A Paradigm Shift in the Monitoring of Patients With Acromegaly: Last Available Growth Hormone May Overestimate Risk

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Context: Acromegaly is associated with reduced life expectancy, which has been reported to be normalized if treatment is successful in controlling GH/IGF-I levels.

Objective: Most previous studies have invariably used the last available GH/IGF-I, which may be biased as it only assesses exposure at a single point in time. We compared the last available GH/IGF-I analysis to a "time-dependent" and cumulative method, during follow-up to assess risk of mortality in the West Midlands Acromegaly study (n = 501).

Results: Using the last available GH, there was a statistically significant increase in mortality comparing groups as low as GH $\leq$ 1 μg/L vs $>$1 μg/L (relative risks [RR] 1.8, $P = .03$). This was not the case when using the "time-dependent method," where only comparisons of GH values of GH $\leq$5 μg/L vs $>$5 μg/L were suggestive of being associated with an increased risk of mortality (RR = 1.5, $P = .08$). When the time-dependent GH method of analysis was used, the RR of mortality at each level was lower and the associated *P* value was less significant. Irrespective of using the last available or time-dependent method, when IGF-I was divided into levels according to quartile or arbitrary cutoffs, there was no significant increase in mortality with higher levels.

Conclusions: This study emphasizes the potential bias of using the latest available GH/IGF-I levels to predict mortality. Our study again highlights the limitations of IGF-I in predicting mortality. **(*J Clin Endocrinol Metab* 99: 478–485, 2014)**

Acromegaly is associated with reduced life expectancy. Several retrospective studies have demonstrated a two- to three-fold increased mortality in patients with acromegaly compared with age- and sex-matched controls. Death is due predominantly to cardio/cerebrovascular disease, respiratory disease, and, in some studies, malignancy (1–11). Results from more recent studies also demonstrate that the high mortality rates associated with acromegaly can be normalized toward that of the general population if treatment is successful in reducing GH levels to less than 2–2.5 μg/L (2–5, 7, 8, 12, 13). Normalization of IGF-I levels into age-specific reference ranges has also been as-

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Abbreviations: CI, confidence interval; GHU, GH units; IQR, interquartile range; RR, relative risks; SMR, standardized mortality ratios.

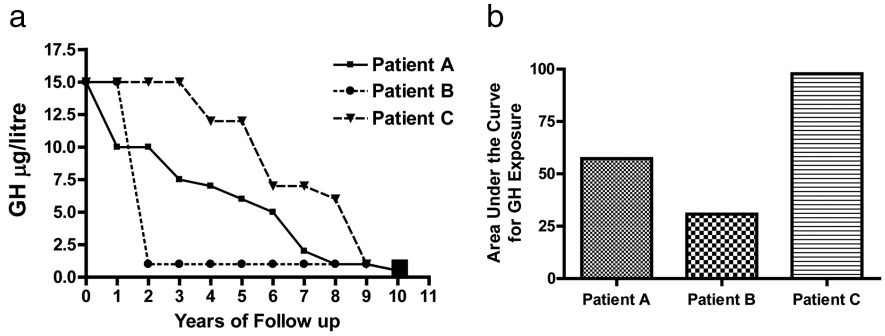

Figure 1. Panel a, Clinical course of three hypothetical patients (A, B, C), demonstrating that not all patients will arrive at the same last available GH level (point ◯) by similar clinical courses. Panel b, The difference in cumulative GH exposure (as assessed by area under the curve) between the three patients. This highlights the potential for bias when using last available GH/IGF-I if we hypothesize that the biological effect of excess GH/IGF-I exposure is a key determinant in increased mortality in patients with acromegaly.

sociated with normalization of mortality in some but not all studies (5, 12, 14, 15). This data have led to a number of consensus statements regarding targets for the management of acromegaly, the most recent of which state that the target for therapy in acromegaly should be a GH of <2.5 µg/L for normalization of mortality, <1.0 µg/L during an OGTT for biochemical control, and <0.4 µg/L for remission and IGF-I in the age-related reference range (16).

Importantly, it should be highlighted that the studies assessing the role of GH and IGF-I in mortality has invariably used the last available GH/IGF-I in the statistical model for analysis. This makes the assumption that this is the level of exposure experienced by the patient from diagnosis until the date of the last measurement. Such an approach may be biased as GH/IGF-I levels tend to decline with time from diagnosis as treatment is instigated; thus, exposure intensity is not constant. The last available measurement is assumed to be constant throughout the entire follow-up because diagnosis is likely to overestimate the mortality associated with high levels of exposure to GH/IGF-I and likely to underestimate the mortality associated with low levels of GH/IGF-I. Examples illustrating this general concept are shown in Figures 1 and 2. From a pathophysiological perspective, one would assume that patients who had elevated GH/IGF-I levels for longer periods of time would be at greater risk of mortality than those with persistently lower levels, but there are little data assessing the hypothesis.

Our hypothesis was that the current method of assessing mortality risk in acromegaly based on the last available GH/IGF-I results in a biased risk associated with levels of GH/IGF-I. Having acquired follow-up data over a long period of time in a large cohort of patients with acromegaly, we aimed to assess mortality risk using a number of methods of analysis including the previously used last available GH/IGF-I, assessments of cumulative GH exposure, and a "time-dependent GH/IGF-I" method.

Patients and Methods

The West Midlands Acromegaly database was established in 1990 and on December 31, 2006 contained retrospective and prospective demographic and clinical details of 501 patients (275 women) with acromegaly from 16 referral centers across the West Midlands region of the United Kingdom. The region has an overall population of 5.7 million. The median duration of follow-up was 14.0 years (interquartile range [IQR] 7.9–21) in the entire cohort with a total of 7567 patient years follow-up (with GH and IGF-I levels yearly available).

All patients had a biochemical diagnosis of acromegaly based on accepted criteria at the time (failure of GH suppression to less than 1 µg/L after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (n = 34) had died before the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site, the Office of National Statistics, and the Patient Information Advisory Group.

One hundred twenty-eight of 501 (25.5%) patients had received surgery alone; 32/501 (6.4%) radiotherapy alone, 43/501 (8.6%) medical therapy alone, and 104/501 (20.8%) received all three treatment modalities. One hundred forty-three of 501 (28.5%) pa-

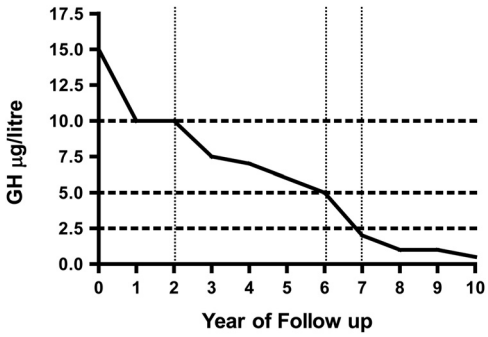

Figure 2. Demonstration of how a single patient may contribute years of follow-up at a particular GH level to many different levels of GH using the time-dependent GH method. This patient would be added to the analysis as 2 years at a GH level >10 µg/L, 4 years at a GH between 5 and 10 µg/L, 1 year at a GH between 2.5 and 5 µg/L, and 3 years at a GH <2.5 µg/L. This is compared with the last available GH level whereby the last GH level (in this patient a GH value of 1 µg/L at 10 years) would be taken to be the level of exposure over the entire 10 years.

tients received surgery and radiotherapy (of these 104/143 patients also received medical therapy), 68/501 (13.6%) surgery and medical therapy, 162/501 (32.3%) radiotherapy and medical therapy (of these 102/162 also received surgery).

In total, 237 received radiotherapy, and 220 received conventional three-field radiotherapy with a median dose of 45Gy (IQR 45–47 Gy) administered over a median of 25 fractions (IQR 25–30). Ten patients received stereotactic radiosurgery and seven received Yttrium implants.

All patients were flagged at the National Health Service Central Registers for vital status and embarkations due to emigration. For each death, an attempt was made to obtain the death certificate and underlying causes of death were coded using International Classification of Diseases, version 9. Three hundred thirty-nine patients were alive on the exit date of the study and 162 patients were deceased (data relating to radiotherapy and last available GH/IGF-I and mortality have been reviewed in 419 [2] and radiotherapy and hypopituitarism in 501 [9] of these patients previously).

Median age at diagnosis was 46.6 years (IQR 11.6–84.2) in the entire cohort, 44.2 (IQR 34.6–53.7) in those who were still alive, and 53.8 (IQR 44.6–61.8) in those who had died.

Endocrine evaluation

Serum GH levels were measured by an in-house RIA in a central laboratory as previously described (the value in mIU/L was divided by a conversion factor of 2 to obtain μg/L) (17). The limit of detection of the assay is 0.5 μg/L and the interassay coefficient of variation is 5.7% at 2 μg/L, 4.3% at 3 μg/L, 5.5% at 7.3 μg/L, and 4.47% at 14.7 μg/L. Data on GH levels during follow-up were available in 470/501 (93.8%) patients. Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described (18). The limit of detection of the assay is 2.0 nmol/L. The interassay coefficient of variation is 5.4% to 8.4% between 16 and 104 nmol/L. IGF-I data were available on 409/501 patients (81.6%) during follow-up. The same GH and IGF-I assay and reference range were used during the duration of the study.

Statistical analysis

Quantifying exposure to GH and IGF-I

External analysis—standardized mortality ratios (SMRs). SMRs for overall mortality, cardiovascular, respiratory, and cerebrovascular deaths were calculated using Stata statistical software (19). The expected number was estimated by multiplying age, sex, and calendar-period–specific death rates in the general population of England and Wales by the person-years at risk accumulated within the age, sex, and calendar-period–specific strata corresponding to the patient cohort. SMRs for overall and cause-specific mortality were also evaluated by GH and IGF-I level.

Internal analysis—Poisson regression. Most of the statistical modeling was internal because such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders. Because GH and IGF-I measurements were available for most patients, the GH value was considered a time-dependent variable. GH values were considered to be constant between two adjacent GH measurements, extrapolated back in time from the most recent measurement. This time-dependent approach avoids bias due to incorrect allocation of person-years to the different GH exposure categories as is likely to be the case when using the GH level that is available at the end of the study follow-up (ie, last available GH). The latter approach assumes that the GH level is constant throughout the whole study follow-up. Such an approach is likely to be biased as the GH tends to decline with time from diagnosis (Figures 1 and 2). The time-dependent approach also allows for a greater number of data points to be collected for each individual patient, to assess the risk of mortality at any given GH/IGF-I level as each GH/IGF-I value during follow-up can be used, not just the last available level. To assess the effect of cumulative exposure to GH on mortality, we derived a GH units (GHU)-year (for example, if a patient was exposed to a GH of 10 μg/L for 2 years, then this corresponds to 20 GHU-years). If the individual experiences a GH of 5 μg/L for the next 6 months, then this corresponds to 2.5 GHU-years. If the individual experiences a GH of 3 μg/L for the next 6 months, then this corresponds to 1.5 GHU-years. In total, for this 3-year period the individual has accumulated 24 GHU-years. This was not performed for IGF-I due to limitations of the dataset.

In an internal analysis a multivariable Poisson regression model was used to calculate relative risks (RR) of mortality based on last, time-dependent, and cumulative GH and IGF-I levels (20). Unless otherwise stated, RRs were adjusted for radiotherapy, hypopituitarism, attained age, sex, calendar period, and period of follow-up.

To assess goodness-of-fit of the Poisson model, we fitted a negative binomial regression model with the same parameters as the original Poisson model. We assessed potential overdispersion by the likelihood-ratio test of the overdispersion parameter α in the negative binomial regression model; no significant evidence for overdispersion was found.

Results

Mortality

All-cause mortality was significantly increased in patients with acromegaly compared with that expected from the general population (SMR 1.7 [1.4, 2.0]; $P < .001$), as we have previously reported (9). Similarly the cause-specific mortality with a significant increase in cardiovascular (SMR 1.9 [1.6, 2.4]; $P < .001$), respiratory (SMR 1.8 [1.1, 2.8]; $P = .01$), and cerebrovascular death (SMR 2.7 [1.9, 4.1]; $P < .001$), but no significant increase in death due to cancer (SMR 1.2 [0.9, 1.7]; $P = .26$) compared with the general population was noted. Data from this study have also previously reported an increased mortality in patients who have received radiotherapy, had ACTH deficiency, and were receiving higher doses of hydrocortisone replacement therapy (9).

Comparison of last available vs time-dependent GH on mortality

Patients were divided into groups according to whether GH was above or below arbitrary cutoff values, and mor-

Table 1. All-cause Mortality in Patients With Acromegaly According to Whether a Patient Was Above or Below Arbitrary GH Cutoff Using Two Methods of Analysis (last available and time-dependent method of analysis)

GH, μg/L	RR	CI	*P* Value
Last available GH			
≤0.5 vs >0.5	1.6	0.9, 2.9	.12
≤1 vs >1	1.8	1.1, 2.9	.03
≤1.5 vs >1.5	1.6	1.0, 2.6	.04
≤2 vs >2	1.6	1.0. 2.4	.05
≤2.5 vs >2.5	1.5	1.0. 2.4	.07
≤5 vs >5	1.7	1.1, 2.8	.02
Time-dependent GH			
≤0.5 vs >0.5	1.4	0.7, 2.5	.32
≤1 vs >1	1.5	0.9, 2.5	.094
≤1.5 vs >1.5	1.4	0.9, 2.2	.16
≤2 vs >2	1.4	0.9. 2.1	.16
≤2.5 vs >2.5	1.2	0.8, 1.9	.42
≤5 vs >5	1.5	0.9, 2.4	.08

Reference value for analysis is the lower value (eg, reference value is ≤0.5 and comparator is >0.5). Data adjusted for radiotherapy, gender, attained age, follow-up, calendar year, and pretreatment GH levels.

tality (as RR) was assessed. Using the last available GH, there was a statistically significant increase in mortality in groups as low as ≤1 μg/L vs >1 μg/L (RR 1.8, $P = .03$; Table 1). When using the "time-dependent method," RR were generally lower and only GH values of ≥5 μg/L were suggestive of being associated with an increased risk of mortality (RR = 1.5, $P = .08$; Table 1).

Patients were then divided into groups based on ranges of GH

Using the last available GH, levels >5 μg/L were associated with significantly increased mortality levels (Table 2). This was still evident with the last available GH values from 1 to <2.5 μg/L (RR 1.7, $P = .08$). However, when the time-dependent GH method of analysis was used, the RR of mortality at each level were generally lower and the associated *P* values were less significant. This was also true for the likelihood ratio test for a trend in mortality with increasing GH levels (Table 2).

Comparison of last available IGF-I vs time-dependent IGF-I

Irrespective of using the last available or time-dependent method when IGF-I was divided into levels according to quartile (Table 3) or arbitrary cutoffs (Table 4), there was no significant increase in mortality with higher levels. In all models, radiotherapy, attained age, gender, calendar year, and follow-up period were included as potential confounders.

The effect of cumulative GH on mortality

When the effect of cumulative exposure of GH on the risk of mortality was assessed (having adjusted for attained age, gender, calendar period, and pretreatment GH), there was a trend to increased mortality in patients who had the greatest exposure to GH as assessed by elevated GHU-year exposure (*P* for trend = .06). When radiotherapy was introduced into the model, the significance of trend decreased (*P* for trend = 0.15; Table 5).

Discussion

Our results suggest that the widespread method of assessing mortality risk in patients with acromegaly based on last available GH leads to a moderate overestimation of

Table 2. All-cause Mortality in Patients With Acromegaly According to Range of GH, Using Two Methods of Analysis (last available and time-dependent method of analysis)

GH, μg/L	RR	CI	*P* Value	Deaths	Person-years
Last available GH					
Reference 0 to <1	1			28	2491.5
1 to <2.5	1.7	0.9, 3.1	.08	31	1847.1
2.5 to <5	1.6	0.8, 3.1	.16	29	1211.3
5 to <25	2.5	1.4, 4.6	.003	48	1548.4
≤25 to <50	4.3	0.8, 22.2	.08	3	41.6
>50	11.8	2.9, 47.1	.0005	4	96.7
	P trend .001				
Time-dependent GH					
Reference 0 to <1	1			28	1656.0
1 to <2.5	1.6	0.9, 2.9	.13	31	1601.9
2.5 to <5	1.3	0.7, 2.6	.37	30	1324.1
5 to <25	1.9	1.0, 3.6	.04	53	2115.1
≤25 to <50	2.1	0.4, 10.1	.36	3	192.9
>50	7.1	1.9, 27.0	.0037	5	200.1
	P trend .019				

Data adjusted for radiotherapy, gender, attained age, follow-up, calendar year, and pretreatment GH levels.

Table 3. All-cause Mortality in Patients with Acromegaly According to the Level of IGF-I Using Two Methods of Analysis (last available and time-dependent method of analysis)

IGF-I, nmol/L	RR	CI	*P* Value	Deaths	Person-years
Last available IGF-I					
0–24	1			31	2089.7
25–49	0.85	0.50, 1.42	.5307	28	20 101.0
50–74	1.28	0.65, 2.52	.4811	13	594.2
>75	1.55	0.79, 3.02	.2016	14	293.1
	P trend .194				
Time-dependent IGF-I					
0–24	1			34	1893.3
25–49	1.19	0.7, 1.9	.48	35	1939.7
50–74	0.94	0.5, 1.7	.84	18	1014.0
>75	1.5	0.8, 2.8	.21	18	968.8
	P trend .43				

Data adjusted for radiotherapy, age, gender, calendar year, and follow-up.

the RR of mortality at high GH levels compared with the time-dependent approach. We have again documented that IGF-I did not significantly predict mortality. Recently, Jayasena et al (21) have shown increased morbidity with increased GH exposure (increased abnormal glucose tolerance and ischemic heart disease) and IGF-I exposure (cerebrovascular disease and cardiomyopathy). For the first time, we have shown that increased cumulative exposure to GH leads to a trend toward increased RR of mortality, but this relationship was diluted once radiotherapy was included in the model (highlighting the confounding effect of radiotherapy). Both radiotherapy and ACTH deficiency are associated with increased mortality in this patient cohort (9). Hypopituitarism per se is also associated with reduced life expectancy (SMRs 1.5–2.5) (22). These observations have therapeutic implications; in an attempt to lower GH levels to existing targets, we often use radiotherapy or repeat surgery, which, although frequently effective in reducing GH/IGF-I, has other detrimental effects, including hypopituitarism. Although we would not argue against the importance of reducing GH levels in patients with acromegaly (2, 3, 5, 8, 23), our data indicate that the GH cutoffs suggested in current consensus guidelines may lead to the increased use of radiotherapy, repeat surgery, or medical therapy, which may themselves cause adverse events.

Table 4. All-cause Mortality in Patients With Acromegaly According to Quartile of IGF-I Using Two Methods of Analysis (last available and time-dependent method of analysis)

Quartile	RR	CI	*P* Value
Last available IGF-I			
1	1		
2	0.95	0.49, 1.84	.88
3	0.79	0.39, 1.61	.52
4	1.3	0.7, 2.42	.40
	P trend .366		
Time-dependent IGF-I			
1	1		
2	1.16	0.68, 1.99	.58
3	0.91	0.52, 1.61	.76
4	1.06	0.61, 1.86	.83
	P trend .95		

Data adjusted for radiotherapy, age, gender, calendar year, and follow-up.

Impact of GH levels on mortality in acromegaly

In the early 1990s, two studies demonstrated that the increased mortality associated with acromegaly can be decreased if treatment is successful in reducing last available GH levels to less than 5 mU/L (2.5 μg/L), whether this is measured as the mean of a GH day profile or as a random GH level (3, 8). In the first of these studies by Bates et al (3), in a cohort of 79 patients with acromegaly, the SMR fell from 2.6 to 2.0 if treatment reduced GH levels to less than 10 mU/L (5 μg/L). Even more significant was the fact that mortality was reduced to normal if posttreatment GH levels of less than 5 mU/L (2.5 μg/L) were achieved. The second study by Rajasoorya et al (8) in a cohort of 151 patients with acromegaly showed on both univariate and multivariate analysis that higher GH levels were associated with reduced survival.

Over the last two decades a number of studies have reported similar findings reaching a consensus in showing that posttreatment GH values of less than 2.5 μg/L restores SMR to normal and providing an evidence base for targeted reduction of GH concentrations (16, 24–26). However, GH cutoff points of 2.5 μg/L for normalization of mortality and <1 μg/L to define biochemical control of acromegaly have been arbitrarily adopted, with little scientific basis for this selection. Previously, we have published results from the West Midlands Acromegaly study, which showed that when comparing crude death rates per 1000 population, a last available GH of 2 μg/L may be a more appropriate treatment target, with a step-up in the

Table 5. Effect of Level of Cumulative Exposure to GH on All-cause Mortality and Effect of Radiotherapy on this Effect

Cumulative Exposure to GH (GHU-years)	No. of Deaths	No. of Patient-years	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI) With Radiotherapy in Model
0–49	6	407	1.0		1.0
50–99	20	993	1.3 (0.5, 3.4)	.536	1.1 (0.4, 2.8)
100–199	28	1438	1.7 (0.7, 4.1)	.249	1.4 (0.6, 3.4)
200–499	31	1442	2.0 (0.8, 5.4)	.127	1.7 (0.7, 4.1)
500–999	15	752	2.1 (0.8, 5.4)	.142	1.7 (0.6, 4.4)
1000+	7	390	2.0 (0.7, 6.0)	.224	1.4 (0.5, 4.5)
P for trend			.06		.15

Likelihood ratio test for linear trend in RRs, $P = .06$.

Adjusted for attained age, sex, calendar period, assuming pretreatment GH level existed for 8 years before diagnosis.

death rate once GH exceeded 2 μg/L (2). Data from Holdaway et al (5) suggested a further improvement in outcome if GH can be lowered to under 1 μg/L. Similar results were seen in this current study; using a last available GH cutoff value as low as <1 vs >1 μg/L appeared to show improvement in survival. In a recent meta-analysis focusing on the relationship between biochemical measurements and mortality during follow-up after treatment for acromegaly, mortality was close to the expected level when the last available GH was <2.5 μg/L (SMR 1.1, 95% confidence interval [CI] 0.9–1.4), but was significantly elevated in those with the last available GH >2.5 μg/L (SMR 1.9, 95% CI 1.5–2.4), and the RR for a serum GH >2.5 μg/L was 1.7 ($P < .05$) (27). On the basis of this background, therefore, the consensus is that the target for normalization of mortality in acromegaly should be a reduction of GH values to less than 2.5 μg/L.

However, we feel these data may be an overestimation of the effect of GH on mortality; when we used a more appropriate time-dependent method of analysis, we did not see as great RR of mortality or statistical significance as in the potential statistically biased method using the last available GH method. There was a trend toward significance for a greater GH cumulative exposure being associated with increased mortality in acromegaly. This is the first time the effect of cumulative exposure to GH has been assessed in patients with acromegaly and strengthens the already strong argument that GH concentrations are a factor driving mortality in this patient cohort.

Impact of IGF-I levels on mortality in acromegaly

IGF-I is now widely used as a first-line investigation for the diagnosis and therapeutic monitoring of patients with acromegaly (28). Indeed, the introduction of GH antagonists as medical treatment for acromegaly necessitates the use of IGF-I as the only tool for the biochemical monitoring of patients treated with these agents (29). However, the relationship between mortality and last available IGF-I level is not as strong as it is for the last available GH. Swearingen et al (15) reported that in a cohort of 162 patients (12 deaths), those patients who were surgically cured, defined by a normal IGF-I, had mortality similar to that of the general population of the United States, whereas those with active disease as defined by a persistently elevated IGF-I had reduced life expectancy for the period that the IGF-I was elevated. A further study also concluded that IGF-I normalization reduced mortality to expected levels; however, serum IGF-I was not an independent predictor of mortality when both GH and IGF-I measurements were included in the multivariate analysis and was only significant when looking at SD scores >2 for IGF-I compared with normal IGF-I levels (5). In the recent meta-analysis by Holdaway et al (27), 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 ($P < .05$). However, it should be noted that two of the largest studies, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between posttreatment IGF-I levels and mortality (RR 1.2, CI 0.71–2.02, $P = .05$) and (0.46, CI 0.17–1.26, $P = .13$), suggesting last available serum IGF-I may not be as reliable a predictor of future mortality in acromegaly as last available GH (2, 23). In our study, we assessed the role of IGF-I on mortality by a number of methods including dichotomous (normal vs elevated), quartiles of IGF-I and IGF-I according to biochemical cutoffs after adjusting for a number of potential cofounders. We did not find a significant relationship between IGF-I and mortality risk in patients with acromegaly whether using the last available or the time-dependent IGF-I method of analysis. It should be noted that in patients who receive pegvisomant as a therapy for acromegaly IGF-I is the only reliable method for monitoring disease control. Therefore, notwithstanding the above data and until further evidence is available with

regard to mortality in patients receiving pegvisomant, the target for patients receiving this therapy should be an IGF-I within the normal range for age and gender.

This study highlights that although normalization of GH and IGF-I has been, and should continue to be, a target of therapy in acromegaly alongside tumor volume control and alleviation of symptoms, that a risk-benefit assessment for each patient is essential. If normalization of GH and IGF-I is at the cost of exposing the patient to pituitary radiotherapy or inducing hypopituitarism (in particular, ACTH deficiency), then the risk of remaining at an elevated GH/IGF-I must be weighed against the possible detrimental effects of this therapy. We have previously showed an increased mortality in this patient cohort in patients treated with radiotherapy (particularly from cerebrovascular disease) and ACTH deficiency (9). However, it should be highlighted that as this is a historic cohort radiotherapy technique and that the number of patients receiving radiotherapy has changed in recent years. The above detrimental effects are particularly relevant given the significant effects of medical therapy on biochemical control (29–31) (and in the case of somatostatin analog therapy tumor volume reduction) (32).

Importantly, patients with acromegaly have abnormal glucose metabolism, blood pressure, cardiac structure, and lipid profiles, all of which are associated with increased cardiovascular morbidity and mortality (33). No study to date has studied the effect of modern vascular risk factor reduction on mortality in acromegaly. One could speculate that the improvement in the last two decades in SMR for patients with acromegaly may reflect greater awareness of these complications and the introduction of better therapies for glucose control, lipid abnormalities, and treatment of blood pressure and cardiac abnormalities such as left ventricular hypertrophy rather than reductions in GH/IGF-I per se.

In conclusion, our study emphasizes the potential bias of using the latest available GH and IGF-I levels to predict mortality. These may have overestimated true risk and the adoption of target levels may have paradoxically led to increased risk through radiotherapy and hypopituitarism-related mortality. An unbiased method, using time-dependent GH values, suggests that higher GH cutoffs of 5 μg/L may be acceptable but further work is needed to assess this in prospective studies. Our study again highlights the limitations that IGF-I may have in predicting outcome. Therapy for each patient should be individualized and future detrimental outcomes depending on treatment modalities should be assessed on a risk-benefit basis.

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