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Serum IGF-I levels in the diagnosis and monitoring of acromegaly

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Abstract Insulin-Like Growth Factor-I (IGF-I) is a reliable marker of disease activity and growth hormone (GH) status in acromegaly, but its clinical utility has been hampered over the years by various issues including a lack of robust reference range data and variability in assay sensitivity and specificity. In acromegaly IGF-I correlates well with GH activity and nadir GH on oral glucose tolerance test (OGTT) and is the most sensitive and specific test in diagnosis, where serum IGF-I is persistently seen to be elevated to a range that is distinct from that in healthy individuals. However it should not be relied on exclusively for diagnosis or used as the sole indication of disease severity and GH burden. Successful medical or surgical treatment of acromegaly is usually associated with normalisation of serum IGF-I but there is discordance between GH and IGF-I in some patients. Patients with a normal IGF-I but an abnormal GH suppression to OGTT are at risk of relapse and therefore it should not be used alone to establish disease remission. In contrast to the diagnosis of acromegaly, there is also considerable overlap in serum IGF-I with normality after primary treatment of disease, even in the presence of persisting GH excess. Gender, age and prior radiotherapy alters the relationship between GH and IGF-I and reliance on one marker of disease activity such as IGF-I is particularly precarious in certain disease states. However an elevated serum IGF-I has been shown to be associated with excess mortality and normalising IGF-I normalises mortality making it a useful marker. The tightening up of the assays means that establishing absolute concentrations as well as standard deviation scores are essential to allow cross-study comparisons. This becomes especially important in the use of Pegvisomant, where IGF-I becomes the sole biochemical marker of disease activity.

Keywords Acromegaly · IGF-I · Diagnosis

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Introduction

Acromegaly is the condition that results from prolonged excessive circulating growth hormone (GH) in adults. The main action of GH is to induce synthesis of peripheral insulin-like growth factor-I (IGF-I), mostly in hepatocytes, which leads to cell proliferation and inhibition of apoptosis. Therefore, IGF-I is potentially a reliable marker of disease activity and GH status in acromegaly, but its clinical utility has been hampered over the years by various issues including a lack of robust reference range data and variability in assay sensitivity and specificity. Biochemical criteria for diagnosis and remission of acromegaly have changed in the last decade as more specific and sensitive assays for GH and IGF-I have become available. Acromegaly has previously been associated with a up to a 3.3-fold increase in mortality [1], although recent data suggest a more modestly increased standardised mortality ratio of 1.3–1.8 [2, 3]. The increased morbidity and mortality associated with the disease makes reliable methods of assessment essential. IGF-I is a useful tool in diagnosis, post-operative assessment of remission or 'cure' and continuing monitoring of active acromegaly and each of these will be discussed in turn.

Diagnosis of acromegaly

Once the clinical suspicion of acromegaly has been raised, a number of biochemical markers may be used to establish a diagnosis. These include serum IGF-I, mean 24-h serum GH (measured every 10–20 min or on a 5 point day curve), urinary GH and GH suppression on a prolonged oral glucose tolerance test (OGTT). Traditionally failure of suppression of serum GH has been regarded as the 'gold standard' diagnostic test but recently serum IGF-I has been proposed as the first line investigation for the diagnosis of acromegaly [4, 5].

Most actions of GH are via IGF-I. This is supported by the fact that in GHR mutations, with no innate production of IGF-I, excess replacement of IGF-I leads to features of acromegaly [6]. In addition, use of the GHR antagonist Pegvisomant, which blocks signal transduction and transcription of serum IGF-I [7], results in resolution of symptoms, signs (ring size and soft tissue swelling) and metabolic features of acromegaly, despite a persistently elevated GH [8, 9].

Insulin-like growth factor-I correlates well with GH activity as measured by mean GH concentration over a 24-h period in healthy individuals. In patients with acromegaly, there is a positive logarithmic-linear relationship with GH and IGF-I, respectively [10, 11]. Serum IGF-I also correlates well with nadir GH on OGTT in patients with acromegaly [12]. Serum IGF-I is not pulsatile and its measurement is a simple test with little variability in the sampling over 24 h [13], unlike GH, which remains pulsatile even in active acromegaly. When bound in a ternary complex of insulin-like growth factor binding protein-3 (IGFBP3) and acid-labile subunit (ALS) it has a half-life of 15 h (unlike 20 min for GH). This means that a single measurement of IGF-I usefully reflects disease activity and severity. IGF-I correlates with signs such as heel thickness ($r = 0.73$), fasting glucose ($r = 0.74$) and 1-h post-prandial glucose ($r = 0.77$) [14]. Moreover, changes in serum IGF-I after treatment match clinical improvement. Normalising serum IGF-I, leads to a reversal of the syndrome of acromegaly, both clinically and metabolically [8].

In patients with active acromegaly, IGF-I levels are persistently seen to be elevated to a range that is distinct from that in healthy individuals [10, 14–16] and this is key to its use in diagnosis. Occasionally, there are subtle elevations in serum GH, which may not induce a high serum IGF-I [17].

Insulin-like growth factor-I is extremely useful in the diagnosis of disease, but can it reliably be used as the sole diagnostic test? IGF-I is more specific than mean 24-h GH assessments, especially with mild degrees of excess, where GH frequently overlaps with the normal population [10, 18]. In fact, despite similar mean serum GH between control subjects with normal GH pulsatility and patients with acromegaly, the serum IGF-I is higher in those patients with acromegaly [10, 19]. Disparity between GH and IGF-I measurements are frequently seen. In one report of 16 patients with a histologically proven somatotroph adenoma an elevated serum IGF-I was seen in all patients while eight showed a nadir GH < 1 μg/l (2 mU/l) on OGTT and 12 had a mean 24 h integrated GH of <2.5 μg/l (5 mU/l) [18]. In fact, in the same study, the mean 24-h GH overlapped with controls in all cases. Other studies have also demonstrated minimally elevated or normal GH but abnormally high-circulating serum IGF-I [10, 14, 20, 21].

As GH assays have become more sensitive, the criterion for diagnosis of acromegaly using nadir GH on OGTT has been tightened. Despite this, there remains discordance between GH and IGF-I. Freda et al. suggested an upper limit of normal for nadir GH of 0.14 μg/l (corrected to assay standard of 0.21 μg/l), although in another series by Dimaraki et al., using these criteria, there was still one patient with clinical acromegaly, an elevated serum IGF-I and a glucose suppressed serum GH below this cut off value of 0.14 μg/l [18]. Again, despite supposedly normal nadir GH, removal of the tumour returned the IGF-I to normal. This was associated with improvement of symptoms of arthralgia, headaches, sweating, sleep apnea and acral enlargement. The reliance on glucose suppression of GH in assessment of acromegaly is further complicated by its alteration in certain physiological and disease states such as puberty, pregnancy, hepatic and renal disease, anorexia and diabetes mellitus.

Therefore, IGF-I remains the most sensitive and specific test in the diagnosis of acromegaly. However it should not be relied on exclusively for diagnosis or used as the sole indication of disease severity and GH burden. At very elevated serum GH (>40 mU/l or 20 μg/l) there is discordance as IGF-I plateaus [11]. IGF-I is also altered in puberty and pregnancy as well as certain diseases. An age related decline in IGF-I is still seen, even in active acromegaly, and reliable local age related reference ranges are essential [22].

In 2004, the Consensus guidelines for diagnosis of acromegaly suggested that the nadir GH on OGTT does not add diagnostic value when the IGF-I is high, but does serve as an assessment of carbohydrate intolerance [23]. In addition, GH is a valuable tool in assessing the severity of GH excess and as a baseline against which to audit the success of attempted surgical adenectomy or the response to medical therapy. However, if only one or other of GH or IGF-I is abnormal further investigation, including pituitary imaging, should be carried out.

Post-operative assessment of cure and remission

Surgical resection remains the primary treatment of acromegaly. Cure is defined as restoration of normal pulsatile GH secretion, a normal IGF-I and full suppression of GH with glucose. Remission is seen when there is persistently detectable GH, with or without full suppression with glucose, but to 'safe' levels of GH and IGF-I associated with a normal prognosis. Post-operative cure or remission has generally been assessed by nadir GH on glucose challenge and normalisation of IGF-I, with additional information about the burden of disease from mean serum GH. However, what comprises suppression of GH with glucose and which part of the normal age related reference range for IGF-I is 'optimal' is still debated.

The most accurate time period for IGF-I assessment is 12 weeks post-operatively. This is based on a study measuring serum IGF-I (and GH) at 1, 2, 3, 8 and 12 weeks post-procedure. Although nadir GH on OGTT was highly reproducible after 1 week, IGF-I fluctuated and only stabilised at 12 weeks [24]. However stabilisation of IGF-I can be occasionally delayed to 12 months. Formal assessment should be carried out 3 months after surgery, unless pre-treatment with somatostatin analogs precludes accurate analysis.

Successful medical or surgical treatment of acromegaly is associated with normalisation of serum IGF-I [8, 9, 25–27]. IGF-I appears to be a more sensitive marker for remission than GH. Gullu et al. showed if remission is defined as a basal GH <2.5 μg/l, then 15 of 21 patients with low GH levels had an elevated age adjusted serum IGF-I [28]. Even using GH nadir on OGTT of <1 μg/l, 14 of 20 had an elevated IGF-I. In contrast, all of the patients who had GH >1 μg/l on OGTT or >2.5 μg/l basally had an elevated serum IGF-I. In addition those patients with normal serum IGF-I had suppression of GH to <0.3 μg/l on OGTT [28]. A further study also demonstrated that 50% of patients who suppress GH to <1 μg/l on OGTT have a persistently elevated IGF-I [29].

The degree of GH suppression defining remission, in the context of the modern assay, has recently been challenged. Freda et al. showed all patients with a normal IGF-I post-operatively fulfil current criteria of nadir GH on OGTT of <1 μg/l for remission of disease [29]. However, the normal population suppressed to <0.14 and 1 μg/l may be too crude a cut off for normality [29, 30]. They showed that out of the 76 patients with a normal IGF-I post-operatively, 50 of these had a nadir GH on OGTT (<0.14 μg/l) on IRMA and 26 had nadir GH above this and separate from the normal population. Those patients with less suppression on OGTT had higher serum GH despite similar IGF-I. There was no difference in quartiles for mean IGF-I in those who have nadir GH <0.14 μg/l and those >0.14 μg/l [30]. In these cases the IGF-I alone was unable to predict the nadir GH. It would appear from this data that IGF-I is the more reliable marker, however cannot be used exclusively to define remission or cure.

In fact there is discordance between GH and IGF-I in up to 27% of patients [31]. Ayuk et al. showed that after treatment with surgery and or radiotherapy, 10% of cases had a persistently elevated IGF-I, but a mean GH (on OGTT or 5 point day curve or random GH) <2 μg/l, while 19% had a normal serum IGF-I but a GH >2 μg/l [32]. A further study demonstrated 37.5% of patients with an elevated serum IGF-I despite mean GH <2.5 μg/l and 5% with normal IGF-I despite a persistently elevated GH (>2.5 μg/l) [33]. Similar discrepancies were seen with Kaltsas et al., with persistently elevated IGF-I in 13% with mean GH <2.5 μg/l and normal IGF-I with raised mean GH (>2.5 μg/l) in 18% of patients [34]. This discordance may be due to recovery of GH sensitivity, leading to fluctuating IGF-I until a new equilibrium is set between GH secretion and responsiveness. This subtle abnormality in GH or IGF-I secretion is relevant if it can predict those most likely to show biochemical or clinical relapse.

Disease relapse is uncommon if there is a GH nadir on OGTT of <1 μg/l, mean GH <2.5 μg/l or a normal age related serum IGF-I [2, 5, 35, 36] and the majority of patients remain in remission after long-term follow up. However despite apparent remission, there are occasional biochemical recurrences [30, 37]. One study showed a 2% biochemical recurrence, demonstrated by elevated IGF-I, amongst patients who had normal serum IGF-I immediately post-operatively [37]. Relapse is particularly seen when there is discordance between IGF-I and GH.

On follow-up of 19 patients who had normal serum IGF-I but a nadir GH of >0.14 μg/l on OGTT, five developed an elevated serum IGF-I over 2–6 years [30]. In all five patients the IGF-I had always been in the upper half of the age related reference range [30]. Those patients with a normal IGF-I post-operatively but GH >0.14 μg/l continued to have more glucose induced suppression of GH than those in the active acromegaly group (with an elevated IGF-I) suggesting an intermediary degree of GH dysregulation. Biochemical recurrence, following a normal post-operative IGF-I, has not been seen in all studies. Ronchi et al. showed patients with a post-OGTT GH nadir <1 μg/l, but >0.19 μg/l, continued to have a normal age-adjusted IGF-I over a median follow-up of 14 years with no clinical signs of acromegaly [37]. However these studies have all involved small numbers of patients. It is difficult to be certain whether the abnormal suppression of GH really represents GH hypersecretion or merely GH dysregulation. Even with a risk of biochemical recurrence, this low level of secretion is almost certainly associated with normal mortality and continued close follow up will identify those

with biochemical relapse before clinical signs of acromegaly are present.

Long-term monitoring of persisting disease

Persistent elevation in serum IGF-I post-surgical resection correlates well with hypersecretion of GH and nadir GH on OGTT [28, 38]. However in contrast to the diagnosis of acromegaly, there is considerable overlap in serum IGF-I with normality after primary treatment of disease, even in the presence of persisting GH excess [10, 16]. IGF-I is a valuable addition when assessing post-operative disease but, given these discrepancies, it is usually measured in combination with GH.

The aim of treatment should be to normalise IGF-I and mean GH, thus rectifying the increased mortality associated with acromegaly. The majority of studies examining IGF-I and GH targets in the context of mortality have used retrospective data and concentrated on GH measurements alone [32, 39–41]. Basal GH concentration <2.5 μg/l in treated acromegaly is associated with a normal lifespan. Excess mortality is confined to poorly controlled patients and possibly those who have received conventional radiotherapy [3, 32].

Two studies have demonstrated excess mortality associated with elevated serum IGF-I [40, 42] and that normalising IGF-I normalises mortality [39–41]. IGF-I may be the more sensitive marker for assessment of mortality risk in those patients who are not cured [42]. The importance of whether both IGF-I and GH have to be normalised is yet to be determined. There was also a non-significant trend towards increased mortality in both patients with high IGF-I and normal GH and normal IGF-I and high GH [32]. Moreover there may be a survival advantage if the IGF-I is below the middle of the normal range [39], but this has not been a universal finding. However, given that it is well-established that 30% of patients with proven severe GH deficiency have an IGF-I in the lower half of the reference range, lowering IGF-I too much may lead to pharmacological GH deficiency.

Cardiovascular disease is the major cause of decreased life expectancy observed in acromegaly [1, 39]. Normalisation of IGF-I with somatostatin analogs has been shown to improve cardiac performance with exercise, but it deteriorated in those patients who did not achieve a normal IGF-I [43, 44]. Disease specific risk factors for cardiovascular mortality include an increase in insulin resistance and glucose intolerance, increase in blood pressure, alteration in procoagulants and perhaps effects directly of GH on vasculature. Patients with high serum IGF-I are less insulin sensitive (irrelevant of their response of GH on OGTT). However, patients with normal IGF-I show no difference in insulin sensitivity compared to control subjects, independent of whether they had a GH that suppressed on OGTT to <0.14 μg/l or not [45]. Insulin sensitivity was highest in the first (lowest) quartile of IGF-I reference range and decreased as the IGF-I increased [45]. Signs and symptoms of acromegaly and blood pressure were no different within the age-related reference range for IGF-I [45]. IGF-I is more predictive of insulin sensitivity and clinical symptoms than serum GH when there is discordance at low levels of GH secretion. In those patients with discordance, additional information such as monitoring of cardiovascular function (including echocardiographic evaluation), pulmonary status, blood sugar control, sleep apnoea and rheumatological complications may be useful to guide treatment and control of IGF-I.

More information about the importance of IGF-I alone in morbidity and mortality will be established with use of the selective GHR antagonist Pegvisomant. Given there is no inhibition of GH secretion, GHR antagonists necessitate the use of IGF-I as the marker of disease status. Pegvisomant suppresses IGF-I to normal in more than 90% of patients after dose stabilisation [7]. However an element of caution should be applied as Pegvisomant is generally used in those patients who have failed other modalities of treatment and therefore may reflect a more severe end of the spectrum of acromegaly with longer disease duration and growth hormone burden, which may affect mortality data.

Discordance between GH and IGF-I make it impossible to rely on one or other alone as the sole marker of disease. Gender, age and prior radiotherapy alters the relationship between GH and IGF-I. In GH replacement higher concentrations of GH are needed to restore IGF-I in females than males [46]. Female patients on oestrogen require a higher GH dose to achieve the same serum IGF-I [46, 47]. Testosterone and DHEAS have been shown to increase IGF-I in the context of GH replacement [47–49].

Insulin-like growth factor-I is difficult to interpret in certain physiological states such as pregnancy and puberty. The huge IGF-I surge in puberty means a value outside the ‘normal’ age related reference range and does not necessarily signify acromegaly. IGF-I also shows an age dependent decrease of 10–16% per decade, even in acromegaly [50–52]. There may be GH dysregulation following cure [53], alteration in the normal IGF-I/GH relationship by somatostatin analogs [29] and disruption of somatostatin tone due to radiotherapy leading to a more rapid fall in GH than IGF-I [54].

Approximately 85% of serum IGF-I is produced in liver with the remainder from kidney, pituitary gland, gastrointestinal tract, muscle and cartilage [55]. Progressive liver disease leads to a reduction in IGF-I and

alcohol reduces IGF-I and bioavailability [56]. The same is true in starvation or serious intercurrent illness. Prolonged fasting can reduce IGF-I by as much as 50% [57], which may be by a resistance to GH action leading to a reduction in IGF-I production. Although serum IGF-I is maintained in renal disease with reduced glomerular filtration rate, the binding proteins are reduced, thus reducing bioavailable IGF-I [58]. Hypothyroidism and poorly controlled diabetes are also associated with suppression of serum IGF-I [59]. However in contrast to GHD, GH remains the predominant determinant of IGF-I levels in acromegaly and, therefore, measurement of IGF-I is still valid.

When IGF-I and GH do not correlate, other markers have been used to assess disease activity, such as IGFBP3 and ALS, which are regulated by GH. About 1% IGF-I is free, uncomplexed molecules, the remainder bound to IGFBP-3 in ternary complex with ALS [60]. Measurement of IGFBP3 and ALS adds little benefit over IGF-I alone [15, 61, 62]. In fact in active acromegaly IGFBP3 shows considerable variance and overlap between controls and patients [16]. Even free IGF-I, which is probably more closely related to disease activity, is not as sensitive [22, 24, 63]. A low-mean leptin in females is also seen in active acromegaly, but is not sensitive or specific. These extra assays may provide complementary information, but are not useful in routine diagnosis and monitoring.

The advances in methodology of IGF-I measurement is critical in consideration of the accuracy of previous trials and comparisons to GH assays. Most modern assays have a low-cross reactivity for IGF-II and binding proteins. The problems of the assays include a lack of age adjusted normal data, lack of standardisation, interference from binding proteins and lack of a pure international reference population. These problems are fixed with a robust IGF-I assay, which is particularly important now it is the sole marker of disease activity when patients are on the GHR antagonist, Pegvisomant.

So in summary, even if serum IGF-I is normal after treatment, an abnormal GH dynamic on OGTT represents persisting impaired neuroregulation of GH secretion and a higher risk of recurrence. The consensus statement in 2004 suggested a formal OGTT in those circumstances when there is discordance between IGF-I and GH [23]. If there is discordance then therapy may be indicated depending on clinical symptoms of active acromegaly and the presence of comorbidities, such as glucose intolerance, sleep apnoea, hypertension or cardiac dysfunction. To this end, additional measures such as insulin sensitivity, leptin and echocardiography may give valuable information as to risks to the tissues long-term.

Conclusion

Insulin-like growth factor-I is a sensitive disease related marker in acromegaly and corresponds to disease activity. It is the most useful marker for detection of acromegaly but should not be used as the sole indicator of severity of disease. Discordance between IGF-I and GH is seen more frequently in persistent acromegaly and both tests should be used together to achieve optimal control of disease. An IGF-I alone cannot be used to establish disease remission as we know that patients with normal IGF-I but an abnormal GH suppression to OGTT are at risk of relapse and knowledge of this may alter the follow-up strategy. Reliance on one marker of disease activity such as IGF-I is particularly precarious in certain disease states. The tightening up of the assays means that establishing absolute concentrations as well as standard deviation scores are essential to allow cross-study comparisons. From our knowledge with long-term mortality data, a mean GH <2.5 μg/l (5 mU/l) should be a target, but additionally new data emerging suggests in addition that we should also be aiming for a normal IGF-I. Given that mortality is less likely to be a major concern with normalisation of GH or IGF-I, our attention should turn to morbidity associated with mildly abnormal GH secretion. Further information is required to deduce which part of the age related reference range of IGF-I we should be aiming for. This becomes especially important in the use of Pegvisomant, where IGF-I becomes the sole biochemical marker of disease activity.

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