CLINICAL STUDY

A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly

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Abstract

Objective: Formal studies of acromegaly have found increased mortality associated with the disorder, although reduction of serum levels of GH and IGF-I by treatment appears to improve survival. A meta-analysis of mortality studies in acromegaly has thus been performed to assess the effect of lowering serum GH and IGF-I on survival.

Design and methods: Medline was searched for studies under 'acromegaly', 'mortality' and 'cause of death' (1965–2008), and abstracts of recent meetings of the US Endocrine Society were hand searched. Studies were restricted to those presenting mortality data according to serum GH and IGF-I at last follow-up, and with mortality expressed as a standardized mortality ratio (SMR).

Results: Patients with random serum GH < 2.5 µg/l following treatment, mostly measured by standard RIA, had mortality close to expected levels (SMR 1.1, 95% confidence interval (CI) 0.9–1.4) compared with an SMR of 1.9 (95% CI 1.5–2.4) for those with final GH > 2.5 µg/l. Similarly, a normal serum IGF-I for age and sex at last follow-up after treatment was associated with an SMR of 1.1 (95% CI 0.9–1.4) compared with an SMR of 2.5 (95% CI 1.6–4.0) for those with continued IGF-I elevation. There was a significant trend for reduced mortality in series reporting frequent use of somatostatin analogues and in studies reporting high (> 70%) rates of biochemical remission after treatment.

Conclusions: Clinicians treating acromegalic patients should aim for random serum GH < 2.5 µg/l measured by RIA (probably < 1 µg/l measured by modern sensitive immunoassay) and normal serum IGF-I values, to restore the elevated mortality of the condition to normal levels.

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Introduction

Acromegaly is a state of chronic growth hormone (GH) excess associated with a range of complications including soft tissue overgrowth, hypertension, diabetes, obstructive sleep apnoea, arthropathy and impaired cardiac function. Estimates of mortality from older studies indicate that despite traditional forms of treatment, including pituitary surgery and radiotherapy, death rates in the disorder were significantly elevated compared with the general population (1). This increased mortality has been attributed mainly to increased rates of death from cardiovascular disease, stroke and a possible increase in death rates from cancer. However, more recent reports have found a lesser impact of acromegaly on mortality, with the 95% confidence intervals (CI) from standardized mortality ratios (SMRs) often overlapping unity. It seems likely that these improved mortality estimates reflect better techniques for treating the disorder and its complications. A recent meta-analysis of mortality studies by Dekkers and colleagues has confirmed that more recent reports have found lower mortality estimates compared

with earlier findings (2). The purpose of the present study was to confirm and extend the findings of Dekkers *et al.* by concentrating on the relationship between biochemical measurements and mortality during follow-up after treatment.

Methods

Mortality from acromegaly

In January 2008, Medline was searched for all studies published between 1965 and 2008 using the terms 'acromegaly', 'mortality' and 'cause of death'. We also hand-searched abstracts of recent meetings of the US Endocrine Society, and the reference lists of retrieved studies and published reviews.

To be eligible for inclusion, the study must have presented mortality data for the group with acromegaly and the expected mortality for the population in the form of an SMR. A total of 325 papers and 20 abstracts were found related to mortality in acromegaly, and of these, 18 provided estimates of SMR (3–20). Two

reports (21, 22) were subsequently updated either in a later study (12) or in an abstract report (9), thus only results from these latter publications were included in the analyses. Similarly, Ayuk and colleagues reported their findings concerning mortality of acromegaly in 2004 (6), but also provided additional information concerning mortality in abstract form (23). Data were extracted independently by two authors and any disagreements were resolved by consensus. The 95% CI for the SMR was recalculated wherever possible using the mid-exact P method (Openepi, www.openepi.com). Where insufficient data were reported to permit this calculation, the CIs reported in the paper were used.

Mortality according to remission rates and serum levels of GH and insulin-like growth factor-I (IGF-I)

Eligible studies were reviewed for reporting of SMR estimates according to remission rates and measured levels of GH or IGF-I following treatment. Twelve studies (3, 5–8, 10–13, 17, 18, 20) reported information on biochemical remission of acromegaly. We grouped these studies into higher remission (>70%) and lower remission (<70%) groups using the individual authors' definition of remission. The criteria for remission used by the study authors in the different reports were various groupings of post-treatment serum GH levels with or without IGF-I measurements. The division above or below biochemical remission rates of 70% was chosen arbitrarily based on analysis of reports of biochemical remission following pituitary surgery for acromegaly, where an average remission rate of 53% was noted, but with a minority describing remission in more than 70% of cases (1). Five older studies (4, 9, 14, 15, 19, 22) did not provide biochemical data for remission but are very likely to have had relatively low rates of biochemical remission as defined by modern criteria. We therefore included these studies in the lower remission group.

Nine studies reported SMR data for mortality divided according to serum GH levels at last follow-up after treatment (3, 5, 7, 8, 10, 12, 13, 15, 18), and one abstract reported an SMR value for those with elevated GH levels (>2.5 µg/l) at last follow-up (23). In six of these studies, specific estimates of mortality were provided according to GH levels above and below various arbitrary cut-off points. In four studies (5, 7, 13, 15), mortality was divided above or below a post-treatment GH level of 2.5 µg/l; in one study (12), the GH cut-off point was 2 µg/l; and in another report, the GH level was 5 µg/l (3). However, in this latter study, 82% of those with GH at last follow-up <5 µg/l were also <2.5 µg/l. For the purposes of this analysis, these six studies have been grouped to provide mortality estimates for 'serum GH greater than or less than 2.5 µg/l'. In addition, three studies (8, 10, 18) included a mortality cut-off point for GH of 2.5 µg/l in a

composite biochemical end point of remission, which also included IGF-I greater than or less than normal, and glucose-suppressed GH greater than or less than 1 µg/l. These latter three studies have also been included in the analysis, although it is unclear exactly how many individuals met just the 2.5 µg/l cut-off point in the remission/non-remission groups. In three of the above studies, the group classified here as '>2.5 µg/l' were patients with final GH 2–5 µg/l (12), 2.5–5 µg/l (5) or 2.5–9.9 µg/l (15) and data for the whole group with GH >2.5 µg/l were not provided. In one study, serum GH was reported as the mean of a day profile of GH (7), and in the remainder GH was either measured in random serum samples or the sampling technique was not clear.

Five studies reported SMR data according to normal or elevated levels of serum IGF-I at last follow-up (8, 12, 13, 17, 18); and in one study, the SMR estimate was restricted to those with normal IGF-I alone (10). In all of these studies, the normal range of IGF-I was adjusted according to age and sex. In four studies (10, 12, 13, 17), SMR data were reported according to IGF-I greater than or less than normal; and in two studies (8, 18), IGF-I measurements were included as a composite remission end point also including random serum GH and glucose-suppressed serum GH. As with the assessment of mortality according to random serum GH measurements in these reports, these latter two studies have been included in the IGF-I analysis; although it is unclear as to exactly what number of individuals specifically had normal or elevated IGF-I levels.

Statistical analysis

Pooled SMR estimates were calculated for all eligible studies using a fixed effects model. In the presence of significant heterogeneity ($P < 0.10$), a random effects model was also run in an attempt to incorporate the differences between studies into the analysis. Funnel plots for each model were inspected and no evidence of publication bias was evident (data not shown). Groups with different SMRs were compared by the method of Armstrong (24), assuming that the age-specific rates of death were proportional to the rates in the reference population in the various studies. All tests were two-tailed; a P value of <0.05 was considered statistically significant and 95% CI are presented. All analyses were carried out using Review Manager (RevMan, Version 4.2 for Windows, The Cochrane Collaboration).

Results

SMR estimates for subjects with acromegaly are shown in Fig. 1, drawn from 18 studies totalling 4806 patients and including 1116 deaths during follow-up. Despite the fact that almost all of these individuals had

Figure 1 Pooled standardized mortality ratios (SMRs) in studies of acromegaly. Data are SMR (95% confidence interval).

undergone treatment for the disorder, mortality was significantly increased (SMR 1.7, 95% CI 1.5, 2.0).

Figure 2 shows the SMR estimates for the 17 studies that reported remission data (as assessed by the individual study authors), grouped by the rate of biochemical remission. Those studies claiming >70% remission rate following treatment had a pooled SMR of 1.2 (95% CI 1.0, 1.5) compared with SMR of 2.0 (95% CI 1.6, 2.3) for those studies with (or likely to have had) a lower remission rate (risk ratio 1.7, $P < 0.05$). These results were not significantly altered if the older studies where remission data were not provided were omitted from the analysis.

Figure 3 shows the SMR estimates from ten studies grouped according to final GH level following treatment. Mortality was close to the expected level when final GH was $< 2.5 \mu\text{g/l}$ (SMR 1.1, 95% CI 0.9, 1.4), but was significantly elevated in those with final GH $> 2.5 \mu\text{g/l}$ (SMR 1.9, 95% CI 1.5, 2.4). The risk ratio for a serum GH $> 2.5 \mu\text{g/l}$ was 1.7 ($P < 0.05$). When the three studies reporting final GH level as part of a composite end point were excluded from the analysis, the results were similar ($< 2.5 \mu\text{g/l}$ SMR 1.0, 95% CI 0.7, 1.5; $> 2.5 \mu\text{g/l}$ SMR 1.7, 95% CI 1.4, 2.1). No study reported mortality subdivided according to levels of GH during oral glucose tolerance test (OGTT) alone, although in three studies (8, 10, 18) serum GH greater than or less than $1 \mu\text{g/l}$ after OGTT was included as part of a composite remission end point. When these studies were

analysed as if OGTT GH level was the sole remission variable, SMR values were 1.2 (95% CI 0.9, 1.7) for GH $< 1 \mu\text{g/l}$ and 2.3 (95% CI 1.0, 5.3) for GH $> 1 \mu\text{g/l}$.

Figure 4 shows the SMR estimates from six studies grouped according to normal or elevated IGF-I at last follow-up. Those with normal IGF-I had mortality close to the expected values for the general population (SMR 1.1, 95% CI 0.9, 1.4), whereas the SMR for those with elevated IGF-I at last follow-up remained significantly increased (SMR 2.5, 95% CI 1.6, 4.0). The risk ratio for an elevated serum IGF-I was 2.3 ($P < 0.05$). If the analysis was restricted to just those studies reporting IGF-I alone as the remission end point (excluding those studies where IGF-I measurements were part of a composite end point), the figures were similar (normal IGF-I SMR 1.1, 95% CI 0.8, 1.5; raised IGF-I SMR 2.3, 95% CI 1.4, 3.8).

Medical treatment of acromegaly using somatostatin receptor analogues (SSRAs), either as primary treatment or as adjuvant therapy following unsuccessful pituitary surgery, became widespread in most countries in the 1990s or later. Six studies (3, 5, 10, 13, 17, 18) reported >30% use of SSRAs for patients not in remission following surgery, six studies (4, 7, 9, 11, 14, 19) were completed before widespread use of these agents, three studies reported very low/zero usage (6, 8, 12), while in two studies (15, 16) the extent of use of SSRAs is uncertain. Grouping the studies according to >30% use of SSRAs or <30% use of SSRAs produces

Figure 2 Pooled standardized mortality ratios (SMRs) in studies of acromegaly grouped according to actual or likely remission rate. Data are SMR (95% confidence interval).

the same subgroups as grouping the studies by remission rates shown in Fig. 2, with the same difference in SMR.

Finally, to determine whether mortality has changed in more recent studies, the studies were ranked according to the mean calendar year in which subjects were entered. The pooled SMR for the six studies (4, 7, 9, 11, 12, 14, 19, 22) with mean year of patient entry before 1984 was 2.2 (95% CI 1.8, 2.8) compared with SMR of 1.3 (95% CI 1.1, 1.6) in the seven studies (3, 5, 8, 10, 13, 17, 18) with mean year of entry after 1984 ($P < 0.05$).

Discussion

A recent meta-analysis of mortality in acromegaly reported by Dekkers *et al.* (2) confirmed that acromegaly carries a significantly increased mortality despite treatment. In the New Zealand acromegalic cohort (12), which had an SMR of 2.7, overall life expectancy was reduced by 20 years, although this estimate could be biased to some extent by movement in life expectancy over the time of follow-up. Although age- and sex-matched reference populations were not available to

calculate the same data for the entire group of studies, it would be reasonable to suppose that similar reductions in life expectancy would be seen in other patient populations. However, as shown here, more recent studies, and those reporting high rates of biochemical remission as judged by individual authors, have mortality closer to levels expected for the general population, suggesting a significant effect from modern treatment of the condition and its complications. Of significance, studies reporting greater use of somatostatin analogues appear to have significantly lower mortality. The present analysis has focused on the relationship between mortality and the serum levels of IGF-I and GH achieved by treatment, since these variables are commonly used by clinicians as biochemical markers of the activity of acromegaly. The findings indicate that reduction of serum GH to $< 2.5 \mu\text{g/l}$, measured by RIA, or normalization of serum IGF-I for age and sex is associated with mortality indistinguishable from the general population, whereas a higher level of these hormones carries a significant mortality risk. The number of individuals in these studies is, however, sufficiently less so that a residual increased mortality in those with serum GH below $2.5 \mu\text{g/l}$ or normal IGF-I concentrations cannot be

Figure 3 Pooled standardized mortality ratios (SMRs) in studies of acromegaly grouped according to GH level at final follow-up. Data are SMR (95% confidence interval).

excluded, as a result of previous tissue damage from increased GH and IGF-I levels prior to treatment.

In support of these findings, serum GH, and to a lesser extent serum IGF-I, has been identified in several studies as important determinants (often the major determinant) of mortality in acromegaly when assessed by multivariate analysis (12, 13, 25). There is less data for IGF-I than for GH in this respect, although one study found IGF-I to have a significant influence on mortality in a multivariate analysis when substituted for GH in the assessment (12). However, two studies have not found IGF-I to be a significant independent predictor of mortality when assessed by relative mortality risk for those with normal compared with elevated IGF-I measurements (6, 13). Two studies (12, 13) have performed detailed multivariate analysis of factors that could potentially influence mortality in acromegaly (Table 1). Both found GH at last follow-up was the strongest predictor of outcome, and one study (12) found that IGF-I became a strong predictor of survival if substituted for GH in the analysis. The second study (13) did not find IGF-I to be an independent predictor of mortality, even when IGF-I replaced GH in the model. The number of patients in the studies in whom IGF-I measurements were performed was substantially less than the number with GH data, which may explain why in some instances serum IGF-I did not appear to be a

significant predictor of survival. Other variables found to influence outcome included the presence of hypertension, duration of the disorder prior to treatment, age, and whether GH excess was due to a pituitary microadenoma (Table 1). The duration of the disorder prior to diagnosis has also been found to influence mortality in an analysis adjusted for age and sex (10).

Variables influencing mortality in acromegaly have been assessed in some studies by estimating the relative risk of mortality according to the presence or absence of various potential risk factors. In this type of analysis, conventional pituitary radiotherapy has been identified as a possible risk factor for mortality (6, 25). In a further study (20), there was a significant increase in SMR in irradiated patients compared with non-irradiated individuals, although another two studies reporting SMR data according to use/non-use of radiotherapy did not find a significant increase in SMR in the irradiated group when adjusted for age and sex (10) or multiple variables (13).

Although mortality from cardiovascular disease was found to be increased in acromegaly in several studies (4, 12, 14, 22), the only cardiac risk factor identified in multivariate analysis that might directly impact on mortality was hypertension (Table 1). However, it is likely that low patient numbers or incomplete data have underemphasized a potential influence of other classical

Figure 4 Pooled standardized mortality ratios (SMRs) in studies of acromegaly grouped according to IGF-I level at final follow-up. Data are SMR (95% confidence interval).

cardiovascular risk factors on mortality, such as diabetes, smoking and dyslipidaemia. However, the apparent lack of impact of traditional cardiac risk factors, in the face of elevated cardiovascular mortality in acromegaly, emphasizes the specific deleterious effect of increased serum levels of GH and IGF-I on cardiac function as detailed by Colao *et al.* (26). A possible increased death rate in acromegaly from stroke has also been identified in several studies (4, 6, 14, 19), and a potential relationship between use of radiotherapy and stroke has been suggested in acromegalic individuals (6). The presence of hypertension as a mortality risk factor in multivariate analysis (12) suggests an influence of this variable on mortality from stroke in these patients. It also remains possible that

microvascular abnormalities specific to acromegaly (27, 28) may contribute to deaths from stroke in this condition.

The present analysis identifies serum GH and IGF-I as important variables contributing to the increased mortality of acromegaly, and correction of overproduction of these hormones appears to return mortality to expected levels for the general community. Uncertainty remains, however, about the translation of GH levels from the studies reported here, mainly measured by relatively insensitive GH RIAs which are no longer in use, to GH data generated by modern- or ultra-sensitive two-site sandwich immunoassays for GH. The listed studies employed competitive RIA up until the early-mid 1990s in most instances, and sensitive two-site non-competitive assays were only used for a minority of patient assessments. Information helpful for the comparison of results using these different types of assay comes from the New Zealand study (12) where, in the process of updating data prior to closure of the study, living patients frequently had measurements performed using a sensitive chemiluminescent assay with detection limit 0.05 µg/l. When the subjects in this study were divided according to different GH levels, the lowest mortality, indistinguishable from the general New Zealand population when assessed by Kaplan–Meier plot, was seen in those with final GH <1 µg/l. This supports the likelihood that remission levels of GH, associated with normal life expectancy, will need to be lower than found by RIA in the studies reviewed here, when measured by more sensitive techniques. Further mortality studies solely employing modern GH assays are needed to address this point. In the

Table 1 Variables affecting mortality in acromegaly assessed by multivariate analysis.

Study	Variable	P value
Holdaway <i>et al.</i> (2004) (12) ^a	GH post-treatment	0.001
	IGF-I post-treatment ^b	0.02 ^b
	Age	0.006
	Years delay before diagnosis	0.035
	Hypertension at follow-up	0.043
Kauppinen-Makelin <i>et al.</i> (2005) (13) ^c	Age	<0.001
	GH post-treatment	0.007
	Male gender	0.015
	Microadenoma ^d	0.045

^aVariables tested were GH, IGF-I, age, gender, hypertension, diabetes, arthritis, hypopituitarism and years delay before diagnosis.
^bValue obtained when IGF-I was substituted for GH in the model.
^cVariables tested were GH, IGF-I, age, gender, radiotherapy, tumour size, use of GH lowering medication and use of surgery.
^dAssessed after controlling for post-treatment GH and IGF-I.

meantime, it would be reasonable for clinicians to aim for their acromegalic patients to achieve normal IGF-I levels, random GH by modern assays $<1 \mu\text{g/l}$ and/or normal GH following OGTT (probably $<0.4 \mu\text{g/l}$ by chemiluminescent GH assay (29) or $<0.14 \mu\text{g/l}$ by ultrasensitive GH assay (30)).

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