Remission criteria for the follow-up of patients with acromegaly

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Abstract

Objective: The aim was to evaluate the validity of current remission criteria in acromegaly, a random GH level of <2.5 µg/l, a glucose-suppressed GH level of <1 µg/l and a normal IGF-I level.

Design: In forty-one patients treated for acromegaly (23 males and 18 females, 20–69 years) and 94 healthy subjects (50 males and 44 females, 20–78 years), basal GH and IGF-I levels and nadir GH levels after 75 g oral glucose were evaluated in decade blocks; these were assayed by sensitive immunoradiometric assays.

Results: Basal GH levels varied widely from 0.022 to 10.4 in healthy subjects and were >2.5 µg/l in 19%. The mean post-glucose GH nadir was 0.067±0.009 µg/l (range 0.003–0.4 µg/l) and the upper limit of the GH nadir was 0.26 µg/l (means ± 2 S.D.) in healthy subjects. Thirty-five patients with acromegaly had high-for-age IGF-I levels in relation to our healthy subjects. In this group, 15 (42.9%) patients had basal GH levels of <2.5 µg/l, 14 (40%) patients had nadir GH levels of <1 µg/l, and three (8.6%) patients had GH suppression to <0.26 µg/l which was defined as normal GH suppression in our healthy subjects. Only six patients with acromegaly had normal-for-age IGF-I levels and all of these patients had basal GH levels of <2.5 µg/l and all but one had nadir GH levels of <0.26 µg/l.

Conclusions: A basal or random GH level of <2.5 µg/l is not a reliable criterion for remission in acromegaly and the currently accepted normal upper limit of 1 µg/l for post-glucose GH suppression is too high. Post-glucose nadir GH levels, measured with sensitive assays, can be <1.0 µg/l in 40% and basal GH levels can be <2.5 µg/l in 43% of the active acromegalic patients. IGF-I levels appeared to correlate better with a nadir GH cut-off of 0.26 µg/l rather than 1 µg/l in the determination of disease activity.

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Introduction

Acromegaly is a severe slow developing disease caused by growth hormone (GH) hypersecretion resulting almost invariably from a pituitary adenoma (1). GH-based criteria, random or basal GH values and glucose-suppressed GH levels, and insulin-like growth factor-I (IGF-I) levels are the most widely used biochemical parameters, in contrast to the mean integrated 24-h GH level which is neither practical nor cost-effective, for the diagnosis and follow-up of acromegalic patients (2–7). The accepted normal cut-off limits for basal and glucose-suppressed GH levels in both healthy subjects and in patients with acromegaly have changed over the years due to the improved sensitivity and specificity of GH assays as well as the availability of accurate IGF-I measurements (8–13). Currently, GH suppression after an oral glucose tolerance test (OGTT) to less than 1 µg/l with sensitive assays and IGF-I levels reduced to the age-adjusted normal range are recommended for the decision of remission, and basal GH values less than 2.5 µg/l have been suggested to be safe biochemical parameters for the control of acromegaly (13–16). However, some evidence in healthy subjects and acromegalic patients, using highly sensitive assays, has recently suggested that the cut-off value for the GH nadir after oral glucose administration is much lower than 1.0 µg/l (17–20). Thus, there is a need for the re-appraisal of normal GH suppression criteria and revision of the consensus statement. We therefore evaluated basal and glucose-suppressed GH levels in conjunction with IGF-I levels in 94 healthy subjects and 41 patients treated for acromegaly, using sensitive assays, in order to determine the basal and post-glucose nadir GH levels in normal subjects and whether they can be useful in evaluating the disease status of patients with acromegaly.

Subjects and methods

Normal subjects

The study included 94 healthy adult subjects (50 men and 44 women, mean age 42.6±1.5 years; range,
20–78 years) who were selected based on their health status. They had no endocrine, renal or hepatic disease, were taking no medications (including oral contraceptives) and were within 10% of ideal body weight. The mean body mass index (BMI) of the healthy subjects was 23.1±0.2 kg/m². Premenopausal women were studied in the early follicular phase of the menstrual cycle (days 1–5).

**Treated acromegalic patients**

From a cohort of 86 acromegalic patients, who have been followed-up in our outpatient clinics, we studied 41 patients (23 men and 18 women, mean age 46.7±2.1 years; range, 20–69 years) who had previously been submitted to different treatment modalities (surgery and/or radiotherapy) at various times before the study. Acromegalic patients who had any other endocrine disease, including diabetes mellitus, glucose intolerance and hypopituitarism, and active hepatic or renal disease were not included in the study. Five patients were treated with both surgery and radiotherapy, and two patients were treated only with radiotherapy. All operated patients were studied for at least 6 months after surgery, with a mean period from surgery to evaluation of 6.6 years (range, 6 months to 34 years). Seven patients had undergone radiotherapy from 1 to 9 years before testing. Fourteen patients had been treated with bromocriptine and/or octreotide in the past but neither GH-suppressive medication had been taken for at least 3 months in any of these subjects. The mean BMI of the patients was 30.4±0.8 kg/m².

**Study procedures**

After an overnight fast for 10 h, all subjects underwent an OGTT. They came to the dynamic test unit at 0730, had an i.v. cannula inserted into a forearm vein, and then remained seated from 0800 h until the end of the test. Blood samples for GH and glucose measurements were collected through the cannula at −30 and 0 min and then 30, 60, 90 and 120 min after drinking 75 g glucose in 300 ml lemon-flavoured water. After the separation of serum at each time point, glucose levels were measured and then the serum was frozen at −80°C in multiple aliquots. According to WHO criteria, subjects were considered to be normal with a basal serum glucose level less than 126 mg/dl and a 2-h post-glucose level less than 200 mg/dl. This protocol was approved by the University Hospital Ethics Committee and informed written consent was obtained from all subjects.

**Assays**

Plasma glucose concentrations were measured by the glucose oxidase method using an autoanalyzer. GH was measured all together and in duplicate by a highly sensitive immunoradiometric assay (IRMA) obtained from BIOCODE S.A. (Liege, Belgium). The standards contained 22 kDa recombinant human GH and were calibrated to the first WHO International Reference Preparation of human GH (code 88/624). The intra- and interassay coefficients of variation were 3.2 and 5.2% respectively. The assay sensitivity in our laboratory is 0.003 μg/l. Plasma IGF-I levels were determined all together and in duplicate by an active non-extraction IRMA obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX, USA). The standards contained recombinant human IGF-I and were calibrated to the WHO International Reference Reagent for IGF-I for immunoassay (code 87/518). The intra- and interassay coefficients of variation were 7 and 7.4% respectively. The minimum detectable amount of IGF-I was 2.06 ng/ml.

**Statistical analysis**

The baseline glucose level was defined as the average of plasma glucose levels at two time points before ingestion of glucose, and the peak glucose level was defined as the highest value at any time point after oral glucose administration. The random or basal GH level was defined as the average of GH levels at two time points before ingestion of glucose, and the nadir GH level was defined as the lowest value at any time point after oral glucose administration. The upper limit of the normal nadir GH was defined as the GH value 2 S.D. above the mean nadir of the healthy subjects. Since serum GH levels were not normally distributed, non-parametric tests, Wilcoxon–Mann–Whitney tests for comparisons and Spearman correlation tests were used where appropriate for statistical analysis. The relationship between IGF-I and age was compared by regression analysis. Statistical significance was assumed at P < 0.05. The data are expressed as the mean±S.E.

**Results**

**Healthy subjects**

There were no significant differences between male and female subjects in basal or post-glucose peak plasma glucose levels. GH levels in 16% of all serum samples were below the sensitivity of the assay and 83% of these were from the nadir GH serum samples. Basal GH values varied widely, from 0.022 to 10.4 μg/l, and the mean value was significantly higher in women than in men (2.02±0.34 vs 0.68±0.18 μg/l, P < 0.001). Basal GH levels were above 2.5 μg/l in 19% (18 of 94) of healthy subjects. In all healthy subjects, the mean decline from basal GH concentrations was 84±4%, and this decrease was significantly greater in women than in men (86±6% vs 82±5%;
Table 1 Basal GH and nadir GH levels with the upper limit of normal and basal IGF-I levels in each age and sex group of healthy subjects.

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Gender</th>
<th>Basal GH (µg/l)</th>
<th>Nadir GH (µg/l)</th>
<th>IGF-I (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(mean±s.e.)</td>
<td>(mean±s.e.)</td>
<td>(mean±s.e.)</td>
</tr>
<tr>
<td>20–29</td>
<td>F (11)</td>
<td>3.29±0.97*</td>
<td>0.17±0.04*</td>
<td>305±20</td>
</tr>
<tr>
<td></td>
<td>M (11)</td>
<td>1.13±0.45*</td>
<td>0.05±0.02*</td>
<td>325±24</td>
</tr>
<tr>
<td></td>
<td>T (22)</td>
<td>2.21±0.57</td>
<td>0.11±0.03</td>
<td>315±15</td>
</tr>
<tr>
<td>30–39</td>
<td>F (10)</td>
<td>1.75±0.65*</td>
<td>0.02±0.01</td>
<td>269±24</td>
</tr>
<tr>
<td></td>
<td>M (10)</td>
<td>0.07±0.02*</td>
<td>0.01±0.03</td>
<td>238±21</td>
</tr>
<tr>
<td></td>
<td>T (20)</td>
<td>0.91±0.33</td>
<td>0.02±0.01</td>
<td>256±16</td>
</tr>
<tr>
<td>40–49</td>
<td>F (9)</td>
<td>2.68±0.73*</td>
<td>0.07±0.03</td>
<td>207±17</td>
</tr>
<tr>
<td></td>
<td>M (10)</td>
<td>0.87±0.50*</td>
<td>0.07±0.03</td>
<td>189±21</td>
</tr>
<tr>
<td></td>
<td>T (19)</td>
<td>1.73±0.48</td>
<td>0.07±0.02</td>
<td>198±14</td>
</tr>
<tr>
<td>50–59</td>
<td>F (7)</td>
<td>0.88±0.34*</td>
<td>0.08±0.04</td>
<td>135±28</td>
</tr>
<tr>
<td></td>
<td>M (9)</td>
<td>0.74±0.63*</td>
<td>0.05±0.02</td>
<td>168±18</td>
</tr>
<tr>
<td></td>
<td>T (16)</td>
<td>0.80±0.37</td>
<td>0.08±0.02</td>
<td>153±16</td>
</tr>
<tr>
<td>60 and over</td>
<td>F (7)</td>
<td>0.68±0.25</td>
<td>0.08±0.03</td>
<td>128±24</td>
</tr>
<tr>
<td></td>
<td>M (10)</td>
<td>0.57±0.19</td>
<td>0.07±0.03</td>
<td>138±21</td>
</tr>
<tr>
<td></td>
<td>T (17)</td>
<td>0.61±0.15</td>
<td>0.08±0.02</td>
<td>135±16</td>
</tr>
</tbody>
</table>

* Gender difference is significant at P < 0.05 (Mann–Whitney).

F, female; M, male; T, total.
All patients with acromegaly were divided into two groups based on their IGF-I levels for age in relation to normal and high-for-age IGF-I levels. The first group contained the subjects with normal-for-age IGF-I levels and the second one contained subjects with high-for-age IGF-I levels. Table 4 shows basal GH and IGF-I levels and nadir GH levels after OGTT in these two groups of patients and in healthy subjects.

Table 2 Reference values of serum IGF-I concentrations in relation to age in healthy subjects.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number (male/female)</th>
<th>IGF-I (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 s.o. Mean +2 s.o.</td>
</tr>
<tr>
<td>20–29</td>
<td>22 (11/11)</td>
<td>171 315 459</td>
</tr>
<tr>
<td>30–39</td>
<td>20 (10/10)</td>
<td>112 254 396</td>
</tr>
<tr>
<td>40–49</td>
<td>19 (10/9)</td>
<td>78 198 318</td>
</tr>
<tr>
<td>50–59</td>
<td>16 (9/7)</td>
<td>27 153 279</td>
</tr>
<tr>
<td>60 and over</td>
<td>17 (10/7)</td>
<td>13 135 257</td>
</tr>
</tbody>
</table>

Table 3 Distribution of patients with treated acromegaly based on current and newly proposed GH criteria for remission as a function of IGF-I being normal or high.

<table>
<thead>
<tr>
<th>IGF-I (ng/ml)</th>
<th>Normal IGF-I</th>
<th>High IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal GH &lt;2.5 μg/l (n = 21)</td>
<td>6 28.6 15 71.4</td>
<td></td>
</tr>
<tr>
<td>Basal GH &gt;2.5 μg/l (n = 20)</td>
<td>0 0 20 100</td>
<td></td>
</tr>
<tr>
<td>Nadir GH &lt;1 μg/l (n = 20)</td>
<td>6 30 14 70</td>
<td></td>
</tr>
<tr>
<td>Nadir GH &gt;1 μg/l (n = 21)</td>
<td>0 0 21 100</td>
<td></td>
</tr>
<tr>
<td>Nadir GH &lt;0.26 μg/l (n = 8)</td>
<td>5 62.5 3 37.5</td>
<td></td>
</tr>
<tr>
<td>Nadir GH &gt;0.26 μg/l (n = 33)</td>
<td>1 3 32 97</td>
<td></td>
</tr>
</tbody>
</table>

Subjects with acromegaly with elevated IGF-I levels

Thirty-five subjects with acromegaly had normal basal GH levels but lower than the maximum nadir GH level, which was 0.4 μg/l, observed in our healthy subjects.

Subjects with acromegaly with normal IGF-I levels

Six patients operated for acromegaly showed normal-for-age IGF-I. All of these patients had basal GH levels less than 2.5 μg/l. The mean nadir GH in this group was significantly lower than that in the high IGF-I group (P < 0.001) and was significantly higher than that in healthy subjects (P < 0.01) (Table 3). The nadir GH range in this group was 0.02–0.3 μg/l, and the majority of subjects (five of six) had nadir GH values that fell within the normal range defined by our healthy subjects (i.e. <0.26 μg/l). One remaining patient, who had an IGF-I level of 30 ng/ml, had GH suppression to 0.3 μg/l, which was above 0.26 μg/l, but lower than the maximum nadir GH level, which was 0.4 μg/l, observed in our healthy subjects.

There was no gender difference in basal GH, nadir GH and IGF-I levels in acromegalic patients with high IGF-I levels. Basal GH levels correlated significantly with nadir GH levels in all acromegalic patients (r = 0.853, P < 0.001). This was the case for both the high IGF-I group (r = 0.791, P < 0.001) and the normal IGF-I group (r = 0.948, P < 0.01). There were no correlations of basal GH and nadir GH levels with age or BMI in acromegalic subjects. IGF-I levels...
correlated negatively with age \( (r = -0.333, \ P = 0.034) \) but not with BMI in acromegalic subjects.

Figure 1 illustrates nadir GH values in the different groups of subjects. In healthy subjects and in patients with normal IGF-I levels, neither basal nor nadir GH levels correlated with IGF-I levels. In patients with high IGF-I levels both basal and nadir GH levels correlated significantly with IGF-I levels \( (r = 0.397, \ P = 0.018 \) and \( r = 0.450, \ P = 0.007 \) respectively).

**Discussion**

Since even minimal biochemical activity of acromegaly can be associated with the full-blown severe clinical syndrome and, when inadequately treated, persistent excess GH secretion is associated with increased morbidity and mortality, aggressive control of GH and IGF-I levels as tightly as possible is necessary \( (20–27) \). Residual disease activity is most widely evaluated by biochemical tests; however, the definition of remission for acromegaly is controversial. The issue is whether we should attain normalized GH responses or safe levels. Some define remission as a random GH level less than 2.5 \( \mu g/l \) and an OGTT-derived GH level less than 2 \( \mu g/l \) measured by RIA and/or normalization of the IGF-I level, by using the data obtained from epidemiological studies \( (14, 16, 22–25) \). Most endocrinologists use the biochemical definition of remission in acromegaly as a glucose-suppressed GH level of <1 \( \mu g/l \) measured with a sensitive assay and a normal age-related IGF-I level \( (12, 13, 27) \). However, studies to date do not provide a robust definition of biochemical remission of the disease based on correlation with the long-term outcome \( (16) \).

In our opinion, basal GH level is not a reliable criterion for the disease activity of acromegaly, since GH secretion is pulsatile and varies over a wide range. In the present study, although a basal GH cut-off value of 2.5 \( \mu g/l \) seems to be a good predictor of high IGF-I level in acromegalic patients, 19% of normal subjects had basal GH level of ≥2.5 \( \mu g/l \) and could not be regarded as acromegalic. Furthermore, 43% of acromegalic patients with high IGF-I levels had basal GH values of <2.5 \( \mu g/l \) and could not be regarded as being in remission. It is obvious that discrepant GH and IGF-I values can be seen in acromegalic patients.

With OGTT, older criteria defined remission in acromegaly as a suppression of GH to less than 2 \( \mu g/l \) as measured by assays with limited sensitivity \( (8–10) \). With the development of more sensitive GH assays, it has been suggested that GH should be suppressed to less than 1 \( \mu g/l \) after oral glucose for the decision of remission \( (13) \). In the present study, the highest glucose-suppressed GH level measured by a sensitive IRMA was 0.4 \( \mu g/l \) and the calculated nadir GH cut-off value was 0.26 \( \mu g/l \) in all healthy subjects. In the patients with clinically and radiologically active acromegaly, GH was suppressed as low as 0.15 \( \mu g/l \) in three patients overlapping with the normal range defined in our healthy subjects and, in 40% \( (14 \text{ of } 35) \) of these patients, nadir GH levels were less than 1 \( \mu g/l \). In the inactive group, all patients but one had a normal GH suppression and, in the patient with an abnormal suppression, the GH nadir was 0.3 \( \mu g/l \), i.e. over the defined cut-off value (0.26 \( \mu g/l \)) but lower than the maximum value (0.4 \( \mu g/l \)) obtained in our healthy subjects. If we adopt the GH nadir limit of 1 \( \mu g/l \), the currently accepted criterion, 48.8\% of all treated patients \( (20 \text{ of } 41) \) and 40\% of the treated acromegalic patients with high IGF-I levels \( (14 \text{ of } 35) \) would be considered to be in remission. This means that a cut-off of 1 \( \mu g/l \) will fail to identify 40\% of patients with active disease. Using a sensitive GH assay, the cut-off of the GH nadir less than 0.26 \( \mu g/l \) is more closely related to normal age-appropriate IGF-I levels and disease activity in treated acromegalic patients. Our findings show that the post-glucose GH nadir is lower than previously believed in healthy subjects and suggest a lower cut-off value.

Recently, with the availability of highly sensitive assays for GH and accurate IGF-I measurements, new cut-off values have also been suggested by others \( (17–20) \). Previously Hattori et al. \( (17) \) reported a median nadir GH level after oral glucose ingestion as 0.15 \( \mu g/l \) \( (0.047–1.3 \mu g/l) \) in healthy adults, using an enzymeimmunoassy \( (17) \). Later Chapman et al. \( (18) \) reported normal GH response to glucose, using an ultrasensitive chemiluminescence assay, as suppression below 0.5 \( \mu g/l \) \( (\text{means} + 2 \text{ s.d.)} \) in healthy individuals. Subsequently, Freda et al. \( (19) \) reported an upper
limit of nadir GH as 0.14 μg/l (means + 2 s.d.), using a sensitive IRMA, in healthy adults. They also found that, in 50% of the active acromegalic patients with high IGF-I levels, GH was suppressed to less than 1 μg/l, between 0.33 and 1 μg/l. As recently reported by Dimaraki et al. (20) the difficulty is not only in the post-treatment disease activity decision but also in the diagnosis of acromegalics with biochemically mild disease. In their study, they found GH suppression to less than 1 μg/l in 50% of newly diagnosed acromegalic patients who had elevated IGF-I levels. When they used their upper normal limit of 0.21 μg/l they found abnormal GH suppression in all but one patient.

Our findings also suggest a sex difference in the suppression of GH after OGTT in healthy subjects. We found higher basal GH levels and a greater fall in GH from baseline in women than in men. However, when we evaluated GH suppression in different age groups this sex difference was only observed in the third decade. Therefore we suggest that there is no need for separate OGTT criteria for remission in female and male acromegalic patients. Although Chapman et al. (18) previously reported a sex difference, Freda et al. (19, 28) could not find a significant gender difference in the nadir GH levels of healthy subjects.

These earlier results, taken together with ours, suggest that a new cut-off value should be defined. But what should this value be? Very recently, Trainer et al. (19, 28) could not find a significant gender difference in the nadir GH levels of healthy subjects.

In conclusion, our data indicated that currently used criteria for remission including basal GH levels of less than 2.5 μg/l and a normal upper limit of 1 μg/l for GH after oral glucose do not discriminate between active and inactive patients with acromegaly. If the goal of the treatment is the normalization of GH and/or IGF-I levels, one should decide what the normal is. It seems that the accepted GH suppression levels after oral glucose are much higher than they should be, but this must be confirmed. On the other hand, it should be kept in mind that any desire to adopt aggressive GH and IGF-I criteria for remission may increase the risk of associated hypopituitarism and mortality per se. It seems that new epidemiologic mortality studies, using new criteria proposed by the present and previous studies, are needed for defining the safe cut-off values.

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References


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