New developments in the management of acromegaly. Should we achieve absolute biochemical cure?

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Introduction

Acromegaly is an uncommon condition with a prevalence in European populations of about 40 per million, and an incidence of four to six new cases per million population per year. The vast majority (99%) of cases of acromegaly are due to a pituitary somatotrophinoma, the occasional rare case being caused by ectopic production of growth hormone–releasing hormone by bronchial carcinoid, pancreatic neuroendocrine, or hypothalamic tumours, giving rise to somatotroph hyperplasia. The onset of the condition is most often very insidious, especially so in the older patient; photographs may reveal evidence of acral expansion 5–10 years before biochemical confirmation of the diagnosis. This long exposure of tissues to excessive secretion of growth hormone (GH) before treatment may be significant with respect to the long-term mortality outcome. Furthermore, it may also explain why about 60–70% of somatotrophinomas are macroadenomas (>1 cm in diameter) at diagnosis, and only a minority (30–40%) are microadenomas.

The presentation of acromegaly is very variable, and a fair proportion of cases are diagnosed coincidentally on the basis of the characteristic appearance of a patient presenting with unrelated problems. However, the consequences of GH excess such as enlargement of the hands, feet, jaw and face, sweating, greasy skin and carpal tunnel syndrome are the most common forms of presentation, although the metabolic consequences of diabetes mellitus, hypertension and renal calculus formation may provide the initial clues to the diagnosis. Other patients may present with symptoms directly attributable to an expanded pituitary gland, such as headache, visual impairment or hypopituitarism.

This varied presentation and rarity of the condition often means that the disease goes unrecognised by the non-specialist physician. Accordingly, the specialist endocrinologist frequently encounters the patient when complications have developed. Moreover, the endocrinologist is committed to the long-term care of patients with acromegaly because of the implications of the complications and GH excess for long-term morbidity and mortality. This is not a condition that should be managed by generalists.

Morbidity and mortality in acromegaly

Over the past 25 years, several retrospective studies have reported that there is excess mortality in patients with acromegaly of between two and three times that of an age- and sex-matched cohort from the respective population (Table 1). Treatment modalities in these reports have varied and involved all the standard methods, including medical treatment with bromocriptine, which was introduced in the early 1970s. Because treatment is usually required for relief of symptoms, decompression of the sella or management of complications, there are no data available from an unselected large series of untreated patients with acromegaly that might be compared directly with a treated group, to determine whether treatment itself influences mortality. However, Alexander et al. (1980) commented in the discussion of their data that the overall mortality rate in their treated patients was 22%, compared with 40% in the untreated group. Because mortality was greater than expected in these retrospective surveys, the assumption was that treatment was not very effective in modifying the long-term outcome. However, the findings of more recent studies (Bates et al. 1993, Rajasoorya et al. 1994) suggested that this is not the case, and that treatment is beneficial. There appears generally to be no sex difference, in that males and females each have increased mortality, but an exception was the Middlesex Hospital (London) cohort (Nabarro 1987), among whom men younger than 55 years, and women, had significantly increased observed:expected mortality rates, although the whole cohort did not (Table 1). Not only is the death rate increased in patients with acromegaly, but the median/mean age of death is reduced, to around 60 years (Table 1). Although the age of death of the non-acromegalic population over the relevant time period was not recorded in these reports, it is likely that this does represent at least a 5–10 year reduction in life expectancy.

When the causes of excess deaths among patients with acromegaly are examined, they generally reflect those of the general population (Table 2). If the numbers of deaths are sufficient for further analysis, it is clear that excess mortality from vascular disease is a major contributor. For example, in the series from New Zealand the
observed:expected mortality ratios for cardiovascular (3:1) and cerebrovascular disease (3·3:1) were highly significant ($P<0·001$), although no confidence intervals were given (Rajasoorya et al. 1994). In a recent retrospective UK study of more than 1300 patients, excess mortality was evident from cardiovascular disease (2·5-fold), cerebrovascular disease (2·6-fold), respiratory disease (4·8-fold) and malignant disease (1·27-fold) (Orme et al. 1996).

The causes of death from malignant disease deserve some discussion because of the suggested association between colonic polyps and acromegaly, and the propensity of polyps to progress to malignancy (Klein et al. 1982, Ituarte et al. 1984, Brunner et al. 1990, Ezzat & Melmed 1991, Ron et al. 1991, Vasen et al. 1994). A preliminary report of a very large (>1300 patients) retrospective survey from the UK showed that the overall colon cancer incidence was 1·77 times that of the normal population and that the mortality rate from this cause was 3·03 times greater than expected (Orme et al. 1996). This is acquiring more relevance, as newer and more precise screening methods for the detection of colon cancer are being adopted. Patients with acromegaly should be entered automatically into any such screening programmes. However, the majority of studies did not directly determine the prevalence of colonic neoplasms compared with that in a control population. The colonoscopic study by Vasen et al. (1994) was the first to show an increased incidence of polyps in an acromegalic cohort, compared with an age- and sex-matched non-acromegalic group having abdominal complaints believed to be due to irritable bowel syndrome or constipation and who underwent colonoscopy to exclude serious pathology. Eleven of 49 patients with acromegaly (22%) had histologically proven colonic adenomas, compared with five of 57 (8·8%) in the control population. Low-graded dysplasia was found in nine of the 11 adenomas in the patients with acromegaly and three of the five controls. As this histological feature is believed to be a precursor to invasive cancer, this study clearly indicates that patients with acromegaly are at increased risk. In this study, the numbers of patients with acromegaly and colonic adenomas were too small to permit the determination of a relationship between concentrations of GH or insulin-like growth factor (IGF)-I, although the authors stated that 54% of patients with adenomas had ‘active disease’, compared with 26% of patients without adenomas (N.S.). A larger prospective colonoscopic study is required to answer these questions.

### Predictors of increased mortality in acromegaly

The retrospective mortality surveys have considered clinical features that may be present at diagnosis or develop subsequently, and which may relate to long-term outcome. As might be predicted from their known associations with vascular mortality, the presence or development of either diabetes or hypertension was significantly more frequent in those who had died compared with those

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#### Table 1 Mortality in acromegaly. Values for age at death are means or †medians

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of patients</th>
<th>Observed:expected death ratio</th>
<th>$P$</th>
<th>Age at death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al. (1970)</td>
<td>194</td>
<td>1·9</td>
<td>&lt;0·002</td>
<td>Not given</td>
</tr>
<tr>
<td>Alexander et al. (1980)</td>
<td>164</td>
<td>3·3</td>
<td>&lt;0·001</td>
<td>57</td>
</tr>
<tr>
<td>Nabarro et al. (1987)</td>
<td>256 (overall)</td>
<td>1·3</td>
<td>N.S.</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>M &lt;55 years</td>
<td>1·9</td>
<td>&lt;0·05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F all ages</td>
<td>1·7</td>
<td>&lt;0·05</td>
<td></td>
</tr>
<tr>
<td>Bengtsson et al. (1988)</td>
<td>166</td>
<td>3·2</td>
<td>&lt;0·01</td>
<td>64</td>
</tr>
<tr>
<td>Bates et al. (1993)</td>
<td>79</td>
<td>2·7</td>
<td>&lt;0·001</td>
<td>63†</td>
</tr>
<tr>
<td>Rajasoorya et al. (1994)</td>
<td>151</td>
<td>Not reported</td>
<td></td>
<td>57†</td>
</tr>
</tbody>
</table>

M, males; F, females.

#### Table 2 Causes of death in patients with acromegaly. Values are given as proportion of all deaths (%)
still alive, even allowing for the generally older age of those who had died (Wright et al. 1970, Rajasoorya et al. 1994). Not all studies have shown this (Bengtsson et al. 1988, Bates et al. 1993), although the study by Bates et al. (1993) was too small to permit such an analysis.

Although it is difficult to quantitate accurately, the relationship between estimated duration of acromegaly before diagnosis and influence on mortality has been examined in some (Wright et al. 1970, Rajasoorya et al. 1994) although not all studies (Alexander et al. 1980, Nabarro 1987, Bengtsson et al. 1988, Bates et al. 1993), with conflicting results. Wright et al. (1970) could find no difference in estimated duration of acromegaly before diagnosis between those still alive and those who had died, while Rajasoorya et al. (1994) found that duration of disease before diagnosis was significantly longer in those who had died than in those still alive and with minor symptoms (10 and 5 years, respectively). However, the total duration of acromegaly (Rajasoorya et al. 1994) or duration of disease since diagnosis did not influence long-term outcome. Thus early diagnosis and effective treatment are essential if an impact is to be made on long-term mortality outcomes.

Because of the retrospective and rather imprecise nature of some of these data, and the small total numbers of patients and thus few deaths, a large prospective multi-centre study with accurate ascertainment of time of first symptoms is required before meaningful conclusions can be drawn about some of the aforementioned relationships and their relative contribution to mortality. Such a study has been initiated in the UK.

**Relationship of GH and IGF-I levels to long-term outcome in acromegaly**

Accurate determination of circulating concentrations of GH has been the widespread practice since the mid to late 1960s; measurement of IGF-I was introduced much later (1980s). Thus the earlier surveys of mortality (Wright et al. 1970, Bengtsson et al. 1988) did not examine the relationship between serum GH or IGF-I and mortality or morbidity. However, many previous studies have examined the relationship between serum concentrations of GH and improvement in the clinical features of acromegaly. Only two studies have attempted to relate serum GH levels, both at diagnosis and during follow-up, and mortality/long-term morbidity outcomes (Bates et al. 1993, Rajasoorya et al. 1994). Although these must be regarded as preliminary, in that small numbers of patients were involved, the conclusions, if replicated, will provide an important guide to the desirable biochemical outcome for modification of long-term outcomes. It is therefore relevant to discuss these two reports in some detail.

The study by Bates et al. (1993) was a retrospective analysis of the case records of 79 patients studied in a single centre between 1967 and 1991, with a median duration of follow-up of 10 years. Twenty-eight patients died during the follow-up period (35% of the cohort). Unlike those in most reported series, the majority of these patients (50 of the 79) were treated by radiotherapy. GH status was assessed annually by a serum GH day profile (four or five measurements between 0800 and 1800) and the average value taken. The serum concentrations of GH before or after treatment, whether expressed as mean average values over the duration of follow-up or the lowest average values recorded during follow-up (usually the latest assessment), were significantly higher in those who had died compared with those that were still alive (Fig. 1).

We then considered whether mortality could be related to the level of GH achieved after treatment, by taking arbitrarily defined ‘cut-off’ GH values. We chose 10 mU/l (5 ng/ml), because this had previously been used in several surgical series to define ‘cure’. However, more recent studies (Lindholm et al. 1987) have shown resolution of clinical features and normal IGF-I levels in a greater proportion of treated patients with acromegaly when a GH value of <5 mU/l (2·5 ng/ml) was chosen. The analysis shown in Table 3 clearly suggests that the mortality in those who achieve a lowest GH of <5 mU/l is not significantly different from that in the normal population, whilst with GH <10 mU/l it remains double that of the normal population. However, it must be emphasised that the number of deaths is small, and moreover the observed:expected ratio of 1·42 for the <5 mU/l cohort still represents a 40% increased mortality. Much larger numbers are required to allow for further stratification with a group having lowest mean GH levels <2 mU/l, and to confirm these preliminary results. Although we could not relate serum IGF-I values to mortality because these were not measured in all patients who died, our data showed that if the GH value was <5 mU/l, nine of 18 patients had a normal IGF-I, but for GH values between 5 and 10 mU/l, only two of 13 had normal IGF-I values, confirming the results of Lindholm et al. (1987). Rajasoorya et al. (1994) studied 151 New Zealand patients with acromegaly over the period 1964–1989, with a median duration of follow-up of 11 years. The primary treatment modality was surgical in 50% and irradiation in 50% (equal proportions of yttrium–90 implants and external radiotherapy). At last follow-up, 32 patients (21%) had died, 67 had major complications (visual failure, diabetes mellitus requiring treatment or disabling arthritis requiring regular analgesia), and 47 had minor symptoms (controlled hypertension, headache, arthritis not requiring analgesia, sweating or carpal tunnel syndrome) or none at all. Thus for purposes of comparison there were three subgroups: dead, major complications or minor complications. While the merits of the aforementioned stratification may be argued, the results for long-term outcome were quite dramatic. Those who had died or who had major
complications were older and had a longer estimated interval from onset of symptoms to diagnosis. When it came to comparison of GH concentrations between these cohorts, those who had died had a GH concentration at diagnosis (191±58 mU/l) that was double that of those with minor complications (92±13 mU/l). Even more strikingly, the last known GH was 66±35 mU/l in those who had died, compared with 10±2 mU/l and 8±1 mU/l for the major and minor complications cohorts respectively. These data are consistent with those of Bates et al. (1993) (Fig. 1). Of particular interest was the product of the GH at diagnosis and the interval from onset of symptoms to diagnosis, a surrogate estimate for the extent of exposure to GH before treatment. This product was 2213±781 mU/l in those who had died, 904±304 mU/l in those with major complications, and 589±131 mU/l in those with minor complications. By Cox’s multivariate analysis, the strongest predictor of clinical outcome, including mortality, was the last known GH value. Although this New Zealand study did not stratify observed:expected death ratios according to lowest GH level achieved, it clearly supports our own conclusion that the lower the serum GH level after treatment, the lower the mortality.

However, a further analysis of the factors influencing long-term outcome after surgical treatment of acromegaly in New Zealand (Wrightson et al. 1994) has revealed that survival for 10 years after treatment is significantly better if last serum GH is <10 mU/l than if it is >10 mU/l. This conclusion applied if age at treatment was <40 years or between 40 and 55 years. Moreover, although the numbers are much smaller, a similar trend applied for survival at 15 and 20 years. This study also showed that, if the last known GH concentration was between 0 and 4 mU/l, the IGF-I value was normal in 32 of 34 patients, whereas if the GH concentration was >10 mU/l, all patients had increased IGF-I, confirming the importance of a GH value of <5 mU/l to achieve a normal IGF-I value. A further aspect of this study was that the chances of a ‘good’ clinical status at last follow-up were improved if last known GH values were <4 mU/l rather than >10 mU/l (Wrightson et al. 1994). Moreover, a patient’s chance of being dead

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**Figure 1** Growth hormone (GH) concentrations in patients with acromegaly who had died during follow-up and in those still alive. Follow-up values are presented as both the mean of all the average (n=5/time) GH concentrations obtained during the course of follow-up (middle pair), and the lowest average value achieved (right-hand pair). At all time points, GH concentrations were significantly (P<0.05) lower in those still alive (statistical comparison by Mann–Whitney U test).

**Table 3** Mortality in acromegaly according to concentrations of GH achieved after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Observed deaths (O)</th>
<th>Expected deaths (E)</th>
<th>Ratio O:E (95% CI)</th>
<th>p (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest* of GH day series &lt;10 mU/l</td>
<td>48</td>
<td>9</td>
<td>4.48</td>
<td>2.01 (0.9–3.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lowest of GH day series &lt;5 mU/l</td>
<td>31</td>
<td>5</td>
<td>3.52</td>
<td>1.42 (0.46–3.31)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

CI, confidence interval.
*Average of five samples taken between 0800 and 1800.
being greater in women (van den Berg et al. 1996). Moreover, the amplitude of GH secretory episodes was both age- and sex-dependent, decreasing with age and in adults, and that for the remainder of the time GH was secreted in a few short-lived bursts in any 24-h period in adults, and that for the remainder of the time GH was undetectable (<1 mU/l) using conventional RIA or more sensitive immunofluorimetric assays (van den Berg et al. 1996). Moreover, the amplitude of GH secretory episodes was both age- and sex-dependent, decreasing with age and being greater in women (van den Berg et al. 1996). GH pulse frequency is increased in acromegaly, and about 50% of GH is secreted in a non-pulsatile fashion, compared with normal individuals, in whom 95% of GH is secreted in pulses (Hartman et al. 1990, Ho et al. 1994, van den Berg et al. 1994). The persistence of non-pulsatile GH secretion may contribute to high IGF-I levels. In addition to the abnormal GH pulse pattern in acromegaly, the paradoxical GH response to glucose and GH release after administration of thyrotrophin-releasing hormone (TRH) (and sometimes gonadotrophin-releasing hormone) are well documented.

An ‘absolute’ biochemical cure would therefore consist of: (1) restoration of ‘normal’ secretory dynamics including undetectable interpulse GH values; (2) abolition of the paradoxical responses; (3) return of basal GH and IGF-I values to age- and sex-related normal ranges. The pertinent issues are: (a) how often are these stringent criteria achieved after treatment (usually surgical), and (b) is it necessary to meet these targets in order to achieve clinical remission and elimination of the increased long-term mortality in acromegaly?

Two studies have examined GH secretory dynamics after surgery. The 14 patients reported by van den Berg et al. (1994) were studied 9 or 10 days after successful transsphenoidal adenectomy as defined by normalisation of GH responses to oral glucose, basal GH levels, and IGF-I values. These were compared with normal sex-matched controls, rather than being themselves studied both before and after surgery, which would have been the most appropriate study design (Ho et al. 1994). Nevertheless, this study (van den Berg et al. 1994) showed that the increased GH pulse frequency, amount of GH secreted per pulse, and nadir concentrations of GH returned to control values after successful surgery. Moreover, as has been shown previously in several studies, paradoxical responses to TRH were abolished. In contrast, Ho et al. (1994) failed to show any change in GH pulse frequency after successful surgery, although mean GH, interpulse GH values, and GH pulse amplitudes all had normalised when studied 2 months after surgery, as had the paradoxical GH responses to glucose and TRH, and the IGF-I levels. It is of interest that four of 13 patients apparently cured at 2 months developed persistently increased IGF-I levels 5–26 months after surgery, despite basal GH values less than 10 mU/l and normal dynamic responses to glucose and TRH. It is not clear if these four patients had GH secretory dynamics that differed from those of patients in whom the IGF-I levels remained normal for this period of time. One interpretation of these results is that a persistently greater frequency of GH pulses may be associated with biochemical relapse in a proportion of patients. Further follow-up in the others is required to determine if there are any more ‘biochemical’ relapses.

While dynamic testing may provide evidence of restoration of physiological patterns of secretion after surgical adenectomy, the question remains whether this really offers any practical advantage over basal GH and IGF-I values in the routine management of patients with acromegaly. The answer is ‘probably not’, especially as the definition of biochemical cure in these dynamic studies was based on the latter measurements anyway. It would probably have been more informative to perform the GH secretory dynamic studies in all patients after surgery, irrespective of clinical or biochemical cure, and then relate these to the basal GH and IGF-I values.

Thus, while it may not be necessary to define a strict physiological biochemical cure, it is necessary to define target basal GH and IGF-I values that will reliably achieve clinical remission and significantly reduce or eliminate long-term morbidity and mortality. Those values of basal GH and IGF-I would not then be defined as a ‘cure’, but rather as ‘safe’ values, which is a more realistic concept in clinical practice.

What, then are safe values? On the basis of findings outlined in the preceding section, currently available evidence suggests that basal concentrations of GH should be at least <5 mU/l (2.5 ng/ml), accompanied by normal age-related IGF-I levels. Using these as standard criteria, one can then evaluate the outcomes of surgical treatment. A very real difficulty associated with previous reports of surgical outcome has been the variable and non-standard criteria used for definition of cure, making it impossible to compare series. The advantage of these simple criteria of safe values is that they will enable a valid audit of outcomes between surgical centres, and this is currently under way in the UK.

How well does transsphenoidal surgery perform in achieving safe target levels of GH?

The pre-1990 surgical series describing the treatment of acromegaly defined the outcome ‘cure’ as basal GH levels decreased from 0·13 to 0·07 in a logistic regression model at GH values of 10 mU/l and <4 mU/l respectively. This latter evidence is consistent with our own data (Bates et al. 1993) on mortality and last known GH value.
Despite the somewhat disappointing results of transsphenoidal surgery with a target GH of 5 μU/l, this modality remains the initial treatment of choice for several reasons: (1) it is the most rapidly effective treatment for alleviating symptoms and decreasing serum GH; (2) it is a safe and cost-effective procedure; (3) even if the tumour cannot be removed in its entirety, it is likely that a prior debulking operation will render adjuvant treatment more effective at achieving the target GH values.

### References


Hartman ML, Veldhuis JD, Vanc M, Faria ACS, Furlanetto RW & Thorner MO 1990 Somatotropin pulse frequency basal concentrations are increased in acromegaly and are reduced by successful therapy. *Journal of Clinical Endocrinology and Metabolism* 79 1375–1384.


Dr P Belchetz (Leeds, UK):

I would like to refer to some of our work which was presented in abstract form in San Diego. We are currently refining the analysis, but let me just say that the total cohort came from about 15 UK centres. It involved nearly 1400 patients and about 17 000 patient years — a very large series. Overall, the data very strongly support the findings that Dr Clayton has reported, but with the larger numbers and, I think, with greater statistical certainly. We were also able to look at different causes of mortality, and found a dose-related reduction in mortality as the dose level fell. The cut-off figures were 20, 10 and 5 mU/l (10, 5 and 2.5 µg/l) for cardiovascular and for respiratory disease; and there was a statistically significant reduction of death from colon cancer as one brought the levels down.

In none of the separate conditions, or the overall mortality, did we find any relationship with the pre-diagnosis GH level, which is in contradiction to the findings which Dr Clayton reported.

Dr H-J Quabbe (Berlin, Germany):

May I just add that I think, when we use several so-called basal GH samples from 24-h studies, it is preferable to use closely-spaced samples. I think also, taking into consideration the dynamics of GH secretion as determined in the 30-min sampling, that it would probably be much more useful to have five, six or seven samples spaced every 15 or 30 min, rather than larger intervals.

Dr R N Clayton (Stoke-on-Trent, UK):

What we really need is a much more integrated assessment of GH secretion throughout the day. Perhaps urinary GH measurement would fulfil this role?

Dr R Fahlbusch (Erlangen, Germany):

I agree that a safe GH level is more important than normalization or cure, but should a safe GH level also include a prognostic value? That is to say, how sure are you that no recurrences will occur with your recommended value? How frequently do you have to control your patients? And do you stop controlling GH levels when you reach the recommended value?

Clayton:

We have no data of our own on that. The Newcastle data from Pat Kendall-Taylor (Osman et al. 1994 Quarterly Journal of Medicine 87 617–623) show that when GH levels fell to below 5 mU/l (2.5 µg/l), and GH levels were suppressed to less than 2 mU/l (1 µg/l) after OGTT, very few, if any, recurrences occurred over a mean of seven years’ follow-up after surgery, with annual assessments of glucose tolerance and random GH levels.
Dr A Barkan (Ann Arbor, USA):

I agree entirely with Dr Quabbe on the value of GH measurements. We should realise that the methodology has changed; we used to measure GH by radioimmunoassay, that allowed us to measure reliably GH levels down to about 1.5–2 µg/l. Now, with the chemiluminescent assay, one can reliably measure 10 ng/l. And the integrated normal GH ranges from frequent blood samples in perfectly normal young men of 25–35 years old vary between 0.4 and 10 µg/l. This is an enormous range, and I would be reluctant to assign a single ‘normal’ GH value as a gold standard. On the other hand, I would view IGF-I measurement as equivalent to measuring HbA1c in diabetes, or urinary free cortisol in Cushing’s syndrome.

Clayton:

I agree with that, and that we should also be normalising IGF-I. The point is that with most of the studies reported so far that used the methods we are familiar with, a mean GH level of 5 or 6 mU/l (2.5–3.0 µg/l) has been associated with a normal IGF-I level in 70–80% of cases. But that is not perfect; it suggests to me that the way we interpret the data is also flawed, and that we need to be more sophisticated about that.