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Factors Influencing Mortality in Acromegaly

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Studies of acromegaly have shown a doubling of mortality compared with the general population. With the development of new modalities of treatment, it has become important to identify prognostic factors relating to mortality. Between 1964 and 2000, 208 acromegalic patients were followed for a mean of 13 yr at Auckland Hospital. Treatment was by surgery or radionuclide pituitary implantation, and all except 27 patients received pituitary radiation. Over the duration of the study, 72 patients died at a mean age of 61 ± 12.8 yr. Those dying were significantly older at diagnosis, had a higher prevalence of hypertension and diabetes, and were more likely to have hypopituitarism. The observed to expected mortality ratio (O/E ratio) fell from 2.6 (95% confidence interval, 1.9–3.6) in those with last follow-up GH greater than 5 μg/liter to 2.5 (1.6–3.8), 1.6 (0.9–3), and 1.1 (0.5–2.1) for those with GH less than 5, less than 2, and less than 1 μg/liter, respectively ($P < 0.001$). Serum IGF-I, expressed as an SD score, was significantly associated with mortality, with O/E mortality ratios of 3.5 (95% confidence interval, 2.8–4.2) for those with an SD score greater than 2, 1.6 (0.6–2.6) for those with an SD score less than 2 (normal or low levels), and 1.0 (0.1–3) for those with an SD score less than zero. When assessed by multivariate analysis, last serum GH ($P < 0.001$), age, duration of symptoms before diagnosis ($P < 0.03$), and hypertension ($P < 0.04$) were independent predictors of survival. If IGF-I was substituted for GH, then survival was independently related to last IGF-I SD score ($P < 0.02$), indicating that GH and IGF-I act equivalently as predictors of mortality. These findings indicate that reduction of GH to less than 1 μg/liter or normalization of serum IGF-I reduces mortality to expected levels. (*J Clin Endocrinol Metab* 89: 667–674, 2004)

ACROMEGALY IS ASSOCIATED with considerable morbidity (1–5) and increased mortality (6–17), and there has been considerable interest in defining criteria for cure of the condition. Several factors make this issue important. Firstly, GH is released in a pulsatile fashion, so normal and abnormal ranges are not easily defined, although suppression with glucose loading or measurements over the day may help to standardize the assessment (18). Secondly, complete surgical excision of the underlying pituitary adenoma is not achieved in a significant proportion of patients, and further treatment is often needed after surgery to reduce GH levels. Further information about the criteria of remission and, potentially, cure of the condition based on factors predicting mortality would thus be helpful when planning treatment and advising patients. In this report factors influencing mortality in acromegaly have been evaluated in a group of patients treated at a single center, including an assessment in a subgroup of individuals to investigate whether normalization of serum IGF-I is a useful predictor of mortality.

Subjects and Methods

Subjects

Data from 208 consecutive patients with acromegaly treated at Auckland Hospital between 1964 and 2000 were studied. All except 3 patients underwent a surgical procedure to the pituitary (transfrontal surgery, n = 29; transsphenoidal surgery, n = 141; radionuclide pituitary implantation, n = 35), and postoperative external beam radiotherapy was given to 143 patients. Overall, 181 patients were exposed to pituitary radiation treatment. The study predated the use of long-acting somatostatin analogs in routine practice in New Zealand, and no patients in the series had been treated with these agents. Most subjects were reviewed at the Endocrine Clinic at Auckland Hospital for long-term follow-up, but in a small number of cases where patients had moved to other centers in New Zealand or to Australia, information was obtained from local physicians or one of us traveled to the appropriate center to review patient notes. Baseline entry GH and IGF-I samples were taken in the fasting state from the time zero sample of a glucose suppression test. GH and IGF-I samples at follow-up were obtained as singleton ambulant samples without glucose suppression during routine outpatient assessment, mostly (>90%) by random sampling, and the remainder while fasting. Date and cause of death were ascertained from general practice or hospital records (n = 59) or from death certificates where the cause of death was uncertain from the records (n = 13). The project was approved by the Health Funding Authority ethics committee of Auckland.

Laboratory methods

GH was measured by RIA as previously described (12) until 1995 and thereafter by immunoradiometric assay. The original assay was calibrated against HS 1863 (1.6 U/mg; supplied by Dr. A. Wilhelmi under the auspices of the U.S. National Pituitary Agency). In the mid-1970s the assay standard was changed to WHO First International Reference Preparation 66/217 (2 IU/mg), and in the mid 1980s the assay standard was changed again to WHO 80/505 (2.6 IU/mg). The original assay had a sensitivity of 1 μg/liter, and since the mid 1970s the sensitivity has been approximately 0.5 μg/liter. The within- and between-assay coefficients of variation at midrange (6 μg/liter) in the most recent assay were 1.1% and 3.9% respectively. Serum IGF-I was measured in three different assays over the course of the study. From 1983 to 1991 an RIA was employed using recombinant IGF-I (Ciba 810288, Ciba Pharmaceuticals, Basel, Switzerland) as standard, as previously described (19). Nineteen (12%) of the IGF-I measurements obtained at last follow-up used this assay. An updated RIA was used between 1991 and 1998, with recombinant IGF-I (Genentech, South San Francisco, CA) as assay standard (20). From 1998 the Nichols Institute (San Juan Capistrano, CA) immunoradiometric IGF-I assay was used. The within- and between-assay coefficients of variation for the present assay were 3.5% and 7.8%, respectively. The normal ranges obtained with the Nichols assay and the

Abbreviation: O/E ratio, Observed to expected mortality ratio.

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1991–1998 RIA were almost identical and were age and sex standardized. However, the normal range of the original IGF-I assay was lower than those for the later assays and was not age standardized. Results have been calculated as SD scores, *i.e.* the number of SD the measurement differs from the mean of the normal range, assuming the normal range as equivalent to the mean ± 2 SD for ages 20–39, 40–54, and more than 54 yr (subdivided for sex). The IGF-I assay used before 1991 had a single normal range for all ages, and for ease of comparison with the later results, SD scores were calculated from the mean of this range, assuming the limits of the normal range were ±2 SD regardless of patient age.

Statistics

Comparison of continuous normally distributed dependent variables was performed using ANOVA with *post hoc* testing of significant main or interaction effects using Tukey's method. The χ^2 test was used for categorical data. Kaplan-Meier survival analysis was performed on the time from the date of diagnosis to death or last follow-up. For multivariate analysis of competing risks, Cox's proportional hazards approach was adopted. A variety of iterative (stepwise, forward, and backward selections) model-building strategies were used. Analyses were performed using the statistical analysis system (version 8.2, SAS Institute, Inc., Cary, NC). All tests were two-tailed, and a 5% significance level was maintained throughout.

Results

Of the 208 patients, 40% were female, and 60% were male. Ethnic origin included 72% European, 13% Maori, 9% Pacific Islanders, 3% Chinese, and 2% other races, with these proportions being approximately those expected from the racial proportions in the New Zealand census data. The mean ± SD duration of patient follow-up was 13.4 ± 9.9 yr (median, 12.2 yr). The mean delay in years from estimated onset of the disorder to diagnosis as determined from serial photographs or family information was 7.7 yr (median, 6 yr). The mean ± SD age at initial diagnosis was 42 ± 13 yr.

Of 103 subjects for whom smoking history was known, 53% were smoking at the time of diagnosis, and 5% had previously been smokers. Only 50% had their alcohol intake clearly recorded at diagnosis, with 29% of these being nondrinkers, and 10% consuming more than four standard units of alcohol per day.

The mean ± SD baseline serum GH level at diagnosis was 53 ± 110 μg/liter (range, 3–1160 μg/liter; median, 25.5 μg/liter). The serum IGF-I level was elevated in all 86 subjects in whom pretreatment measurements were performed, commencing with the initial IGF-I assay in 1983.

At last follow-up, the mean ± SD serum GH level in the total patient group was 13.1 ± 59 μg/liter (median, 1.7 μg/liter; range undetectable to 670). Serum IGF-I measurements were available for 153 patients at last follow-up, with 39% still having elevated levels. The mean ± SD IGF-I SD score at last follow-up was 1.96 ± 4 (median, 1.1; range, −4 to 17.3). Ten percent had an SD score below −2 at last follow-up, one third had an SD score below zero, and 61% had an SD score below 2. One hundred and forty-six patients (70%) had a serum GH level at last follow-up below 5 μg/liter, 108 patients (52%) had a GH level at last follow-up below 2 μg/liter, and 64 (31%) had a GH at last follow-up below 1 μg/liter.

Mortality data

During the period of follow-up 72 patients died (35% of the total group), with the mean ± SD age at death being 61 ± 12.8 yr. The causes of death are shown in Table 1. The proportions dying from neoplastic disease or stroke were broadly similar to the values expected for the general New Zealand community, but cardiovascular deaths were increased compared with expected values. Two patients died as the result of relentless local invasion of the original pituitary adenoma. Clinical features in the deceased group at diagnosis and last follow-up were compared with similar data at diagnosis and last follow-up in surviving patients (Table 2). Those dying were significantly older at diagnosis, had more hypertension and diabetes at diagnosis and at last follow-up, and had more osteoarthritis at last follow-up. The deceased group was more likely to have developed hypopituitarism after treatment. A greater proportion of the surviving group had stopped smoking at last follow-up compared with deceased patients. There was, however, no significant difference in the proportion who was smoking at last follow-up, but this analysis was restricted to 100 patients for whom the relevant data had been recorded. Alcohol intake (not shown) did not differ significantly between the groups.

Predictors of mortality

Biochemical data from the deceased group are compared with the surviving patients in Table 3. Serum GH levels were similar in the two groups at diagnosis, but were significantly lower at last follow-up in surviving patients. Significantly more surviving patients had a final GH level below 2 μg/liter or below 5 μg/liter compared with the deceased group. There was a trend for surviving patients to have a lower serum IGF-I SD score at last follow-up than that seen in the deceased group, but this did not reach statistical significance.

The influence on mortality of reducing the serum GH to levels below 1 μg/liter, below 2 μg/liter, and below 5 μg/liter at last follow-up is shown by Kaplan-Meier analysis in

TABLE 1. Causes of death in the patient group (n = 72)

Cause of death	n	%	% expected[a]
Cardiovascular	36	50	32
Myocardial infarct	33		
Cardiomyopathy	1		
Rheumatic heart disease	1		
Bowel ischemia	1		
Cerebrovascular	8	11	9
Malignancy	17	24	26
Colon	8		
Breast	2		
Melanoma	1		
Mesothelioma	1		
Stomach	1		
Pancreas	1		
Chondrosarcoma	1		
Lymphoma	1		
Cerebral glioma	1		
Respiratory	2		
Progressive adenoma invasion	2		
Other	7		
Lactic acidosis	1		
Fractured femur	1		
Appendix abscess	1		
Traffic accident	1		
Hypocortisol crisis	1		
Unknown	2		

[a] From New Zealand Mortality Statistics 1996.

TABLE 2. Clinical features in patients with acromegaly according to survival status

Variable	Surviving patients (n = 136)		Deceased patients (n = 72)	
	At diagnosis	At last follow-up	At diagnosis	At last follow-up
Age (yr, mean ± SD)	39 ± 13	53 ± 1.2	48 ± 12	62 ± 2
Sex (% male)	63		52	
Current smokers, % (no. known)	44 (99)[a]	17 (117)[a]	46 (13)	29 (14)
Hypertension, % (no. known)	38 (88)[a]	43 (112)[b]	95 (38)[a]	88 (32)[b]
Diabetes, % (no. known)	22 (88)[c]	15 (102)[d]	61 (23)[c]	59 (17)[d]
Arthritis, % (no. known)	53 (104)[a]	58 (108)[c]	87 (39)[a]	87 (23)[c]
Tumor size (% macroadenomas)	82		88	
Hypopituitary at follow-up[e]		58		87[c]
Delay before diagnosis (yr ± SD)	7 ± 6		10 ± 7	

[a] $P < 0.001$ between groups.
[b] $P < 0.001$ between groups.
[c] $P < 0.01$ between groups.
[d] $P < 0.005$ between groups.
[e] Two or more axes deficient.

TABLE 3. Biochemical data in patients with acromegaly according to survival

Variable	All patients	Surviving patients		Deceased patients	
		At diagnosis	At last follow-up	At diagnosis	At last follow-up
GH (μg/liter)		50.3 ± 114 (138)	6.6 ± 21 (135)	60.5 ± 100 (62)	27.8 ± 101[a] (63)
GH <5 μg/liter at last follow-up (%)	75		83		58[a]
GH <2 μg/liter at last follow-up (%)	57		67		35[b]
GH <1 μg/liter at last follow-up (%)	37		44		22
IGF-I SD score[c]		10.8 ± 5 (68)	1.8 ± 3.7 (127)	10 ± 3 (10)	3 ± 3.1 (26)
IGF-I SD score below zero at last follow-up (%)	33		26		53
IGF-I normal or low at last follow-up (%)	54		54		53

Values are the mean ± SD with the number of subjects in *parentheses*.
[a] $P < 0.001$ compared with surviving group.
[b] $P < 0.01$ compared with surviving group.
[c] IGF-I measurements were available only after 1983 (n = 86 at diagnosis; n = 153 at last follow-up).

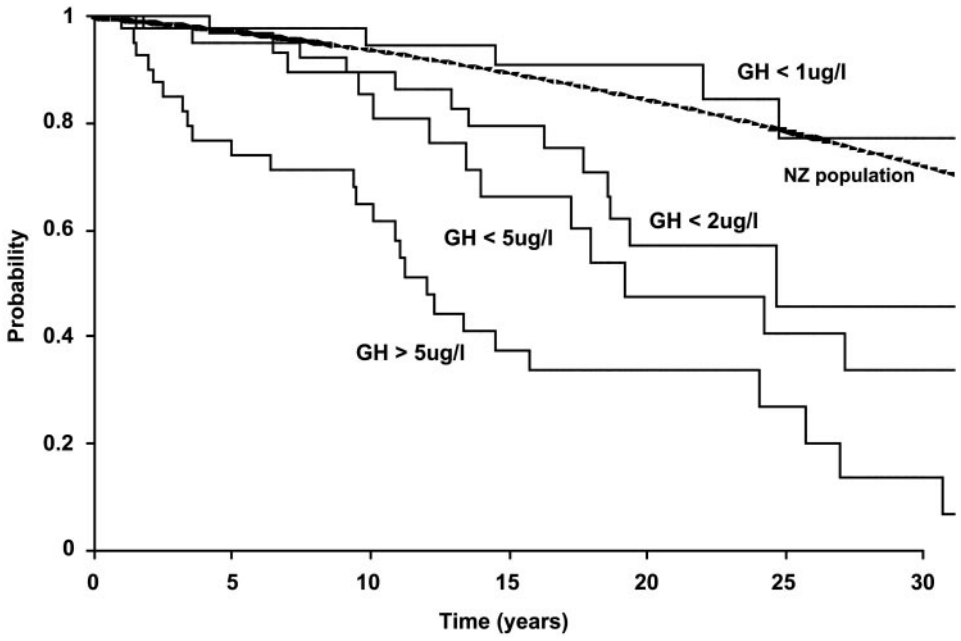

FIG. 1. Probability of survival in acromegaly according to serum GH concentration at last review after treatment (curves different at $P < 0.0001$, by log rank). The *dotted line* represents the probability of survival for the New Zealand population.

Fig. 1. The effect on mortality of reducing serum IGF-I to normal levels is shown in Fig. 2. Those with GH levels less than 1 μg/liter and those with IGF-I in the normal or subnormal range (SD score <2) had survival curves similar to those of the general New Zealand population. The observed to expected mortality ratio (O/E ratio) according to level of GH or IGF-I at last follow-up is shown in Fig. 3. Mortality in the respective subgroups increased steadily as final GH rose from 1 to 5 μg/liter (Fig. 3A and Table 4) and as IGF-I SD score rose from below zero (lower than the middle of the normal range) to elevated levels (Fig. 3B). Those with posttreatment serum IGF-I within the normal range (SD score, <2) appeared

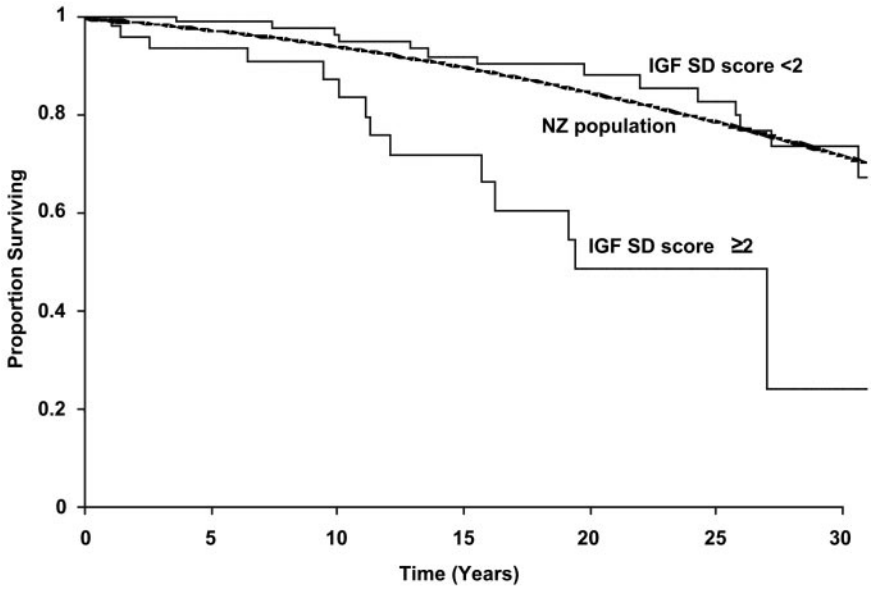

FIG. 2. Probability of survival in acromegaly according to serum IGF-I concentration (expressed as SD score) at last review. See Fig. 1 for details. $P < 0.001$.

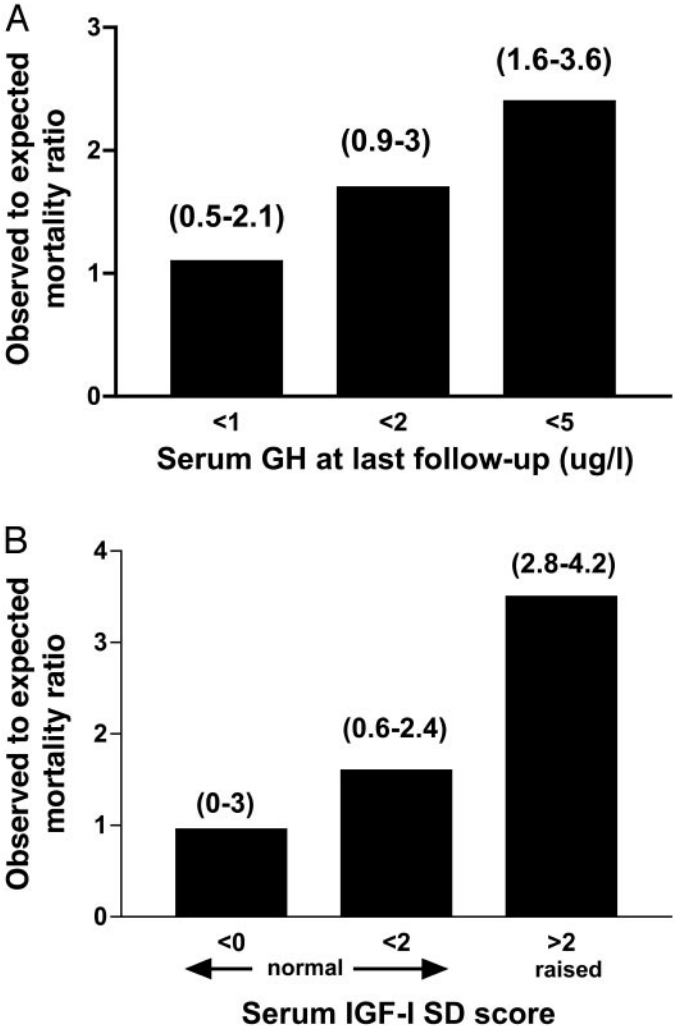

FIG. 3. Mortality according to serum GH and IGF-I at last follow-up. A, Influence of GH. B, Influence of IGF-I. *Parentheses* indicate 95% confidence limits.

TABLE 4. Mortality according to serum GH at last follow-up

	GH (μg/liter) at last follow-up			
	<1	1–2	2–5	>5
n	73	38	36	48
n dead	13	8	14	25
% dead	18	21	39	52[a]
Mean age at death	56	57	52	58

[a] $P < 0.005$ for trend.

to have a slightly elevated mortality (O/E ratio, 1.6), although the 95% confidence interval for the mortality estimate overlapped unity. The same result was obtained if those with subnormal IGF-I levels (SD score, below −2) were omitted from the analysis. Of those with normal or low IGF-I at last follow-up (n = 94), 14% died over the duration of the review, whereas 32% died of the 59 individuals with elevated IGF-I at last follow-up.

The influence of last known GH level on mortality from cardiovascular disease is shown according to Kaplan-Meier analysis in Fig. 4A, with similar data for IGF-I in Fig. 4B. Cardiovascular mortality was significantly increased in those with elevated IGF-I values or serum GH levels of 2 μg/liter or greater. Similar plots for mortality from cancer are shown in Fig. 5. Again, those with elevated GH or IGF-I values had significantly higher mortality from cancer than those with normal IGF-I measurements or GH levels below 2 μg/liter, although overall the cancer-related mortality was not greater than the observed mortality in the general population. It should be noted, however, that the mortality curves for the general population in Figs. 4 and 5 are not disease specific.

Multivariate analysis of predictors of mortality

The clinical and laboratory values in Tables 2 and 3 that significantly influenced mortality were tested by multivariate analysis for their ability to independently predict mortality. When both the last follow-up GH value and the last follow-up IGF-I measurement were included in the analysis,

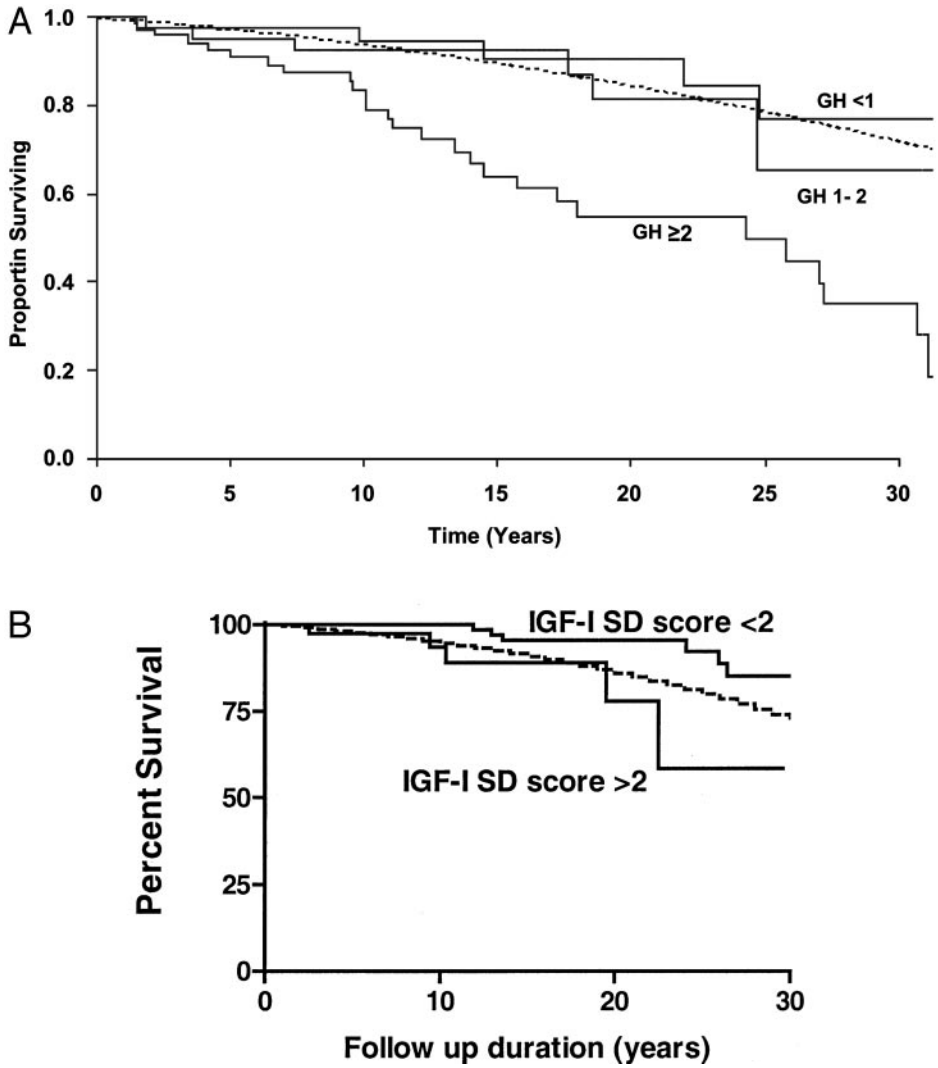

FIG. 4. Mortality from cardiovascular disease according to serum GH level at last follow-up (A) and last follow-up IGF-I level (B). The *dotted line* represents the probability of all-cause mortality in the general New Zealand population. $P < 0.02$ for GH curves; $P < 0.04$ for IGF-I curves.

the significant predictors of mortality were serum GH level at last follow-up, age, the presence of hypertension at last follow-up, and the estimated duration of the disorder before treatment (Table 5). Of these variables, serum GH at last follow-up was the most significant predictor of mortality, whereas serum IGF-I at last follow-up was not an independent predictor of mortality ($P = 0.2$) when both measurements were included in the analysis. As there is a close relationship between GH and IGF-I, the analysis was also performed with inclusion of either variable alone. When IGF-I was omitted, the last posttreatment GH remained the most significant predictor of mortality ($P = 0.001$), and when GH was omitted, the last follow-up serum IGF-I became the most significant predictor of mortality ($P = 0.02$). Neither the presence of pan-hypopituitarism nor the presence of any evidence of hypopituitarism was a significant independent predictor of mortality on multivariate analysis.

Discussion

Previous studies have indicated that patients with acromegaly have accelerated mortality (6–17). Analysis of these studies indicates an average 2-fold increase in the O/E ratio despite attempts at treatment of the condition. Previous reports from Auckland confirmed increased mortality in acromegalics compared with the general New Zealand population (12, 21). The present study extends these earlier observations with a larger cohort followed over a long time span and has explored the predictors and contributors to mortality in more detail, including assessment of the usefulness of IGF-I measurements.

As with our previous study, the death rate of patients after treatment for acromegaly appears to be increased. However, if serum GH is reduced to less than 1 μg/liter, the mortality rate becomes indistinguishable from that expected for the age-matched general community. At a GH level below 2 μg/liter, the confidence limits for observed mortality also overlap unity, although there is a significant trend for mortality to increase once GH levels exceed 1 μg/liter. Others have found mortality to be reduced to a range statistically indistinguishable from expected community levels when GH levels on random sampling were less than 5 mIU/liter (2.5 μg/liter) (13) or less than 5 μg/liter (15), or when the mean of five serum samples obtained over 1 d was less than 2.5 μg/liter (10). A "safe" level of GH for reduction of mortality

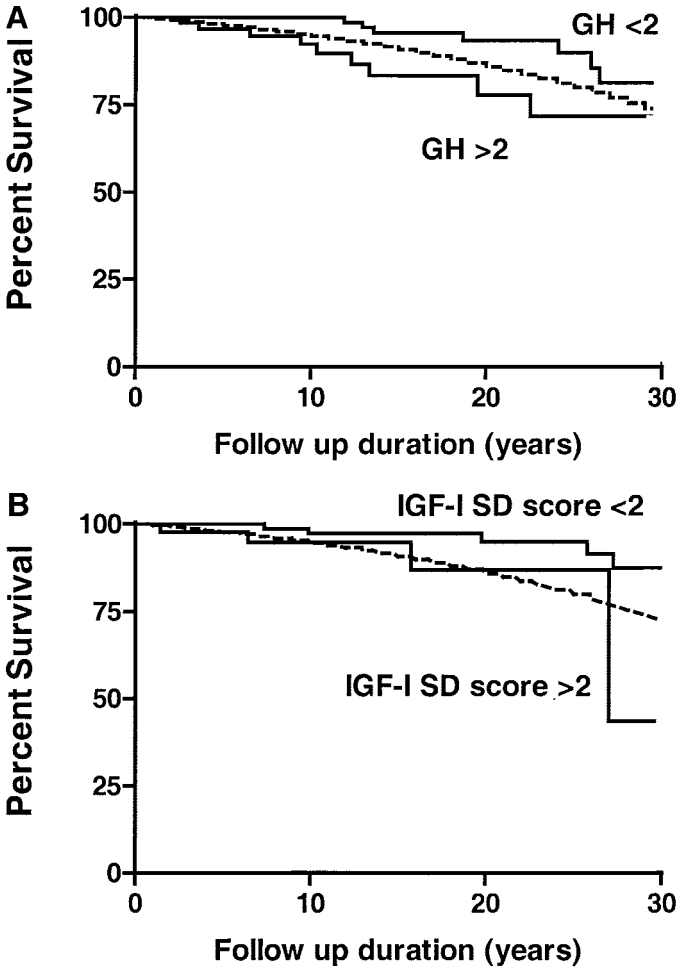

FIG. 5. Mortality from cancer according to serum GH level at last follow-up (A) and last follow-up IGF-I level (B). See Fig. 4 for details. $P < 0.03$ for GH curves; $P < 0.02$ for IGF-I curves.

TABLE 5. Factors predicting mortality in acromegaly (multivariate analysis, including both last known serum GH and IGF-I in the model)

Variable	χ^2	P
Last serum GH concentration	10.7	0.001
Age	5.4	0.006
Yr delay before diagnosis	4.4	0.035
Hypertension at last review	4.1	0.043

thus appears to be on the order of 1–2 μg/liter when measured by polyclonal RIA. It is likely that GH levels lower than this will be required to identify patients in remission when measurements are made using modern two-site GH assays. It is also uncertain whether there will be a similar threshold for posttreatment serum GH associated with restoration of quality of life and prevention of acromegalic complications in surviving patients.

There has recently been interest in the use of serum IGF-I as a criterion for the cure of acromegaly (16, 17, 22, 23). Reduction of IGF-I into the normal range in the present series was associated with return of mortality to the expected level in the general population, and this was particularly evident in those with IGF-I below the middle of the normal range. In multivariate analysis, serum IGF-I was not an independent prognostic indicator of mortality if GH was included in the analysis, but either variable was highly predictive of mortality when the other was excluded. This result could be anticipated from the close dependence of IGF-I on circulating GH levels. To determine whether there may be significant independent effects of either GH or IGF-I on mortality would require a much larger group for analysis.

The ability of IGF-I to predict mortality in the present study may have been weakened by several factors. Firstly, the analysis of the effect of IGF-I on mortality was restricted to a subset of 32 deceased patients for whom follow-up IGF-I measurements were available, so the power of the analysis to detect an IGF-I effect compared with a GH effect was correspondingly reduced. Secondly, several different IGF-I assays were used over the time period of the study, including 12% of individuals sampled using an assay that did not have age-adjusted normative data. It is likely that the use of a single IGF-I assay for all patients would have yielded a more precise estimate of the role of IGF in predicting mortality. Additionally, those with low IGF-I levels could represent a group with GH deficiency and panhypopituitarism who may have increased mortality (24–26), so including them in the group with IGF-I measurements below the upper limit of normal might have biased the analysis. However, there were only 15 patients in the study with IGF-I levels below normal, and when these individuals were excluded from the analysis, the results did not change significantly. It should be recalled that factors other than GH can influence IGF-I levels (27), so IGF-I may not always specifically reflect GH production, particularly in those with diabetes or nutritional abnormalities.

There was a higher percentage of hypopituitary patients in the group who died over the course of the study, consistent with the observed increase in mortality seen in hypopituitary subjects after treatment of nonhormone-secreting pituitary adenomas (24). However, hypopituitarism was not an independent predictor of mortality in multivariate analysis, suggesting a balance between the benefits of reduced GH levels and the possible adverse effects of hypopituitarism. Of note, there was a high degree of correlation between pituitary deficiency and serum GH levels below 2 μg/liter at last follow-up.

The causes of death in the present series were generally similar to those expected for the New Zealand population, but there appeared to be an excess of deaths from cardiovascular disease, which largely explained the increased mortality in the total group. Deaths from cardiovascular disease were significantly related to last known GH level and IGF-I SD score. Deaths from cancer were not significantly increased compared with the general population, but nonetheless, mortality from cancer appeared to relate to last GH level and final IGF-I SD score. There were insufficient numbers of individual cancers to determine whether there was increased mortality from any particular cancer type. These findings are in general agreement with those of Orme *et al.* (13), who identified increased cardiovascular mortality in a large co-

hort of acromegalic subjects and also identified an increased death rate from colon cancer.

The majority of patients in this series received pituitary radiation as part of their treatment, either as fractionated external beam radiotherapy or by direct pituitary implantation of radionuclide, and this is likely to have contributed to the development of hypopituitarism in the treated group. In addition, pituitary irradiation may increase the likelihood of cerebrovascular disease (28), although not all studies have confirmed this possibility (29), and in the present series death from stroke did not appear increased to a major degree compared with the general population. There were no cases of intracranial tumor arising as a late consequence of radiotherapy.

In this series the presence of hypertension at last follow-up was an independent predictor of mortality. This observation emphasizes the importance of treatment of hypertension (and probably other treatable comorbidities, such as diabetes and sleep apnea) in the management of acromegaly. The impact of aggressive treatment of these disorders on the overall mortality of the condition is not able to be evaluated from the present data, but is likely to be substantial.

The present study thus confirms that patients with acromegaly continue to have increased mortality despite treatment of the disorder, but mortality rates can be reduced to expected community levels by achieving serum GH concentrations less than 1–2 μg/liter and by normalization of serum IGF-I levels. The strengths of the study lie in the complete follow-up of the patient group and inclusion of information about the role of IGF-I measurements. Limitations of the study include the relatively small number of subjects available for assessment, GH measurement using insensitive polyclonal RIA (by comparison with more sensitive modern GH assays), and assessment of GH by random sampling, which may allow some degree of misclassification compared with multiple sampling (30) or sampling following glucose suppression. In addition, analysis of the role of IGF-I measurements was limited to 74% of the study group, so the true value of this measurement is still uncertain. Despite these shortcomings, the study provides results remarkably consistent with previous reports and should help to supply information about the goals of treatment for clinicians and patients. In particular, the IGF-I data may be of value for assessment of the response to treatment with pegvisomant (31), where IGF-I is the main biochemical indicator of the activity of the GH-IGF-I axis.

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