGF-I concentrations are expressed as a function of mean 24-h plasma GH concentrations with a sampling rate of every 10 to 20 min (20). Despite this close correlation, serum IGF-I concentrations plateau at very high GH concentrations (Fig. 5).

Therefore, it has recently been proposed that diagnosis of acromegaly should not be based solely on the GH nadir after OGTT but should be made by a combination of clinical features, random GH and IGF-I measurements using a highly sensitive assay (IRMA or ELISA), and the GH nadir concentration after OGTT (21).

**Monitoring the efficacy of treatment**

The limitations of assessments based on serum GH concentration must also be considered when monitoring patients after surgery or during pharmacotherapy. The pulsatile nature of GH secretion, which can lead to errors in estimating disease activity, may persist after these treatments (13, 22). Additionally, Freda et al. found that more than one third of patients in remission, with normal IGF-I values, did not have normal GH suppression as defined by OGTT (18). Kaltsas et al. concluded that combined measurement of mean serum GH concentrations and single IGF-I concentrations are a better biochemical guide to the adequacy of transsphenoidal surgery for acromegaly than 24-h mean or single random GH concentrations or IGF-I measurement alone (15) (Fig. 6). Another study reported a significant correlation between nadir GH concentration and IGF-I concentration in postsurgical patients with active disease or inadequate GH suppression. Conversely, no correlation was found between the two parameters in healthy volunteers or postsurgical patients with adequate GH suppression (18).

**Current practices in IGF-I measurement**

Historically, total unextracted IGF-I was measured clinically with immunoassays (competitive radioimmunoassay (RIA) or IRMA) using antibodies against IGF-I (7). IRMA is the most commonly used assay system in the United States (23). At neutral pH, IGF-BPs bind rapidly and with high affinity to IGF-I, and they can interfere with measurement of IGF-I. In the early
1990s, new assays were developed to measure IGF-I that had been acid-extracted (pH 3.0) from IGFBPs followed by ethanol treatment, which precipitates high-molecular-weight protein and protein complexes. Some of these assays, however, still did not result in complete separation, leaving some remaining IGFBPs in the supernatant. Residual IGFBPs can bind the IGF-I, interfering with the subsequent antibody-binding step (7, 23).

Today, the IGFBP-extracted, insulin-like growth factor-II (IGF-II)–blocked method developed by Blum et al. is widely used (7, 23–25). In this two-step method, IGFBPs are first separated by acidification. Excess amounts of IGF-II, which also binds to the IGFBPs, are then added. The high concentrations of IGF-II saturate the IGFBPs, ensuring that all binding proteins will be precipitated. This method requires the use of highly specific anti-IGF-I antibodies during the subsequent separation process. Since IGF-II was added in excess, some will remain unbound to IGFBPs in the supernatant. The anti-IGF-I antibodies utilised in this assay must be highly specific, with very low cross-reactivity for IGF-II.

Factors influencing IGF-I concentrations

IGF-I production may be influenced by certain factors, which should be considered in the interpretation of IGF-I values. For example, like GH concentrations, IGF-I concentrations are influenced by age – peaking around puberty and declining thereafter. As exemplified in a recent study by our group in more than 500 healthy subjects, IGF-I was shown to decrease with age (26) (Fig. 7). A review of published data on IGF-I reveals an age-dependent decrease of 10–16% per decade (26–33). The variation between studies is due, in part, to different methodologies in measuring IGF-I, and due to the inclusion of different groups of subjects.

Sex hormones also affect IGF-I concentrations, leading to gender-specific differences in the relationship between IGF-I and GH concentrations. Recent data demonstrate that, at a given GH level, IGF-I concentrations are significantly higher in men than in women (34–36). Oral oestrogen further reduced the IGF-I levels in women (34). Helle et al. have recently reported that postmenopausal women have significantly lower plasma IGF-I levels than premenopausal women (37). Androstenedione and dehydroepiandrosterone sulfate (DHEAS) were also positively correlated with plasma IGF-I levels (37). It is well known that healthy women secrete higher levels of GH than men and, to achieve a given IGF-I concentration, GH replacement therapy must be higher for women than for men (34). In men, the decline in IGF-I concentrations parallels the age-related decline in estradiol levels (26). Accurate assessment of IGF-I concentrations thus requires age- and sex-matched control values.

Intercurrent illness, particularly impaired hepatic or renal function, may also confound interpretation of IGF-I measurements. Progressive liver disease, as measured by increasing Child scores, results in declining IGF-I concentrations (Fig. 8), while alcohol abuse causes reductions in IGF-I production and bioavailability (38). Abstinence leads to an increase in IGF-I bioavailability in patients who do not yet have clinically apparent liver disease but not in chronic alcohol abusers with cirrhosis of the liver. Renal impairment does not significantly reduce IGF-I concentrations, but an accumulation of low-molecular-weight IGFBPs, particularly IGFBP-3, inhibits the biological activity of IGF-I (39) (Fig. 9).
IGF-I for monitoring treatment with pegvisomant

Pegvisomant is a new and highly efficacious agent for the treatment of acromegaly. Because of the nature of its mechanism of action, therapeutic monitoring requires measurement of IGF-I concentrations rather than GH concentrations. Pegvisomant is a selective growth hormone receptor antagonist that competitively blocks GH signal transduction, resulting in inhibition of GH activity and a corresponding reduction in the production of IGF-I (40). Pegvisomant does not inhibit GH secretion and therefore serum IGF-I concentrations are the best marker of treatment efficacy.

The results from short- and long-term pegvisomant clinical efficacy trials demonstrate resolution of the clinical and metabolic features of acromegaly with normalisation of serum IGF-I levels (41, 42). In a 12-week study of three doses of pegvisomant (10 mg/day, 15 mg/day, 20 mg/day) patients with acromegaly achieved a dose-dependent decrease in IGF-I concentrations from baseline (−26.7%, −50.1%, and −62.5%, respectively) as well as a dose-dependent increase in the percentage of patients with normalised IGF-I at week 12 (38%, 75%, and 82%, respectively). Similarly, metabolic and clinical parameters, including ring size and soft tissue swelling, improved from baseline with normalisation of IGF-I (41, 42). These data are consistent with the use of IGF-I as the optimal marker of disease activity in acromegaly.

Conclusions

Serum IGF-I concentration is a sensitive measure of integrated GH levels in patients with acromegaly that closely correlates with clinical and biochemical markers of disease activity. Importantly, normalisation of IGF-I concentrations reverses the mortality associated with acromegaly. Accordingly, the primary goal of treatment for acromegaly should be to restore IGF-I concentrations to within the age- and gender-adjusted normal range. Renal or hepatic disease or impaired nutritional status should be viewed as confounding conditions. These conditions may cause alterations in IGF-I production and/or bioactivity, such that the IGF-I concentration may no longer accurately reflect disease activity.

IGF-I is an especially critical marker of disease activity for monitoring patients receiving pegvisomant, the most effective acromegaly treatment developed to date, as random GH concentrations are not meaningful owing to the structure and mechanism of action of this novel compound.

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