ACTH Deficiency, Higher Doses of Hydrocortisone Replacement, and Radiotherapy Are Independent Predictors of Mortality in Patients with Acromegaly

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Context: A number of retrospective studies report that patients with acromegaly have increased morbidity and premature mortality, with standardized mortality ratios (SMR) of 1.3–3. Many patients with acromegaly develop hypopituitarism as a result of the pituitary adenoma itself or therapies such as surgery and radiotherapy. Pituitary radiotherapy and hypopituitarism have also been associated with an increased SMR.

Methods: Using the West Midlands Acromegaly database (n = 501; 275 female), we assessed the influence of prior radiotherapy and hypopituitarism (and replacement therapy) on mortality in patients with acromegaly. Median duration of follow-up was 14.0 yr (interquartile range, 7.9–21 yr).

Results: All-cause mortality was elevated [SMR, 1.7 (1.4, 2.0); $P < 0.001$]. On external analysis, prior radiotherapy, ACTH, and gonadotropin deficiency were associated with an elevated SMR [radiotherapy SMR, 2.1 (1.7–2.6); $P = 0.006$; ACTH deficiency SMR, 2.5 (1.9–3.2); $P < 0.0005$; and gonadotropin deficiency SMR, 2.1 (1.6–2.7); $P = 0.037$].

On internal analysis, the relative risk (RR) of mortality was increased in the radiotherapy [RR, 1.8 (1.2–2.8); $P = 0.008$] and ACTH-deficiency groups [RR, 1.7 (1.2–2.5); $P = 0.004$], but not in the gonadotropin- or TSH-deficiency groups. In the ACTH-deficient group, increased replacement doses of hydrocortisone greater than 25 mg/d were associated with increased mortality compared to lower doses.

Conclusions: Radiotherapy and ACTH deficiency are significantly associated with increased mortality in patients with acromegaly. In ACTH-deficient patients, a daily dose of more than 25 mg hydrocortisone is associated with increased mortality compared to lower doses. These results have important implications for the treatment of patients with acromegaly and also raise issues as to the optimum hydrocortisone treatment regimens for ACTH-deficient patients. **(*J Clin Endocrinol Metab* 94: 4216–4223, 2009)**

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Abbreviations: CI, Confidence interval; CVA, cerebrovascular accident; IQR, interquartile range; RR, relative risk; SMR, standardized mortality ratio.

Acromegaly is characterized by excess GH secretion and IGF-I concentrations, most commonly due to a pituitary adenoma. Several studies have reported an increased mortality in patients with acromegaly with standardized mortality ratios (SMRs) ranging between 1.3 and 3 (1–9). Several factors have been associated with this increased mortality, including elevated GH and IGF-I concentrations and radiotherapy. GH has been linked with excess mortality in a number of studies; decreasing GH levels reverses this increased mortality (1, 2, 6, 10). Some studies have also reported an improvement in mortality if IGF-I is normalized (4, 11), whereas others have not (1, 10). External beam conventional radiotherapy for acromegaly decreases GH to less than 2.5 μg/liter in 60% of patients after 10 yr and approximately 75–80% after 20 yr (12). However, in recent years external beam conventional pituitary radiotherapy has been associated with increased mortality in patients with both acromegaly and other pituitary disorders (1, 13). Hypopituitarism has also been associated with increased mortality, predominantly due to cardiovascular deaths (13, 14).

The dose of hydrocortisone replacement in patients with pituitary disease, which traditionally was 30 mg/d in divided doses, has been shown recently to be an overreplacement compared with cortisol production rates in healthy subjects (15, 16). In a recent study, Filipsson *et al.* (17) assessed the effect of ACTH deficiency and hydrocortisone dose in a large cohort of GH-deficient adults. Patients with ACTH deficiency receiving doses of hydrocortisone greater than or equal to 25 mg/d had an adverse metabolic profile compared with GH-deficient patients on no hydrocortisone replacement and those with ACTH deficiency on lower doses of hydrocortisone (17). Despite these changes in cardiovascular risk profile, there have to date been no studies reporting an increase in mortality associated with higher doses of hydrocortisone replacement in patients with ACTH deficiency. Given the above observations, the aims of our study were to assess the role of radiotherapy, hypopituitarism (in particular the effect of individual pituitary axis deficiency), and the effect of different doses of hydrocortisone replacement therapy on mortality in a large cohort of patients with acromegaly.

Patients and Methods

The West Midlands Acromegaly database was established in 1990, and on December 31, 2006, contained demographic and clinical details of 501 patients (275 female) 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. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1 μg/liter after oral glucose loading and in most cases an elevated IGF-I). All patients with samples showing elevated GH or IGF-I in the West Midlands Regional Endocrine Laboratory were flagged as potentially having acromegaly and were appropriately assessed; therefore, we feel that patient capture is good and there are no grounds to assume that selection bias is substantial. 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 and the Office of National Statistics.

A total of 128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone, and 104 received all three treatment modalities. A total of 143 received surgery and radiotherapy (of these, 104 patients also received medical therapy), 68 surgery and medical therapy, and 162 radiotherapy and medical therapy (of these, 102 also received surgery). In total, 237 received radiotherapy, 220 received conventional three-field radiotherapy with a median dose of 45 Gy [interquartile range (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 registered with the Office of National Statistics (ONS), and death certification data from the ONS were reviewed to obtain information relating to cause of death according to ICD-9 criteria. A total of 339 patients were alive on the exit date of the study, and 162 patients were deceased (data relating to radiotherapy and GH/IGF-I and mortality have been reviewed in 419 of these patients previously) (1).

Median age at diagnosis was 46.6 yr (IQR, 11.6–84.2) in the entire cohort, 44.2 yr (IQR, 34.6–53.7) in those who were still alive, and 53.8 yr (IQR, 44.6–61.8) in those who had died. Median duration of follow-up was 14.0 yr (IQR, 7.9–21) in the entire cohort, with a total of 7567 patient years, and there was no difference in duration of follow-up between those who are still alive and those who had died (14.2 yr and 13.8 yr, respectively).

In total, 178 patients had ACTH deficiency and received hydrocortisone therapy. The daily dose of hydrocortisone (HC) was 15 mg in 15 patients (taken as HC 10 mg/5 mg), 20 mg in 29 patients (five taken as HC 10 mg/5 mg/5 mg; 11 as HC 15 mg/5 mg; and 13 as HC 10 mg/10 mg), 25 mg in 14 patients (13 taken as HC 15 mg/10 mg; and one as HC 15 mg/5 mg/5 mg), and 30 mg in 115 patients (four taken as HC 10 mg/10 mg/10 mg; and 111 taken as HC 20 mg/10 mg); five patients received HC doses greater than 30 mg/d.

Endocrine evaluation

Serum GH levels were measured by an in-house RIA in a central laboratory as previously described (18) (the value in mIU/liter was divided by a conversion factor of 2 to obtain μg/liter). The limit of detection of the assay is 0.5 μg/liter, and the interassay coefficient of variation is 5.7% at 2 μg/liter, 4.3% at 3 μg/liter, 5.5% at 7.3 μg/liter, and 4.47% at 14.7 μg/liter. Data on GH levels during follow-up were available in 470 of 501 patients (93.8%). Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described (19). The limit of detection of the assay is 2.0 nmol/liter. The interassay coefficient of variation is 5.4–8.4% between 16 and 104 nmol/liter. IGF-I data were available on 409 of 501 patients (81.6%).

The presence or absence of hypopituitarism was defined by proven biochemical deficiency of at least one endocrine axis. The hypothalamic pituitary adrenal axis was deficient if the peak cortisol response to short synacthen testing was less than 550

nmol/liter (20) or less than 500 nmol/liter after insulin-induced hypoglycemia during an insulin stress test. The thyroid axis was deficient if the free T_4 concentration was below the local reference range, with an inappropriately low/normal TSH. Hypothalamic-pituitary gonadal dysfunction in males was diagnosed in the setting of a low serum testosterone and inappropriately low/normal gonadotropins. In females, hypothalamic-pituitary gonadal dysfunction was diagnosed in premenopausal females if the patient was amenorrheic (with normal prolactin levels) and in postmenopausal females if the FSH was inappropriately low (<35 IU/liter). The dose and duration of hydrocortisone, T_4, testosterone, and estrogen replacement were documented.

Statistical analysis

SMRs for overall mortality, cardiovascular, respiratory, and cerebrovascular deaths were calculated by using Stata statistical software (StataCorp, College Station, TX) (21). 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 whether patients were treated with radiotherapy; whether patients were ACTH-, TSH-, or gonadotropin-deficient; and whether patients were treated with hydrocortisone. The dose of hydrocortisone was treated as a time-dependent variable; *i.e.* if a patient was on a higher dose of hydrocortisone for any given period, then person-years at that level were contributed; however, if the dosage was reduced, person-years were added to the analysis for the lower dose category. Similarly, radiotherapy was assessed in a time-dependent fashion such that patients only entered the radiotherapy group for assessment of risk on the date they started radiotherapy. Most of the statistical modeling was internal because such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders.

Poisson regression

In an internal analysis, a multivariable Poisson regression model was used to calculate relative risk (RR) of mortality based on tumor size; treatment with radiotherapy; ACTH, TSH, or gonadotropin deficiency; and dose of hydrocortisone received, if applicable (22). Unless otherwise stated, RRs were adjusted for GH level, attained age, sex, calendar period, and period of follow-up. To assess the role of GH/IGF-I level on 11 β-hydroxysteroid dehydrogenase type 1 and mortality in patients on hydrocortisone therapy, an interaction term was added to the above model.

Results

Overall group

All-cause mortality was increased significantly in the overall group of patients compared with the general population [SMR 1.7 (1.4, 2.0); $P < 0.001$]. There was a significant increase in cardiovascular [SMR 1.9 (1.6, 2.4); $P < 0.001$], respiratory [SMR 1.8 (1.1, 2.8); $P = 0.01$], and cerebrovascular death [SMR 2.7 (1.9, 4.1); $P < 0.001$], but no increase in death due to cancer [SMR 1.2 (0.9, 1.7); $P = 0.26$] (Table 1). In the respiratory death category, 16 patients died from pneumonia and four from exacerbations of asthma/chronic obstructive pulmonary disease. There was a significant difference in mortality in patients with macroadenoma [SMR 1.9 (1.6, 2.3)] compared with microadenoma [SMR 1.0 (0.6, 1.7); $P = 0.021$]. On internal analysis having adjusted for GH level, sex, attained age, calendar period, period of follow-up, and pretreatment level of GH, there was also an increase in mortality associated with increased tumor size [microadenoma RR, 1; macroadenoma RR, 1.5 (0.9, 2.6); $P = 0.11$], although this was not significant.

TABLE 1. Cause of death in all patients (n = 501, deaths 162) compared to the general population

Cause of death	O	E	SMR (O/E)	95% CI	*P* value
All	162	95.9	1.7	1.4, 2.0	<0.001
Cancer	36	29.8	1.2	0.9, 1.7	0.26
Cardiovascular	77	39.5	1.9	1.6, 2.4	<0.001
Respiratory	20	11.2	1.8	1.1, 2.8	0.01
Cerebrovascular	25	9.1	2.7	1.9, 4.1	<0.001

O, Observed; E, expected.

The effect of pituitary irradiation on mortality

There was an increase in all-cause mortality in patients who had received radiotherapy compared with the general population: no radiotherapy [SMR 1.4 (1.1, 1.7)] compared with radiotherapy [SMR 2.1 (1.7, 2.6); $P = 0.006$] (Table 2). On internal analysis, correcting for GH level, sex, hypopituitarism, attained age, calendar period, period of follow-up, and pretreatment level of GH, radiotherapy was associated with a significantly increased RR of mortality [RR 1.8 (1.2–2.8); $P = 0.008$] (Table 2). Among those exposed to radiotherapy, there was a significantly increased risk of cerebrovascular death [SMR 4.1 (2.3, 6.6); $P = 0.034$] (Table 3); there was no significant increase in any other specific cause of death. Of the 90 deaths in the 237 patients exposed to radiotherapy, there were seven deaths (in 17 patients, 41.1%) in radiosurgery/yttrium implant groups

TABLE 2. Effect of radiotherapy on mortality in patients with acromegaly

Radiotherapy	SMR	RR	95% CI	*P* value
No	1.4		1.1, 1.7	
Yes	2.1		1.7, 2.6	0.006
No		1		
Yes		1.8	1.2, 2.8	0.008

External analysis is compared to the general population (SMR standardized for sex, attained age, and calendar period). Internal analysis is adjusted for GH level, sex, attained age, calendar period, hypopituitarism, period of follow-up, and pretreatment level of GH.

TABLE 3. Cause of death in acromegaly cohort divided according to radiotherapy exposure, standardized for sex, attained age, and calendar period

Cause of death	Radiotherapy	O	E	SMR (O/E)	95% CI	*P* value
All	No	72	52.9	1.4	1.1, 1.7	
	Yes	90	42.9	2.1	1.7, 2.6	0.006
Cancer	No	17	16.0	1.1	0.6, 1.7	
	Yes	19	13.8	1.4	0.8, 2.2	0.442
Cardiovascular	No	38	22.1	1.7	1.1, 2.4	
	Yes	39	17.4	2.2	1.6, 3.1	0.247
Respiratory	No	9	6.2	1.4	0.7, 2.7	
	Yes	11	5.0	2.2	1.1, 3.9	0.342
Cerebrovascular	No	9	5.2	1.7	0.8, 3.3	
	Yes	16	3.9	4.1	2.3, 6.6	0.034

P value reflects test of homogeneity in SMRs. O, Observed; E, expected.

compared with 83 deaths (in 220 patients, 37.7%) in the conventional radiotherapy group.

The effect of pituitary hormone deficiency on mortality

Patients with ACTH deficiency and gonadotropin deficiency had a significantly increased SMR, but patients with TSH deficiency did not (Table 4). However, on internal analysis, having adjusted for sex, attained age, calendar period, period of follow-up, and radiotherapy, only ACTH deficiency was associated with significantly increased mortality [RR 1.7 (1.2, 2.5); $P = 0.004$] (Table 5). There was no significant linear trend (P trend = 0.515) in RR of mortality with increasing number of pituitary hormone axis deficiency (Supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

The effect of hydrocortisone replacement dose on mortality

Increasing doses of hydrocortisone were associated with an increasing SMR (P for linear trend <0.001) (Table 6). On internal analysis, having adjusted for age, sex, calendar period, period of follow-up, and radiotherapy, there was a significant increase in RR of mortality in patients receiving hydrocortisone daily doses of between 25 and 30 mg [RR 1.6 (1.1, 2.4); $P = 0.014$] and hydrocortisone daily doses greater than 30 mg [RR 2.9 (1.4, 5.9); $P = 0.003$] (Table 6). On internal analysis, there was a significant association between an increasing dose of hydrocortisone and mortality as assessed by the likelihood ratio test for linear trend in relative risks ($P = 0.002$). The main cause of death in the higher dose hydrocortisone group was cardiovascular disease. In the group of patients who were ACTH replete, 26.2% of deaths were due to cardiovascular causes. In the overall group of ACTH-deficient patients, 31.6% of patients died from cardiovascular causes, and there was an increase in cardiovascular death with increasing hydrocortisone dose [HC dose >0 and ≤20 mg/d, 10% cardiovascular mortality; HC dose >20 and ≤25 mg/d, 33.3% cardiovascular mortality; HC dose >25 and ≤30 mg/d, 38.5% cardiovascular mortality; and HC >30 mg/d, 44.4% cardiovascular mortality].

When GH levels were included in the above model as an interaction term with hydrocortisone exposure to account

TABLE 4. Effect of pituitary axis deficiency of mortality compared to the general population, standardized for sex, attained age, and calendar period

Factor	O	E	SMR (O/E)	95% CI	*P* value
ACTH					
No	69	53.8	1.3	1.0, 1.6	
Yes	62	25.1	2.5	1.9, 3.2	<0.0005
TSH					
No	93	57.1	1.6	1.3, 2.0	
Yes	42	19.7	2.1	1.5, 2.9	0.15
Gonadotropins					
No	40	28.8	1.4	0.99, 1.9	
Yes	66	31.4	2.1	1.6, 2.7	0.037

O, Observed; E, expected.

TABLE 5. Internal analysis of the effect of pituitary axis deficiency of mortality, adjusted for radiotherapy, follow-up time, sex, attained age, and calendar year

	RR	95% CI	*P* value
ACTH			
Normal	1		
Deficient	1.7	1.2, 2.5	0.004
TSH			
Normal	1		
Deficient	1.0	0.7, 1.4	0.829
Gonadotropins			
Normal	1		
Deficient	1.2	0.8, 1.8	0.433

TABLE 6. Effect of increasing dose of hydrocortisone (HC) replacement on mortality in patients with acromegaly compared to the general population, standardized for sex, attained age, and calendar period

HC daily dose (mg)	SMR	RR	95% CI	*P* value
None	1.35		1.1, 1.7	0.006
<25	2.26		1.4, 3.7	0.0011
≥25	2.82		2.2, 3.7	<0.00001
None		1		
0 < HC ≤ 20		1.3	0.7, 2.6	0.439
20 < HC ≤ 25		1.4	0.6, 3.3	0.429
25 < HC ≤ 30		1.6	1.1, 2.4	0.014
HC > 30		2.9	1.4, 5.9	0.003

Linear trend in SMR of mortality with increasing dose of HC therapy, *P* value for linear trend <0.001. Internal analysis of the effect of increasing daily hydrocortisone replacement doses on mortality in patients with acromegaly is adjusted for sex, attained age, calendar period, period of follow-up, and radiotherapy. Likelihood Ratio Test for Linear Trend in RRs, $P = 0.002$.

for the possible effect of GH on glucocorticoid metabolism of 11 β-hydroxysteroid dehydrogenase type I, this interaction was not statistically significant ($P = 0.44$). This was repeated with IGF-I instead of GH, but the model did not converge due to lack of power.

Discussion

In a large cohort of patients with acromegaly, we have shown that ACTH deficiency, higher doses of hydrocortisone replacement therapy, and radiotherapy are independently associated with increased mortality. Conventional external beam radiotherapy in acromegaly decreases GH to less than 2.5 μg/liter in 60% of cases after 10 yr and 75–80% after 20 yr (12). However, it has been reported that pituitary radiotherapy is associated with a number of adverse events such as risk of secondary intracranial neoplasms (23), cognitive impairment (24), damage to the optic nerve (25, 26), hypopituitarism (27–29), increased risk of cerebrovascular disease (30, 31), and in some previous studies, increased mortality (1, 13).

Increased cerebrovascular disease and death have been reported in a number of studies after pituitary irradiation. In a series of 156 patients with nonfunctioning pituitary adenoma, increased cerebral infarction rates were found in patients administered higher doses of radiotherapy (31). In a study assessing the role of pituitary radiotherapy in the development of cerebrovascular accidents (CVAs) in 331 patients who received pituitary radiotherapy, it was reported that patients who received radiotherapy had a RR of CVA of 4.1 [confidence interval (CI), 3.6–4.7] compared with the general population (30). On multivariate analysis, the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared with biopsy or no operation, higher doses of radiotherapy, and an underlying diagnosis of acromegaly (30).

In a further study, Brada *et al.* (32) reported that cerebrovascular mortality was increased in patients who had received pituitary irradiation [accounting for 26% of all death (RR, 4.11; CI, 2.84–5.75)], with an even further increase in females compared with male patients (RR, 6.9 and 2.4, respectively; $P = 0.002$). Surgery may also play a role in the increased cerebrovascular mortality reported in this study because patients with prior surgery had an increase RR compared with those with no surgery or biopsy alone (radiotherapy RR, 5.19; surgery alone RR, 1.33; $P = 0.02$) (32).

We have previously shown an increased mortality in 419 patients, 211 of which were treated with radiotherapy for acromegaly in the West Midlands Cohort (1). In patients treated with radiotherapy, overall SMR was 1.58, with an SMR of 4.42 for cerebrovascular death. Similarly, the Finnish national acromegaly database study reported an increased mortality in patients who had received radiotherapy compared with the general population. In 116 of 334 patients treated with radiotherapy, mortality was increased (SMR, 1.69) compared with patients who did not receive radiotherapy (SMR, 0.94) (10).

Radiation leads to damage of both large and small vessels but has a predilection to smaller vessels (33). The vasculature is vulnerable because endothelial cells are radiosensitive, which leads to several ultrastructural changes (33) with resultant increased capillary permeability and intracellular edema that may be followed by platelet and fibrin thrombosis. Larger lesions in arterioles can also occur, leading to myointimal proliferation, foamy macrophage plaques, fibrinoid necrosis of the media or hyalinization of the media leading to narrowing of the vessel lumen (33). There is evidence that these changes may be clinically significant because in a large study of patients with Hodgkin's disease (n = 4665) who received irradiation to the heart, the RR of myocardial infarction was 2.56 times higher than patients who had just received chemotherapy (34).

More than 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiencies within the following decade (27–29). A number of studies have described increased mortality in patients with hypopituitarism compared with age- and sex-matched controls (13, 14, 35, 36). In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. In total, nearly 1900 patients have been included in these studies, and approximately 50% had radiotherapy; in two studies, radiotherapy was not associated with increased mortality (14, 35), and in the third study it was not possible to investigate the link between radiotherapy and mortality because nearly all patients had radiotherapy (36). In the largest series in the literature, Tomlinson *et al.* (13) reported that radiotherapy was associated with significantly increased mortality [SMR, 2.32 (1.7–3.14); $P = 0.004$] compared with the general cohort of patients with hypopituitarism [SMR, 1.87 (1.62–2.16)]. In particular, patients who had received radiotherapy had an elevated cerebrovascular risk [SMR, 4.36 (2.48–7.68); $P = 0.001$]. There is no clear answer to date regarding the causal relationship between hypopituitarism and mortality. In the study by Tomlinson *et al.* (13), only gonadotropin deficiency was associated with increased mortality (sex steroid replacement decreased mortality). Erfurth *et al.* (37) compared radiation regimens and duration of symptoms of hypopituitarism in 342 patients treated with surgery and radiotherapy. They found no significant difference between patients who had died from cerebrovascular disease and a matched cohort who had not died for a number of irradiation

parameters such as maximum absorbed dose, maximum biological equivalent dose, field size, and number of fractions. The only difference found was a longer duration of symptoms of hypopituitarism in the patients who had died from cerebrovascular causes. This led to the conclusion that untreated hormone deficiency may be more directly implicated in cerebrovascular mortality than radiotherapy *per se*. The findings of our study do not support this but rather suggest that both radiotherapy and ACTH deficiency were risk factors for mortality independent of each other.

Recent studies have suggested that patients with primary adrenal failure have an increased risk of mortality compared with the general population (38, 39). Increased cardiovascular event rate (RR, 2.56; CI, 2.18–2.99) has also been described in patients receiving high-dose glucocorticoids (prednisolone ≥7.5 mg/d) (40). However, the association between mortality and secondary adrenal insufficiency from ACTH deficiency is not well described.

In recent years, it has been reported that the cortisol production rate in normal subjects is less than was previously thought [Esteban *et al.* (15), normal cortisol production rate in young adults, 27.3 μmol/d (equivalent to 5.7 mg/m^2/d or approximately 9.9 mg/d); and Kerrigan *et al.* (16), total daily cortisol production rate, 5.7 ± 0.3 mg/m^2/d]. Traditionally, the daily dose of hydrocortisone was 30 mg/d, split into two doses (frequently, two thirds in the morning and one third in the evening); given the recent discovery of lower levels of cortisol production rates, this would lead to levels that were supraphysiological. Indeed, in the study by Esteban *et al.* (15), patients with Cushing's syndrome had daily cortisol production rates of 30.7 ± 9.3 mg/d. The bioavailability of orally administered hydrocortisone is approximately 95% (41, 42); therefore, 30 mg of hydrocortisone per day could achieve levels similar to those seen in patients with Cushing's syndrome, albeit with greater peaks and troughs, because the half-life of orally administered cortisol is only 90 min (43). A single morning dose of 15 mg hydrocortisone leads to supraphysiological serum cortisol concentrations 1–2 h after oral administration and a return to subphysiological or undetectable levels 6–8 h later (44, 45). Glucocorticoid replacement dose has effects on a number of clinical parameters including bone metabolism, glucose metabolism, cardiovascular function, and quality of life (46).

Current glucocorticoid replacement regimens cannot mimic the physiological circadian and ultradian rhythm of endogenous cortisol. There is evidence that continuous, prolonged exposure, compared with intermittent short exposure, to glucocorticoids may have different effects on a number of steroid-responsive enzymes and occupancy of the glucocorticoid receptor (46).

Circadian infusions of hydrocortisone can mimic the normal cortisol rhythm, resulting in beneficial effects in patients with Addison's disease and congenital adrenal hyperplasia (47); using these infusions, it was also possible to reduce the daily dose of hydrocortisone (48). These infusions are obviously cumbersome and not practical; however, over the last few years there has been a push to design orally active, delayed- or sustained-release formulations of hydrocortisone to aid the physiological replacement of hydrocortisone and ultimately to improve quality of life and side effect profiles in patients requiring lifelong glucocorticoid replacement (49).

Filipsson *et al.* (17) have described an adverse metabolic profile in a cohort of GH-deficient patients on higher doses of glucocorticoid replacement. They found that patients on hydrocortisone replacement had increased total cholesterol, triglycerides, waist circumference, and glycosylated hemoglobin compared with the ACTH-sufficient patients; all these factors are associated with increased cardiovascular morbidity. Importantly, subjects who had hydrocortisone-equivalent doses of less than 20 mg/d did not differ in metabolic endpoints compared with the ACTH-sufficient patients. However, when a hydrocortisone-equivalent dose of more than 20 mg/d was administered, patients had an adverse metabolic profile (17).

Acromegaly is associated with increased rates of hypertension and biventricular hypertrophy as well as metabolic complications such as impairment of glucose tolerance and lipid abnormalities (50). These abnormalities are also seen in patients with glucocorticoid excess in Cushing's syndrome (51), and one could speculate that in this study the increased mortality seen in patients receiving higher doses of hydrocortisone replacement therapy may be contributed to by the development of subclinical iatrogenic Cushing's syndrome in these patients. Indeed, patients with Cushing's disease have been reported to have a cardiovascular SMR of 5 (52), which is due to a combination of abnormalities in blood pressure, glucose and lipid metabolism, and coagulation system (51). Importantly, in a recent study, the length of disease was the only predictor of increased cardiovascular risk after multivariate analysis (51). Patients on higher doses of hydrocortisone replacement therapy are often exposed to elevated circulating cortisol levels (although not as severe as many patients with Cushing's syndrome) for many decades, which may explain the increased cardiovascular mortality we have reported in our patients on higher doses of hydrocortisone.

At a tissue level, active glucocorticoid availability to the glucocorticoid/ mineralocorticoid receptor is determined by the interconversion of hormonally active cortisol and inactive cortisone by isozymes of 11 β-hydroxysteroid dehydrogenase (53). Many authors have reported an interaction between the GH/IGF-I system and 11 β-hydroxysteroid dehydrogenase 1 both *in vivo* and *in vitro* (54). This

interaction may be clinically important because it suggests the appropriate dose of hydrocortisone for patients with controlled acromegaly may be lower than that for patients with active disease, although what the exact dose adjustment should be is unknown. However, in this study GH levels had no impact on the effect of mortality in patients on hydrocortisone therapy, but it must be remembered that this was not a physiological study to assess this, but rather an assessment to ensure that this phenomenon did not bias our results.

Regarding the predictive value of size of tumor and future mortality, although the increase in mortality in patients with macroadenomas was not statistically significant ($P = 0.11$), on internal analysis the RR was 1.5 (95% CI, 0.9–2.6), this should be interpreted cautiously because the nonsignificance may be related to sample size and the fact that adjusting for a number of variables may have decreased the power.

In conclusion, ACTH deficiency, higher doses of hydrocortisone, and radiotherapy are independently associated with increased mortality. Further work is needed to assess the relative roles of these risk factors in the premature mortality seen in patients with acromegaly and also to assess the relative importance of these risk factors compared with excess exposure to GH and IGF-I. This is the first study to show an increase in mortality in patients with ACTH deficiency on higher doses of hydrocortisone therapy. Further larger studies are required in patients with ACTH deficiency to assess the optimum therapy; however, our results do highlight the deleterious effects of higher doses of hydrocortisone replacement in these patients.

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