Mortality in Acromegaly: A Metaanalysis

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Context: Several studies have assessed mortality risk in patients treated for acromegaly. All studies found a mortality that was higher than expected for the general population, but most of these increases were not statistically significant. For this reason, it is not formally established whether mortality in acromegaly is different from the general population.

Objective: The objective of the study was to address the all-cause mortality risk in patients with acromegaly.

Design: The study was a metaanalysis.

Methods: Sixteen studies on mortality in patients with acromegaly were included. The principal outcome of the metaanalysis was the weighted average of the standardized mortality ratio (SMR) of all studies. In addition, we performed a subgroup analysis of studies in which more than 80% of the patients were treated by transsphenoidal approach.

Results: The weighted mean of the SMR from all 16 studies was 1.72 (95% confidence interval 1.62–1.83). In studies with transsphenoidal surgery as the primary therapy, the weighted mean of the SMR was 1.32 (95% confidence interval 1.12–1.56).

Conclusions: This metaanalysis shows increased all-cause mortality in acromegalic patients, compared with the general population, even after transsphenoidal surgery. ***(J Clin Endocrinol Metab* 93: 61–67, 2008)**

Acromegaly is a disorder characterized by autonomous overproduction of GH caused by a GH-producing pituitary adenoma. Acromegaly is a rare disorder, with an estimated incidence of 4 per million per year (1). GH excess is associated with pathological conditions such as hypertension, myocardial hypertrophy, diastolic dysfunction, insulin resistance, sleep apnea, and ventilatory dysfunction (2–4). In addition to these disease-specific conditions, mass effects of the pituitary tumor can lead to hypopituitarism and visual field defects.

Many studies have assessed mortality risk in patients treated for acromegaly. In older reports, mortality in acromegaly was clearly increased in comparison with the general population (5–7). These studies have stimulated the search for optimal treatment of acromegaly to reduce this excess mortality. Initially, radiotherapy was a favored treatment (6, 7), but a substantial proportion of the patients did not receive any treatment (7, 8). Subsequently, in the 1970s, microsurgical transsphenoidal techniques were introduced. In more recent articles on acromegaly, most patients were treated by transsphenoidal surgery. Since the 1980s, somatostatin analogs were added when transsphenoidal surgery was not curative (1, 9–13), leading to improved outcome (4). All studies found a mortality that was higher than expected for the general population, but most of these increases were not statistically significant. However, the number of patients was relatively small in many of the studies, which resulted in statistically imprecise estimations of mortality with large confidence intervals. For this reason, it is not formally established whether mortality in patients treated for acromegaly is different from the general population. To address the issue of mortality risk, we conducted a metaanalysis on all-cause mortality risk in patients

Abbreviations: CI, Confidence interval; SMR, standardized mortality ratio.

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with acromegaly. Additionally, we aimed to quantify the decrease in mortality that accompanied the implementation of newer treatment modalities.

Materials and Methods

Eligibility criteria

The all-cause standardized mortality ratio (SMR) was chosen as the principal measure of outcome. Studies reporting an all cause standardized mortality ratio in patients with acromegaly were eligible for inclusion in this metaanalysis. Studies reporting the SMR for subgroups only were included if we were able to extract the number of observed and expected deaths for the whole study population. Studies reporting only cause-specific SMR without certainty about the total number of observed *vs.* expected deaths as well as studies reporting mortality rates without a comparison with the general population were not included in this metaanalysis. Also, studies in which the mortality comparison between patients and the general population was depicted only in a figure could not be included.

Search strategy

We searched Medline, Embase, Web of Science, and the Cochrane Library for studies reporting standardized mortality ratios in patients with acromegaly. Searches were performed using the following search strategy: (acromegaly or acromegal* or inappropriate GH secretion syndrome or inappropriate GH secretion syndrome or somatotropin hypersecretion syndrome or somatotropin hypersecretion syndromes) and (mortality or mortalit* or standardized mortality ratio or standardized mortality ratio or survival rate). Searches were performed in June 2006. In addition, the references of relevant articles were checked for additional articles. Abstracts of meetings and unpublished results were not included in the analysis.

Data review and data analysis

Data extraction and eligibility was assessed by two independent investigators (O.M.D. and N.R.B.). Inconsistencies in data extraction were resolved by consensus.

The SMR was chosen as the principal measure of outcome. The SMR, defined as the ratio of the observed deaths in the group of acromegaly patients, divided by the expected deaths, was extracted from all articles. If no all-cause SMR was reported, the SMR was recalculated wherever possible on the basis of the sum of the observed deaths for several cause-specific SMRs, divided by the sum of the expected deaths. The SE of the SMR was calculated by a shortcut method proposed by Vandenbroucke (14). The principal outcome of the metaanalysis was the weighted average of the SMR. The SMR of the individual studies was weighted according to the inverse of the squared SE of the SMR. Additionally, we performed a subgroup analysis of studies in which more 80% of the patients was treated by transsphenoidal approach. A second subgroup analysis was performed to estimate the SMR for patients considered cured after initial surgical treatment.

Metaregression analysis was performed by two weighted regression models. The SMR of the individual studies was weighted according to the inverse of the squared SE of the SMR. The first model aimed to estimate the difference between old and new treatment modalities with respect to mortality. We divided the studies into two groups, according to year of publication: studies published before 1995 and studies published form 1995 onward. The reason for this division is that the year of publication is a marker of both treatment modalities and cure criteria. In older studies radiotherapy was a favored treatment (6, 7), and a substantial proportion of the patients received no treatment (7, 8). In more recent articles, the majority of patients was treated by transsphenoidal surgery (1, 9–13), with improved cure rates (4). In addition to treatment modalities, cure criteria have also evolved over years. Whereas random GH levels of less than 5 μg/liter were the criterion for cure in older studies, in recent years stricter criteria for cure were applied (random GH < 2.5 μg/liter). This is important, because cure criteria determine postoperative treatment strategies and stricter cure criteria lead to additional treatments at lower levels of GH.

A second exploratory metaregression model was performed to estimate the theoretical SMR associated with a theoretical cure rate of 100% of all acromegaly patients. For this purpose we included studies in which data on the percentage of patients considered cured after multimodality treatment were available. The outcome of this metaregression was obtained by setting the cure rate at 100% in the regression model and calculating the associated SMR.

The I^2 test was used to check for quantitative heterogeneity (15). This measures the proportion of inconsistency between the studies that cannot be explained by chance alone. Review manager 4.2 from the Cochrane's collaboration was used for analysis of the data.

Results

Literature search

We identified 493 studies by search in Medline, Embase, Web of Science, and the Cochrane Library (Table 1). We excluded 437 papers on the basis of title and abstract. Of the 56 potentially relevant papers retrieved for more detailed assessment, 35 could be excluded from further analysis because these studies did not contain original data on mortality in acromegaly. Additionally, four studies with data on all-cause mortality in acromegaly were excluded because SMR was not a principal outcome (16–19). One study was included after a review of references of other articles (20).

In 18 studies on patients with acromegaly, SMRs or observed to expected ratios were reported (1, 6–13, 20–27). In the studies from Alexander *et al.* (5), Nabarro (23), Wright *et al.* (7), Abosch *et al.* (9), and Beauregard *et al.* (11), numbers of observed and expected deaths were reported. We recalculated the SMR based on the sum of the observed and the expected deaths of the subgroups. The studies from Rajasoorya *et al.* (27) and Bengtsson *et al.* (26) were not included in the present analysis because the comparison of all-cause mortality between acromegalic patients and an age-matched general population was provided only in a figure, precluding calculation of the total number of expected deaths. Therefore, a total of 16 studies were included in this metaanalysis (Fig. 1).

Study characteristics

Details of these 16 included studies are summarized in Table 1. Studies on SMR in acromegaly were published between 1970 and 2005, and the number of included patients ranged from 74 to 1362. This long period of time also reflects the difference in initial treatment modalities and cure criteria. In studies published before 1995, not all patients with active acromegaly received treatment (6–8). Moreover, radiotherapy was often used as the primary therapy (6, 7). In studies published from 1995 onward, the vast majority of patients was primarily treated by transsphenoidal surgery, with the exception of the study from Ayuk *et al.* (21). However, in the studies from Shimatsu *et al.* (20) and Orme *et al.* (24), both published after 1995, no data on initial treatment were provided.

TABLE 1. Studies on SMRs in acromegaly

Author	Year of publication	Study period	No. of patients	SMR for all-cause mortality (O/E)	Initial treatment	Criteria for cure (random GH and after OGTT)[a]
Wright *et al.* (7)	1970	1937 to 1967	194	1.89 (54/28.5)	Radiotherapy, 19% Isotope implantation, 23% Surgery, 6%; multimodality treatment, 24%; no treatment, 24%	ND
Alexander (5)	1980	1960 to 1971	164	3.31 (45/13.6)	ND	ND
Nabarro (23)	1987	1963 to 1983	256	1.26 (47/37.2)	TS surgery, 47%	Random, <5 μg/liter
Etxabe *et al.* (8)	1993	1970 to 1989	74	3.23 (10/3.1)	TS surgery, 77% Medication, 12% No treatment, 11%	Random, <5 μg/liter
Bates *et al.* (6)	1993	1967 to 1991	79	2.63 (28/10.44)	Radiotherapy, 67% Surgery, 9%; multimodality treatment, 12%; medication, 5%; no treatment 8%; radioactive implants 4%	Random, <5 μg/liter
Orme *et al.* (24)	1998	ND	1362	1.60 (366/228.8)	ND	ND
Swearingen *et al.* (13)	1998	1978 to 1996	149	1.16 (12/10.3)	TS surgery, 100%	Random, <2.5 μg/liter[b] After OGTT, <2 μg/liter
Abosch *et al.* (9)	1998	1974 to 1992	214	1.28 (29/22.7)	TS surgery, 100%	Random, <5 μg/liter
Shimatsu *et al.* (20)	1998	?-1993	979	2.1 (84/40)	ND	ND
Beauregard *et al.* (11)	2003	1970 to 1999	103	2.14 (18/8.4)	TS surgery, 100%	Random, <2.5 μg/liter OGTT, <1 μg/liter
Arita *et al.* (10)	2003	1977 to 2000	154	1.17 (11/9.4)	TS surgery, 99% TC surgery, 1%	Random, <5 μg/liter
Biermasz *et al.* (12)	2004	1977 to 2002	164	1.33 (28/21.1)	TS surgery, 100%	Random, <2.5 μg/liter
Holdaway *et al.* (22)	2004	1964 to 2000	208	2.7 (72/26.7)	TC surgery, 14% TS surgery, 68% Radioactive implants, 17%; postoperative radiotherapy, 69%	ND
Ayuk *et al.* (21)	2004	1990 to 2001	419	1.26 (95/75.5)	TS surgery, 33% Radiotherapy, 22% Combined radiotherapy and surgery, 29%; medication 17%	Random, <2 μg/liter
Trepp *et al.* (25)	2005	1971 to 2003	94	1.34 (13/9.7)	TS surgery, 93% Radiotherapy, 3%; medication, 3%	Random, <2.5 μg/liter OGTT, <1.0 μg/liter
Kauppinen-Makelin *et al.* (1)	2005	1980 to 1999	334	1.16 (56/48.3)	TS surgery, >80%[c]	Random, <2.5 μg/liter

ND, No data; O/E, observed/expected; TS, transsphenoidal; OGTT, oral glucose tolerance test.

[a] Especially in more recent studies, besides GH, a normal IGF-I was also used as a criterium for cure.

[b] In the early years, 5 μg/liter was the clinical used value.

[c] Data on initial therapy cannot be exactly abstracted from the article.

In all studies a SMR of more than 1 was reported, indicating increased mortality, although in six studies the 95% confidence interval (CI) did include 1.0 (1, 9, 10, 13, 25, 28). The reported SMRs ranged from 1.16 (1) to 3.31 (5). Two studies reported an SMR higher than 3, in three studies the reported SMR ranged between 2 and 3, and in the majority of studies, the reported SMR was between 1 and 2.

Metaanalysis (Figs. 2 and 3)

The weighted mean of the SMR from all 16 studies was 1.72 (95% CI 1.62–1.83), which reflects a 72% increase in mortality in patients with acromegaly compared with the general population (Fig. 2). The I^2 test revealed considerable heterogeneity between the study outcomes: the percentage of to-

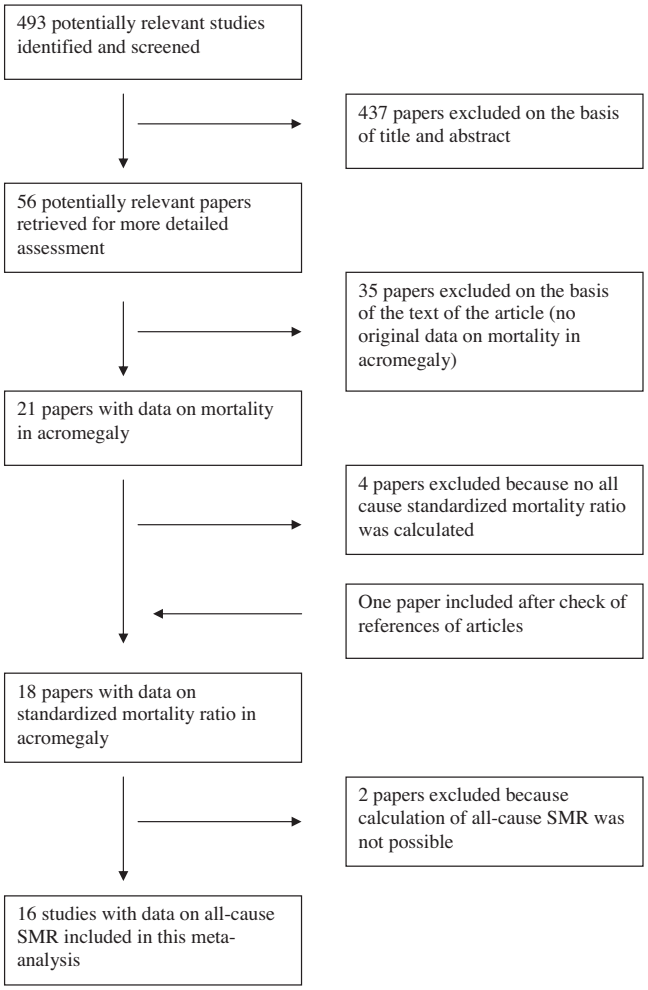

FIG. 1. Summary of study assessment and exclusion stages.

tal variation across the studies not due to chance alone was 80.6%.

Because the study from Orme *et al.* (24) included patients throughout the United Kingdom, it is possible that some patients were also included in the studies from Alexander *et al.* (5) and Wright *et al.* (7). For this reason we also performed the meta-analysis after exclusion of the studies from Alexander *et al.* (5) and Wright *et al.* (7). The weighted mean SMR from this analysis including 14 studies was 1.66 (95% CI 1.55–1.77). The I^2 test again revealed considerable heterogeneity among the 14 study outcomes with a percentage of total variation across the studies not due to chance of 76.7%.

If we included studies in the analysis with only transsphenoidal surgery as the primary therapy in more 80% of patients (1, 9–13), the weighted mean of the SMR was 1.32 (95% CI 1.12–1.56), which still is a 32% increased mortality, compared with the general population (Fig. 3). The I^2 test revealed no heterogeneity in this subgroup (0%).

In three studies data for patients considered to be cured based on postoperative GH levels and IGF-I levels after initial surgical treatment were available (9, 12, 13), and in one study (10) the SMR was calculated according to postoperative GH levels. These four studies were combined to assess the SMR associated with potential curation after initial surgery. Other studies in which data were available only according to the GH or IGF-I values at last follow-up (or remission status at last follow-up) were not included in this subgroup analysis because they cannot shed light on the prognosis after potentially curative surgery. The weighted mean SMR of these four studies was 1.09 (95% CI 0.81–1.46). The I^2 test revealed no heterogeneity in this subgroup (0%).

Metaregression

The division in studies published before 1995 (5–8, 23) and studies published from 1995 onward (1, 9–13, 20–22, 24, 25) reflects differences in treatment modalities as well as cure criteria. We performed a metaregression in a model with the lnSMR as dependent variable and the publication period as independent variable. In studies published from 1995 onward (SMR 1.62), mortality was lower, compared with studies published before 1995 (SMR 2.11).

From six recent studies, data in the number of patients with GH values less than 2,5 μ/liter after multimodality treatment were available, which permitted us to calculate the percentage of patients considered cured after multimodality treatment (1, 12, 13, 21, 22, 25). We performed an exploratory metaregression in a model with the lnSMR as dependent variable and the fraction of cured patients as independent variable. This model predicts that every percentage increase in cure rate decreases the SMR (unstandardized $\beta = -0.857$). Calculated from this model, the estimated SMR in a theoretical situation of 100% biochemical cure was 1.1 (95% CI 0.2–5.4).

Discussion

In the present metaanalysis, we found an overall 72% increase in mortality in acromegaly, compared with the general population, when all published data on SMRs were used. A metaregression pointed toward improved survival in more recent studies, presumably due to modern treatment modalities and more strictly defined cure criteria. In the present metaanalysis, transsphenoidal surgery, which is effective in controlling biochemical GH excess in 60–80% of the patients, is still associated with a significant increased mortality of 32%. Whether there is a surplus mortality in comparison with the general population when patients are considered cured cannot be reliably estimated from these data.

The disadvantage of the pooled estimate of all studies is that it is composed of studies that differ in several important aspects. The differences between these studies are reflected in the large heterogeneity that we found when pooling the SMRs of all 16 studies, pointing toward the need for exploring the reasons of the differences between the studies. This heterogeneity can be explained by differences as well as changes in treatment modalities and the criteria used to define biochemical control of the disease. In older studies radiotherapy was a favored treatment (6, 7), whereas a substantial proportion of the patients was not treated at all (7, 8). In the most recent articles, the majority of patients was treated by transsphenoidal surgery (1, 9–13). An additional important tool in the treatment of acromegaly was the introduction of somatostatin analogs in the mid-1980s, which led to remission in more patients. In addition to changes in time in

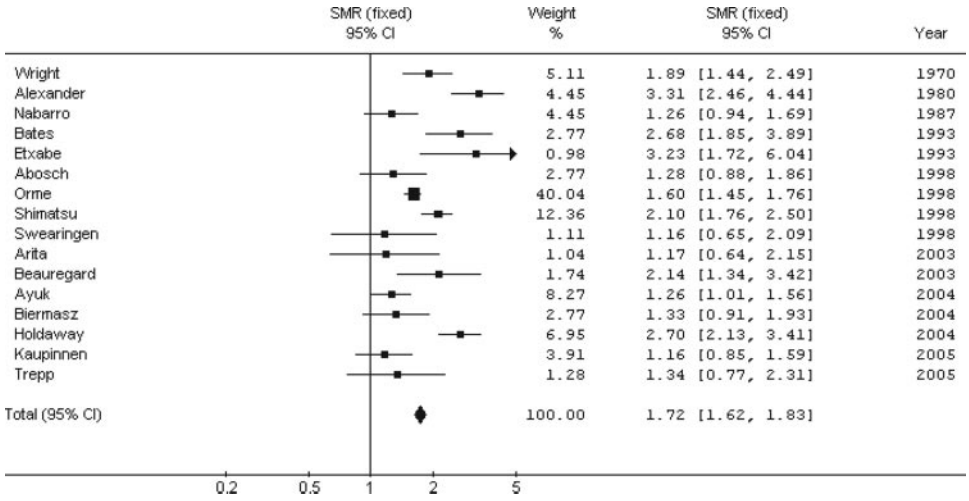

FIG 2. Metaanalysis of SMRs in acromegaly.

treatment modalities, differences between studies with respect to criteria for biochemical cure are important because these criteria determine the postoperative treatment strategies. Although random GH levels less than 5 μg/liter was the criterion for cure in older studies, in recent years stricter criteria for cure were applied (random GH $<$ 2.5 μg/liter and normal IGF-I levels). A limitation of the comparison of GH levels between different studies might be that the assays differ between studies and even within studies. In papers reporting SMRs for different levels of posttreatment GH and IGF-I, the lowest mortality ratios were found in patients with the lowest posttreatment GH and IGF-I levels (6, 21, 22, 24). This indicates that criteria for biochemical cure are a major determinant of mortality in acromegaly. No heterogeneity was found between the studies in which the vast majority of patients was treated by transsphenoidal surgery, reflecting homogeneity with respect to treatment modalities as well as cure criteria and therefore outcome.

Metaregression showed that mortality ratios in studies published before 1995 was higher than mortality ratios in studies published from 1995 onward. This difference reflects that newer treatment strategies are accompanied by a better outcome with respect to mortality. Nevertheless, in all recent studies, mortality ratios were still slightly increased. However, the increases in each study were accompanied by broad confidence intervals and therefore not statistically significant (1, 10, 12, 25). In contrast to these individual studies, we found a statistically significant increase in mortality after transsphenoidal surgery for acromegaly. The explanation may be that transsphenoidal surgery is able to control disease activity in only 60–80% of the patients. In the period that was covered by most studies, only radiotherapy was available as additional treatment, which controls GH excess only after many years. Therefore, this excess mortality in studies using transsphenoidal surgery as main treatment may be related to a relevant proportion of patients with prolonged postoperative disease activity.

Currently in an increasing number of patients, somatostatin analogs are chosen as primary therapy. Mortality data in patients primarily treated with somatostatin analogs are not yet available. Therefore, it is still unclear whether this treatment modality is accompanied by a further decrease in mortality. It will take many years to collect sufficient data on (primary) medical therapy with somatostatin analogs to draw conclusions on the effect on mortality. The same holds true for treatment with pegvisomant, a GH receptor antagonist, which can be administrated alone or in combination with a somatostatin analog (4).

It remains uncertain whether there is still a slightly increased mortality after biochemical control/cure of acromegaly. We included two estimates in the present analysis. One estimate is based on four studies in which postoperative cure rates were available and which showed a 9% increase in mortality in patients considered cured after transsphenoidal surgery. The other estimate was extrapolated from a regression model using the percentage of cured patients, which showed a 10% increase in mortality when the cure rate was set to be 100%. These two

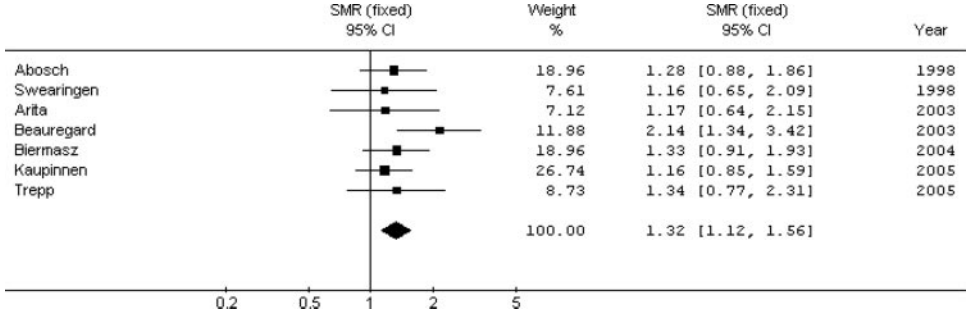

FIG. 3. Metaanalysis on SMRs in studies in which more than 80% of the acromegalic patients had been treated by transsphenoidal surgery.

analyses complement each other because the first is based only on data from cured patients and the second on the percentage cured in each individual study. However, both estimates had wide confidence intervals. In principle, the wide confidence intervals around these estimates are compatible with a decreased mortality (an SMR < 1) after curation, which seems unlikely. Also, it seems unlikely that the SMR in cured patients is higher than the SMR in all patients after transsphenoidal surgery (which was 1.32). Therefore, the question remains about the credibility of a 10% residual mortality, even in patients considered cured. The results from the exploratory metaregression have to be interpreted with caution for several reasons. The analysis is based on small number of studies. Besides, we used a linear model on the log scale, which might not represent the true relationship between cure rate and mortality, and we extrapolated the cure rate to a percentage (100%) that is extrapolated and not observed. Moreover, this analysis did not take into account the effect of different treatment modalities on mortality. The direct estimates on the four studies that had separate data on the patients considered cured point to a similar residual mortality but concern a small number of patients in total, which is the cause of the wide confidence intervals. Still, a small increased mortality in acromegaly, even after curation, does not seem implausible, given our knowledge about the clinical course acromegaly and the effects of GH and IGF-I.

Several factors account for the increased mortality ratio in acromegaly. Contributors to the increased mortality risk in acromegaly in general are related to GH overproduction as well as factors related to treatment and to accompanying hypopituitarism. In patients with acromegaly, there is a diagnostic delay of several years between the onset of the disease and the time of diagnosis. Within this time frame, which can be as long as 35 yr (8, 23), the patient is exposed to GH overproduction. Disease duration is a predictor of mortality in acromegaly patients (29), underscoring the role of GH excess in increased mortality. Exposure to GH excess is associated with increased cardiovascular risk profile due to cardial hypertrophy, diastolic dysfunction, myocardial valve insufficiency, insulin resistance, dyslipidemia, and obesity (2, 30, 31). These conditions may contribute to increased cardiovascular and cerebrovascular mortality in acromegaly (9, 23, 26). The persistent effects of overexposure to GH in the patient's past, even after biochemical cure, cannot be completely reversed and may be one of the main reasons the calculation of a slightly increased mortality in a hypothetical situation with biochemical control in all patients makes sense. Although GH excess is associated with increased morbidity and mortality, the optimal GH and IGF-I values with respect to long-term mortality remain to be determined. Several studies have found that the lowest levels of GH are associated with the lowest mortality rates (6, 21, 22, 24). Moreover, in three studies, IGF-I concentrations were found to be related to mortality (12, 13, 22), although this was not confirmed in another study (21). These results have to be interpreted with caution because retrospectively chosen safe GH levels were not used for treatment decisions.

Several aspects of the treatment in acromegaly may also contribute to increased mortality. Transsphenoidal surgery is associated with a perioperative mortality of about approximately 0.9% (32, 33). Data on the effects of radiotherapy on long-term mortality are conflicting (6, 12, 21, 34). The present metaanalysis does not permit a conclusion of the role of radiotherapy in mortality excess for two reasons. First, there were no homogeneous cohorts in which the majority of patients were initially treated with radiotherapy, which would have enabled a comparison between radiotherapy and transsphenoidal operation. Second, radiotherapy has previously been used for persistent or recurrent disease, *i.e.* during the course of the disease. It was not possible to abstract data on radiotherapy for recurrent disease from the individual studies to perform a time-dependent analysis on the effect of radiotherapy on mortality. Moreover, it is difficult to isolate the effect of radiotherapy *per se* from persistent GH excess and possibly radiotherapy-induced hypopituitarism. Hypopituitarism, present in 10–40% of patients with acromegaly, is associated with increased mortality, despite optimal hormonal replacement therapy (34, 35).

How does the increased mortality risk have to be interpreted? As a matter of perspective, we can imagine a person aged from 50 to 55 yr old. Depending on exact age, comorbidity, and sex, the risk of dying within a year will be about 1%. If this same person develops acromegaly and is treated by transsphenoidal surgery for acromegaly, the mortality risk will be increased by 30%. The risk for dying within a year for this person will be about 1.3%.

In conclusion, this metaanalysis of mortality ratios in patients with acromegaly shows increased all-cause mortality, compared with the general population. Although the mortality risk has decreased due to modern treatment strategies, which include transsphenoidal surgery, there is still a 32% increased all-cause mortality risk in acromegaly. Whether newer treatment strategies in acromegaly are accompanied by a further improvement in survival requires further investigation. However, from our calculation as well as our knowledge of the morbidity associated with GH excess, it is to be expected that even a biochemical cure rate of 100% will not result in complete normalization of mortality rates. Whether a 100% cure rate is accompanied by a normalization of mortality cannot be determined with certainty on the present data.

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