Mortality in acromegaly: a 20-year follow-up study

Elina Ritvonen¹, Eliisa Löyttyniemi², Pia Jaatinen^{3,4,5}, Tapani Ebeling^{6,7},
Leena Moilanen^{8,9}, Pirjo Nuutila^{10,11}, Ritva Kauppinen-Mäkelin¹² and
Camilla Schalin-Jäntti¹

¹Division of Endocrinology, Abdominal Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

²Department of Biostatistics, University of Turku, Turku, Finland

³School of Medicine, University of Tampere, Tampere, Finland

⁴Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

⁵Department of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

⁶University of Oulu, Oulu, Finland

⁷Oulu University Hospital, Oulu, Finland

⁸University of Eastern Finland, Kuopio, Finland

⁹Kuopio University Hospital, Kuopio, Finland

¹⁰Turku PET centre, University of Turku, Turku, Finland

¹¹Department of Endocrinology, Turku University Hospital, Turku, Finland

¹²Center of Internal Medicine and Rehabilitation, Jorvi Hospital, Helsinki University Hospital, Helsinki, Finland

Correspondence
should be addressed
to C Schalin-Jäntti
Email
camilla.schalin-jantti@hus.fi

Abstract

Objective: It is unclear whether mortality still is increased in acromegaly and whether there are gender-related differences. We dynamically assessed outcome during long-term follow-up in our nationwide cohort.

Patients and methods: We studied standardized mortality ratios (SMRs) relative to the general population and causes of death in acromegaly ($n=333$) compared with age- and gender-matched controls ($n=4995$).

Results: During 20 (0–33) years follow-up, 113 (34%) patients ($n=333$, 52% women) and 1334 (27%) controls ($n=4995$) died ($P=0.004$). SMR (1.9, 95% CI: 1.53–2.34, $P<0.001$) and all-cause mortality (OR 1.6, 95% CI: 1.2–2.2, $P<0.001$) were increased in acromegaly. Overall distribution of causes of death ($P<0.001$) differed between patients and controls but not cardiovascular (34% vs 33%) or cancer deaths (27% vs 27%). In acromegaly, but not in controls, causes of deaths shifted from 44% cardiovascular and 28% cancer deaths during the first decade, to 23% cardiovascular and 35% cancer deaths during the next two decades. In acromegaly, cancer deaths were mostly attributed to pancreatic adenocarcinoma ($n=5$), breast ($n=4$), lung ($n=3$) and colon ($n=3$) carcinoma. In acromegaly, men were younger than women at diagnosis (median 44.5 vs 50 years, $P<0.001$) and death (67 vs 76 years, $P=0.0015$). Compared with controls, women (36% vs 25%, $P<0.01$), but not men (31% vs 28%, $P=0.44$), had increased mortality. **Conclusions:** In acromegaly, men are younger at diagnosis and death than women. Compared with controls, mortality is increased during 20 years of follow-up, especially in women. Causes of deaths shift from predominantly cardiovascular to cancer deaths.

Key Words

- mortality
- functioning pituitary adenoma
- acromegaly

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Introduction

Excess growth hormone (GH) production in acromegaly leads to disadvantageous metabolic changes and comorbidities, such as hypertension, cardiovascular diseases, diabetes mellitus, respiratory system dysfunction and malignant neoplasms (Colao et al. 2004, Melmed 2006, Dekkers et al. 2008).

In studies published before 1995, acromegaly was reported to associate with two- to three-fold increases in mortality rates compared with the general population (Wright et al. 1970, Alexander et al. 1980, Rajasoorya et al. 1994). Initially, patients were often treated with radiotherapy (Wright et al. 1970, Bates et al. 1993). After the introduction of transsphenoidal surgery in the 1970s, somatostatin analogs in the 1980s and more stringent criteria for hormonal remission, more recent studies suggested improved survival in acromegaly and standardized mortality ratios (SMRs) between 1.10 and 1.70 (Swearingen et al. 1998, Ayuk et al. 2004, Holdaway et al. 2004, Mestron et al. 2004, Kauppinen-Makelin et al. 2005, Dekkers et al. 2008, Arosio et al. 2012). The most common causes of death have been cardiovascular diseases (Orme et al. 1998, Ayuk et al. 2004, Dekkers et al. 2008, Sherlock et al. 2010), malignancies (Orme et al. 1998, Holdaway et al. 2004, Sherlock et al. 2010, Arosio et al. 2012, Mercado et al. 2014) and, in some studies, respiratory system dysfunction (Wright et al. 1970, Orme et al. 1998, Sherlock et al. 2009). This is thought to reflect hormonally active disease or a long delay between the first symptoms and the diagnosis of acromegaly (Wright et al. 1970, Rajasoorya et al. 1994, Holdaway et al. 2008, Melmed 2009, Arosio et al. 2012, Colao et al. 2014). In addition, it has been suggested that hypopituitarism (Tomlinson et al. 2001, Ayuk et al. 2004, Sherlock et al. 2010, Arosio et al. 2012) and radiotherapy (Ayuk et al. 2004, Holdaway et al. 2004, Dekkers et al. 2008, Sherlock et al. 2009, 2010, Arosio et al. 2012, Mercado et al. 2014) may impair overall prognosis.

In 2005, we reported normal SMR (1.16, 95% CI 0.85–1.54) for our national acromegaly cohort comprising 334 patients diagnosed between 1980 and 1999, and excess mortality in those patients with basal serum GH concentration > 2.5 µg/L (Kauppinen-Makelin et al. 2005). The cut-off limit of 2.5 µg/L has been proposed in many studies (Rajasoorya et al. 1994, Holdaway et al. 2004, 2008), and most previous studies conclude that GH is the strongest prognostic factor in acromegaly (Rajasoorya et al. 1994, Orme et al. 1998, Ayuk et al. 2004, Holdaway et al. 2004, Dekkers et al. 2008, Sherlock et al. 2009).

In some studies, increased serum insulin-like growth factor 1 (IGF1) concentrations associated with mortality (Swearingen et al. 1998, Ayuk et al. 2004, Biermasz et al. 2004, Holdaway et al. 2004, Kauppinen-Makelin et al. 2005, Arosio et al. 2012, Mercado et al. 2014). In 2008, two meta-analyses on patients diagnosed between 1937 and 2000 concluded that mortality is increased in acromegaly, with a pooled SMR of 1.7, and that a random basal GH < 2.5 µg/L after treatment restores mortality rates to normal (Dekkers et al. 2008, Holdaway et al. 2008). Previously, we also observed that men are younger than women at diagnosis (Kauppinen-Makelin et al. 2005); however, most studies give the pooled mean age at diagnosis of acromegaly (Orme et al. 1998, Mestron et al. 2004, Colao et al. 2014). Overall, little is known about possible gender differences and mortality in acromegaly.

Uncontrolled acromegaly consistently increases the risk of colon cancer and thyroid cancer (Popovic et al. 1998, Gasperi et al. 2002, Colao et al. 2005, Matano et al. 2005, Terzolo et al. 2005, dos Santos et al. 2013). However, increased cancer incidence may not directly translate into increased cancer mortality. In addition, more recent studies, including our previous report, suggest a decrease in acromegaly-related comorbidities and mortality in patients diagnosed between 1980 and 2008 (Kauppinen-Makelin et al. 2005, Arosio et al. 2012, Colao et al. 2014, Espinosa et al. 2014, Mercado et al. 2014). However, it is unclear whether cancer mortality is increased in more recent series also after longer follow-up (Ayuk & Sheppard 2008, Loeper & Ezzat 2008). The aim was to assess mortality and the causes of death in our national acromegaly cohort, diagnosed between 1980 and 1999, in comparison with controls after 20 (range 0–33) years of follow-up. In addition, as the available data are scarce, we investigated whether there are gender-related differences with regards to mortality in acromegaly.

Patients and methods

Patients

The study population comprised 333 patients diagnosed with acromegaly in all five university central hospitals in Finland between January 1980 and December 1999, and therefore included all Finnish patients diagnosed with acromegaly during that time period (Kauppinen-Makelin et al. 2005). Of the patients, 123 (36.9%) were from Helsinki University Hospital, 70 (21.0%) from Tampere, 50 (15.0%) from Turku, 49 (14.7%) from Oulu, and 41 (12.3%) from Kuopio University Hospital, respectively. The inclusion

criteria were age over 15 at diagnosis and Finnish residence. Baseline laboratory and clinical information at diagnosis, as well as serum GH and IGF1 concentrations measured a mean of 5.2 (± 4.4) years after primary treatment were studied retrospectively, and obtained from patient records. The diagnosis of acromegaly was based on impaired suppression of serum GH concentration below 1 $\mu\text{g/L}$ on a 75 g oral glucose tolerance test (OGTT), clinical symptoms and a visible pituitary tumor on sellar imaging (Kauppinen-Makelin *et al.* 2005). Biochemical control was defined as post-treatment basal serum GH concentration below 2.5 $\mu\text{g/L}$ and serum IGF1 concentrations below the prevailing upper limit of normal. All assays used in the biochemical measurements have been described previously (Kauppinen-Makelin *et al.* 2005). Patient deaths and causes of deaths until the end of 2013 were retrieved from Statistics Finland.

Statistics Finland

Data on the Finnish general population and a large age- and gender-adjusted control population were obtained from Statistics Finland (www.stat.fi). This is the Finnish public authority producing the majority of official statistics in Finland. Statistics Finland provided mortality data for both the patients and the control population, including the exact date of death, and the immediate and underlying causes of death. In Finland, statistical data are produced annually on the causes of death of persons permanently residing in Finland. The statistics are compiled on the basis of death certificates. The data are supplemented with and verified against data on deaths from the Population Information System of the Population Register Centre. Medical treatment is supported by the national health care system, and for acromegaly, this means referral for diagnosis and treatment to one of our five university hospitals, without extra costs for the patients. It is therefore likely that loss of death information will be at a negligible level, as few patients travel abroad for diagnosis and treatment. Statistics Finland has registered death certificates and data on the causes of death from 1936 onward. Fifteen age- and gender-matched controls were chosen for each study patient. Only those controls alive at the time of the diagnosis of the corresponding patient were chosen. Each control person was included only once; therefore, no duplicates existed. In total, our control population comprised 4995 Finnish persons with an age and gender distribution identical to our acromegaly cohort. In the analyses,

we chose to evaluate the underlying causes of death, as they were always available.

Ethics

The present study was approved by the Institutional Review Board of the Helsinki University Hospital, and the original study protocol was approved by the ethics committees of all the five University Hospitals.

Statistical analysis

Quantitative data are expressed as range (minimum–maximum), mean or as median and interquartile range (IQR, 25–75%), depending on the data distribution. Clinical features (the variables in Table 1), and the distribution of causes of deaths were compared with Fisher's exact test and Wilcoxon rank sum tests. To study associations among gender, study groups (patient with acromegaly and controls) and cause of death, log-linear model was executed. The model included all main effects as well as gender $\times$ cause of death, gender $\times$ group and group $\times$ cause of death interactions.

A *P* value <0.05 (two-tailed) was considered statistically significant. We used a confidence interval (CI) of 95% for all analyses. The statistical analyses were performed with SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL), and SAS software (Version 9.3 for Windows, SAS Institute Inc, Cary, NC, USA).

First, Cox model for proportional hazards was performed to identify factors (age, gender, operation, radiotherapy, basal GH, last known basal GH (less than 2.5 $\mu\text{g/L}$ or more)) associated with time to death of the patients. It was noticed that the proportional hazard assumption was not met for gender; therefore, a time-dependent covariate between gender and time was added to the model. Finally, hazard ratios (HRs) for male/female were estimated from piecewise Cox model, where HR was estimated separately for the first 20 years and for the remaining time.

To compare mortality between the patients and the general Finnish population, SMRs were calculated using life tables of the Finnish population aged 15–79 years by 5-year gender-specific age groups, for the years 1986–1990 as the reference. Overall SMRs were also computed for all patients, and separately for males and females, as well as for each 5-year gender-specific age group. Mortality data were followed until the end of 2013. Differences between patients and the general population were tested with

Table 1 Clinical features in patients with acromegaly according to survival status.

	All patients (n=333)	Surviving patients (n=220)	Patients deceased by the end of 2013 (n=113)	Data missing	Univariate P value (surviving vs deceased)
Gender (F/M)	173/160	110/110	63/50		0.320
Mean age at diagnosis (years (range))	47.6 (17.0–80.0)	43.4 (17.0–76.0)	55.7 (30.0–80.0)		<0.001
Median age at death (years (IQR))			73.6 (62.9–79.3)		
Mean follow-up (years, range)*	20.0 (0–33.0)	22.5 (14.0–33.0)	15.0 (0–33.0)		<0.001
Median basal GH at the time of diagnosis µg/L (IQR)	17.8 (9.5–43.1)	17.5 (9.4–49.9)	18.1 (10.3–35.7)	14	0.480
Elevated IGF1 at the time of diagnosis, n (%)	141 (81)	104 (84)	37 (74)	159	0.168
Tumor size (macroadenoma n, %)	224 (72)	161 (76)	63 (63)	21	0.018
Primarily operated, n (%)	288 (87)	210 (96)	78 (69)	1	<0.001
Radiotherapy, n (%)**	115 (35)	71 (33)	44 (39)	2	0.249
Median last known basal GH (µg/L (IGR))#	1.90 (0.80–3.90)	1.70 (0.60–3.00)	3.00 (1.40–5.80)	23	<0.001
Basal GH <2.5 µg/L after treatment, n (%)#	184 (59)	142 (68)	42 (42)	23	<0.001
Normal serum IGF1 after treatment, n (%)#	181 (76)	129 (77)	52 (73)	95	0.510

*Time between diagnosis and death/the end of 2013; **Treatment given before years 2001–2002; #Measured a mean of 5 years after diagnosis.

χ^2 statistics, and exact 95% confidence intervals were calculated using the Mid-P method.

Survival rates and causes of death of the patients and age- and gender-matched controls were compared by using the Fisher exact test or χ^2 -test, and conditional logistic regression was used to estimate the odds ratio (OR) of all-cause mortality. Comparison of the time period between the date of diagnosis of acromegaly and the date of death, or the common closing date, 31 December 2013, between the patients and the controls, was done with Kaplan–Meier curves and tested with the log-rank test. For the controls, the time in survival analysis was calculated from the date of the corresponding patient's diagnosis to the date of the control's death/31 December 2013. Cox proportional hazard analysis was used for risks

and to compare time to death between the patients and controls, including gender and group (patient vs control) as factors.

Results

Characteristics of the patient cohort

Men were significantly younger at diagnosis than women (median 44.5 (range 18–77) vs 50 (range 17–80) years, $P < 0.001$). Other patient characteristics are given in Table 1. There was an equal contribution of men and women (Table 1). The mean follow-up time after diagnosis until death or the end of 2013 was 20 (range 0–33) years. Eighty-seven percent were

Table 2 Causes of death in patients with acromegaly (n=113) according to gender.

Cause of death	Men			Women			P
	n	%	95% CI	n	%	95% CI	
Cardiovascular diseases	21	42		17	27		0.11
Coronary artery disease	14	28	15.1–40.9	12	19	9.1–29.0	0.27
Other heart and cardiovascular diseases	7	14	4.0–24.0	5	8	1.1–14.8	0.36
Cerebrovascular diseases	6	12	2.7–21.3	6	10	2.1–17.0	0.76
Malignancy	12	24	11.7–36.3	19	30	18.5–41.8	0.53
Pituitary adenoma	1	2	0.0–6.0	4	6	0.2–12.5	0.38
Accidents and violence	4	8	0.2–15.8	2	3	0.0–7.6	0.40
Other causes of death*	6	12	2.7–21.3	15	24	13.0–34.6	0.15
Overall distribution of causes of death	50	100		63	100		$P = 0.34$

*Infections, lung diseases, diabetes, systemic autoimmune diseases.

Overall distribution of causes of death did not differ between females and males (Fisher's exact test).

Table 3 Causes of death in patients with acromegaly ($n=333$) compared with the age- and gender-adjusted control population ($n=4995$).

Cause of death	Deaths in the patient group			Deaths in the general population			P
	n	%	95% CI	n	%	95% CI	
Cardiovascular diseases	38	34		442	33		0.92
Coronary artery disease	26	23	15.1–30.9	332	25	23.0–27.8	0.73
Other heart and cardiovascular diseases	12	11	4.9–16.4	110	8	6.9–9.9	0.38
Cerebrovascular diseases	12	11	4.9–16.4	106	8	6.6–9.6	0.29
Malignancy	31	27	19.1–35.8	355	27	24.7–29.6	0.83
Pituitary adenoma	5	4	0.6–8.3	1	0	0.0–0.2	<0.0001
Accidents and violence	6	5	1.1–9.5	92	7	5.7–8.4	0.70
Other causes of death*	21	19	11.3–25.9	311	23	21.5–26.1	0.29
Missing causes of death	0	0		27	2		0.26
Overall distribution of causes of death	113	100		1334	100		<0.0001

*Infections, lung diseases, diabetes, systemic autoimmune diseases.

The overall distribution of causes of death differed significantly between the groups (Fisher's exact test).

primarily operated on using the transsphenoidal approach, and 35% received radiotherapy. Patients deceased by the end of 2013 were characterized by older age at diagnosis ($P<0.001$), higher basal GH concentrations at diagnosis ($P=0.048$) and smaller adenomas ($P=0.018$) compared with those who survived, and they less frequently underwent surgery as primary treatment ($P<0.001$), had a higher last known

basal GH ($P<0.001$) (Table 1) and more often failed to adequately suppress GH on a 2 h OGTT ($P<0.001$). Of the patients with microadenomas, 58% were women, and mean age at diagnosis was 51 years (range 24–80). Of the patients with macroadenomas, 50% were women and age at diagnosis was 46 years (17–77). Radiotherapy was not associated with increased mortality rates in the univariate analysis (Table 1).

Table 4 Causes of death in the control group ($n=1334$) by gender.

Cause of death	Men			Women			P
	n	%	95% CI	n	%	95% CI	
Cardiovascular diseases	249	37		193	30		0.007
Coronary artery disease	198	29	26.2–33.1	134	21	17.8–24.1	0.003
Other heart and cardiovascular diseases	51	7	5.6–9.7	59	9	7.0–11.4	0.32
Cerebrovascular diseases	48	7	5.2–9.1	58	9	6.8–11.3	0.23
Malignancy	173	25	22.6–29.2	182	28	25.0–32.0	0.32
Pituitary adenoma	0	0		1	0	0.0–0.5	0.49
Accidents and violence	65	10	7.5–12.0	27	4	2.7–5.8	<0.0001
Other causes of death*	133	20	16.9–23.0	178	27	24.4–31.3	0.009
Unknown causes of death	13	2		14	2		0.85
Overall distribution of causes of death	681	100		653	100		<0.0001

*Infections, lung diseases, diabetes, systemic autoimmune diseases.

Bold text indicates statistically significant difference between specific causes of death (Fisher's exact test). The bottom line indicates the comparison of the pattern of causes of death between the two genders.

Figure 1

Kaplan–Meier curves of overall survival in women (black) compared with men (gray) with acromegaly, adjusted for age- and disease-specific factors. During the first two decades, more men than women die, whereafter more women than men die (gender $\times$ time interaction), $P=0.018$.

Mortality in acromegaly in men compared with women

Overall mortality (36% vs 31%, $P=0.35$) and causes of death did not differ between male and female patients ($P=0.34$, Table 2). In patients with acromegaly, men were significantly younger than women (67 (range 35–86) vs 76 (range 39–92) years, $P=0.0015$) at the time of death. During the first two decades of follow-up, more men than women died, whereas during the last decade, more women than men died (Fig. 1, $P=0.018$ for gender $\times$ time interaction).

Standardized mortality ratios

The SMR for the entire patient cohort was 1.9 (95% CI: 1.53–2.34, $P<0.001$) relative to the general population. Significantly increased SMRs were found in the age groups 55–59 (SMR 4.7, 95% CI: 2.66–7.67, $P<0.001$), 65–69 (SMR 2.1, 95% CI: 1.19–3.58, $P<0.001$) and 75–79 (SMR 1.6, 95% CI: 1.06–2.37, $P=0.017$). In women, the overall SMR was 2.5 (95% CI: 1.85–3.40, $P<0.001$), and the result was significant in all age groups except for women aged 40–49. In men, the overall SMR was 1.4 (95% CI: 1.05–1.91, $P=0.018$), and the SMRs by age groups were not statistically significant, except for men aged 55–59 (SMR 4.8, 95% CI: 2.44–8.56, $P<0.001$).

Mortality in acromegaly compared with controls

In total, 113 of 333 (34, 56% women) patients with acromegaly and 1334 of 4995 (27, 49% women) controls

Figure 2

(A) Kaplan–Meier curves of overall survival for patients with acromegaly (gray) and for control population (black), $P=0.002$. (B) Kaplan–Meier curves of overall survival for male patients with acromegaly (gray) and for male controls (black), $P=0.394$. (C) Kaplan–Meier curves of overall survival for female patients with acromegaly (gray) and for female controls (black), $P<0.001$.

died during the follow-up, demonstrating increased all-cause mortality in acromegaly (Table 3, $P<0.001$). The median age at death was 74 years for both groups. However, on univariate survival analysis, the patients died statistically significantly earlier compared with the controls ($P=0.002$, Fig. 2A). When death rates for both groups were analyzed according to the time after diagnosis of acromegaly, 32% of the patients and 27% of the controls died during the first 10 years after diagnosis (Fig. 2).

Gender differences in mortality rates in patients with acromegaly compared with controls

Total death rate was higher in female controls compared with male controls (28% vs 25%, $P=0.01$). Male controls died significantly more often of coronary artery disease, or due to accidents and violence, compared with female controls (Table 4). When the patients and the controls were compared, mortality did not differ in men (31% vs 28%, $P=0.44$), and the survival times were similar (Fig. 2B). Median age at death was 66 (IQR 58–76) vs 68 (IQR 59–77) years for male patients and male controls, respectively. In women, total mortality was increased in patients compared with controls (36% vs 25%, $P=0.001$). Figure 2C illustrates the shorter survival times in the female patients compared with the female controls ($P<0.001$). The median age at death was 76 (IQR 68–84) in female patients and 79 (IQR 69–84) years in female controls. The difference in the mortality rates between the patient and the control group persisted after adjustment for gender.

Causes of death as a function of time in patients with acromegaly and controls

Causes of death are given in Table 3. Cardiovascular diseases, cerebrovascular diseases and malignancies were the most common causes of death in both the patients and the controls. The overall distribution of causes of death differed between the patients and the controls (Table 3, $P<0.001$). Log-linear analysis of patients and controls confirmed that the overall distribution of causes of deaths indeed differed statistically between these subgroups ($P<0.001$), and that this difference was not due to an artifact of the higher mortality observed in female patients compared with female controls.

However, direct comparison of the cause-of-death subgroups between the patients and the controls revealed no significant differences, and neither cardiovascular (34% vs 33%) nor cancer deaths (27% vs 27%) differed

between patients and controls. Overall, 23% of the patients died of coronary artery disease, 11% of other heart diseases, 11% of cerebrovascular diseases, and 27% of malignancies (Table 3). Figure 3 illustrates the distribution of the causes of death in the patients and the controls. In the patients, during the first 10 years of follow-up, cardiovascular disease (44%) was the most common cause of death followed by malignancies (28%). As time after diagnosis passed, a smaller proportion of the patients died of cardiovascular disease (23%) and a higher proportion of malignancies (35%) and other causes (31%) (Fig. 3). In the control group, the proportion of malignancies did not increase over time (Fig. 3). In the controls, during the first 10 years, the percentage of cardiovascular deaths was 34% and that of malignancies 28%, and during the second and third decade of follow-up, the corresponding numbers were 33% and 27–26%, respectively.

Cancer deaths

Of the 113 deaths within the patient group, 12 (24%) males and 19 (30%) females died of cancer; this difference was not statistically significant. The corresponding figures for the control population were comparable, 25% cancer deaths

Figure 3 Distribution of causes of death as a function of time (A) in acromegaly and (B) in controls.

in men and 28% cancer deaths in women (not statistically significantly different). In total, 31 (27%) patients with acromegaly died of cancer. The most common cancer deaths were due to pancreatic adenocarcinoma ($n=5$), breast ($n=4$), lung ($n=3$) and colon ($n=3$) cancer, and three patients died of a cancer of unknown origin. Two patients died of kidney cancer and one of thyroid cancer. Basal GH concentrations were similar in patients who died of cancer compared with those who did not (data not shown).

Factors associated with increased mortality in acromegaly

In univariate analysis (Table 1), having transsphenoidal surgery as the primary treatment (87%, $n=288$) associated with lower death rates ($P<0.001$). Twenty-seven percent (78/288) of the patients having surgery as primary treatment died during follow-up, compared with 81% (35/43) of the patients not having surgery as primary treatment ($P<0.001$). The patients primarily operated on had more often a macroadenoma compared with those not operated on ($P<0.001$), and significantly lower post-treatment GH concentrations ($P<0.001$). Serum GH $<2.5 \mu\text{g/L}$ ($n=184$) associated with lower mortality and was achieved in 65% (140/220) of the surviving patients, compared with 37% (42/113) of the deceased patients ($P<0.001$; Table 1). Of the patients with serum GH $<2.5 \mu\text{g/L}$, 97% had undergone transsphenoidal surgery.

Independent predictors of mortality in acromegaly

The independent predictors of all-cause mortality are presented in Table 5. Age at diagnosis ($P<0.001$), radiotherapy ($P=0.012$) and serum GH $>2.5 \mu\text{g/L}$ ($P<0.001$) were associated with increased all-cause mortality.

Table 5 Factors associated with all-cause mortality on multivariate piecewise cox model.

Variable	HR	95% CI	P value
Age at diagnosis (years)	1.1	1.08–1.13	<0.001
Gender (M/F)			
Up to 20 years from diagnosis	2.5	1.46–4.17	<0.001
After 20 years from diagnosis	0.9	0.42–1.91	0.78
Serum basal GH at diagnosis ($\mu\text{g/L}$)	1.0	0.99–1.01	0.91
Primary operation (no vs yes)	1.5	0.86–2.61	0.15
Radiotherapy (no vs yes)	0.5	0.34–0.88	0.012
Last known basal serum GH $<2.5 \mu\text{g/L}$ after primary treatment (no vs yes)*	1.8	1.21–2.83	0.048

*Measured a median of 5 years after diagnosis.

Discussion

This study demonstrates that after 20 years of follow-up, in contrast to the results at 12 years of follow-up (Kauppinen-Makelin *et al.* 2005), mortality is significantly increased in patients diagnosed with acromegaly in the 1980s and 1990s. In addition, causes of death shift from predominantly cardiovascular to predominantly cancer-related deaths in acromegaly during follow-up; such a change in distribution of causes of deaths was not seen in controls. This study also demonstrates that there are significant gender-related differences in age at diagnosis and age at death in acromegaly.

Based on earlier studies, it is not easy to conclude whether acromegaly is associated with a gender-related difference in mortality or not, and whether it is male or female patients who are at increased risk of death. For instance, in 1980, Alexander and coworkers reported increased mortality in male compared with female patients with acromegaly after 15 years of follow-up (Alexander *et al.* 1980), and in 1993, Etxabe and coworkers reported an SMR for men of 7.0 compared with 1.4 for women with acromegaly after 6.2 years of follow-up (Etxabe *et al.* 1993). By contrast, in 1998, a two-fold SMR was reported for women compared with men with persistent acromegaly after a median follow-up of 11 years (Abosch *et al.* 1998). The present study, which represents a more modern series of patients with acromegaly, all of whom had a follow-up of at least 20 years, sheds some light on this issue. We demonstrate that, in acromegaly, men die at younger age than the women, i.e. more men than women die within the first years of follow-up, while more women than men die after even longer follow-up. In addition, when compared with the background population, death rates are increased especially in women but not in men with acromegaly. Of note, many previous studies on acromegaly do not give the age at diagnosis separately for women and men, but rather the pooled age, and this usually holds true also for the data on mortality (Orme *et al.* 1998, Mestron *et al.* 2004, Colao *et al.* 2014). In line with the present study, Bex and coworkers reported from the Belgian acromegaly register that men were diagnosed at younger age (42 vs 46 years), and also died at younger age (68 vs 74 years), compared with women (Bex *et al.* 2007). That males were diagnosed at a younger age than females was reported also from the German Acromegaly Register and from South Korea (Schofl *et al.* 2012, Kwon *et al.* 2013).

In the present study, older age at diagnosis independently predicted mortality. It is thus possible

that a greater delay in the diagnosis of women with acromegaly contributes to the gender difference observed in mortality compared with the controls in the present study. Fewer women than men (49% vs 62%, $P=0.017$) achieved a $\text{GH}<2.5\mu\text{g/L}$ (Dekkers *et al.* 2008). Post-treatment basal serum GH concentration $>2.5\mu\text{g/L}$ was associated with increased all-cause mortality also in the present study. Ciresi and coworkers reported that the metabolic profile in active acromegaly is gender-specific, with a significantly higher prevalence of the metabolic syndrome in women compared with men (Ciresi *et al.* 2013). We did not try to assess the delay in the diagnosis of acromegaly in the present study. However, Kreitschmann-Andermahr and coworkers reported that the diagnostic process of acromegaly takes significantly longer in females compared with males (Kreitschmann-Andermahr *et al.* 2016). According to a survey among 165 patients with acromegaly, disease duration from the estimated onset of symptoms until last surgery was 5.5 years, with no gender differences (Kreitschmann-Andermahr *et al.* 2016).

Our study indicates that there is a significantly increased, 1.6-fold mortality in our nationwide cohort of patients with acromegaly compared with age- and gender-matched controls, and an increased SMR of 1.9 after 20 years of follow-up. In the patients, the highest SMR of 4.7 was found in the age group 55–59 years, with significantly increased SMRs of 2.1 and 1.6 also in the age groups 65–69 and 75–79 years, respectively. Among the male patients, a significantly increased SMR of 4.5 was found in males aged 55–59 only, whereas in female patients, increased SMRs were found for all age groups except for women less than 50 years of age.

The distribution of causes of death differed significantly between the patients and the controls ($P<0.001$). Importantly, this result was confirmed on log-linear analysis, and was not explained by the observed higher mortality in female patients compared with female controls. However, total death rates for coronary artery disease (26% vs 25%), cerebrovascular disease (12% vs 8%) or cancer (27% vs 27%) did not differ between the patients and the controls after a mean 20 years of follow-up. Although we were not able to detect statistically significant differences in specific causes of death, probably due to the small subgroups, patients demonstrated a tendency toward more cardiovascular deaths during the first 10 years after the diagnosis of acromegaly, whereas malignancies were more common when over 20 years after the diagnosis had elapsed. Such differences in the causes of death over the years could not be detected in the control group. Our results thus provide novel information

regarding the evolving causes of death in acromegaly during very long-term follow-up.

Whether cancer incidence is increased in acromegaly and whether cancer deaths are increased in acromegaly is still a matter of debate. Recently, especially the incidence of thyroid nodules, goiter and thyroid cancer in acromegaly has been debated. Routine thyroid ultrasound (US) screening has been suggested in a recent meta-analysis (Wolinski *et al.* 2014), and in a large, cross-sectional study with extensive US and fine-needle aspiration analyses (Reverter *et al.* 2014). However, in a recent study, Petroff and coworkers reported, by analysing a cohort of 446 German patients with acromegaly, that cancer incidence is not increased in treated patients with acromegaly when compared with the general population, not for any type of cancer studied (Petroff *et al.* 2015). In line with this, in the present study, 31 patients (27%) died of cancer, with an identical cancer death rate of 27% in the large general population during 20 years of follow-up. In the present acromegaly cohort, although the total numbers are small, the most common causes of cancer death were pancreatic adenocarcinoma ($n=5$), breast cancer ($n=4$), lung and colon cancer (both $n=3$), cancer of unknown origin ($n=3$), kidney ($n=2$) and thyroid cancer ($n=1$). That pancreatic adenocarcinoma was one of the most common causes of cancer deaths in acromegaly was an interesting observation that warrants future studies in larger patient series.

In the present study, 87% of the patients underwent surgery as the primary treatment. The patients who survived were more often primarily operated on, compared with those deceased (96% vs 69%, $P<0.001$). In univariate analysis, tumor size associated with better outcomes, which probably reflects the fact that a higher percentage of patients with macroadenomas (95%) compared with those with microadenomas (70%) underwent surgery, and that a higher proportion of patients undergoing surgery reached hormonal remission. No association between tumor size and outcome was seen on multivariate analysis. A recent series of acromegaly patients demonstrated that very high rates of hormonal remission, and a health-related quality of life similar to that of controls can be achieved at specialized centers, using surgery as primary treatment, combined with multimodal postoperative treatments (Karppinen *et al.* 2015, Ritvonen *et al.* 2015). Together, these results underline the importance of surgery as the first-line treatment of acromegaly.

The aim of the present study was to assess mortality and causes of death in acromegaly after very long follow-up. The retrospective setting can be regarded as a

limitation of the study, as the lack of follow-up data on other clinical and biochemical parameters prevented us from analysing the effects of more recent GH and IGF1 measurements, and of all given treatment modalities, such as medical therapies, on all-cause mortality. In our study, survival may be related both to age and time after diagnosis, and these two time measures are inevitably correlated. This confounding factor can be seen as an unavoidable limitation of the study. We did not include IGF1 in the analyses of possible predictors of mortality. Our previous study demonstrated that it did not affect the outcome (Kauppinen-Makelin *et al.* 2005), furthermore, due to missing values for IGF1, the cases included in the analysis would have dropped significantly and weakened the strength of the analyses. As the number of patients in the different cause-of-death subgroups was small, statistical power may have been insufficient to detect possible differences within these subgroups. However, we were able to demonstrate a significant difference in the overall distribution of causes of deaths between patients with acromegaly and controls. We included all patients diagnosed with acromegaly between the years 1980 and 1999 in our country, ensuring that no recruitment bias occurred. Our cohort is fairly large ($n=333$), the follow-up is one of the longest reported, and to increase the power of the analyses, we compared mortality and the causes of death also with those of an age- and gender-adjusted control population of nearly 5000 individuals.

In conclusion, this nationwide long-term follow-up study demonstrates that all-cause mortality in patients diagnosed with acromegaly in the 1980s and 1990s is significantly increased after 20 years of follow-up. There are significant gender-related differences in acromegaly, i.e. in age at diagnosis and age at death, with more men dying during the first decades of follow-up, while during even longer follow-up, more women than men die. In addition, in comparison to the background population, mortality is increased especially in women but not as clearly in men with acromegaly. Therefore, to improve treatment outcomes in acromegaly, it seems important to acknowledge these gender-specific differences in order to tailor the treatments. Further studies are needed to guide us how this is best done. As women are diagnosed at a later age, we should aim at an earlier diagnosis of acromegaly especially in women. To date, absolute cancer death rate is not increased in acromegaly compared with controls; however, the distribution of the causes of death shifts over the years from predominantly cardiovascular- to cancer-related deaths as the most common cause of death. The findings imply that prevention and treatment

of cardiovascular diseases should be emphasized during the first years after diagnosis of acromegaly, and that perhaps more aggressive treatment is warranted especially in male patients, as more men than women die during short-term follow-up. During the later course of follow-up, cancer screening in patients with acromegaly seems to be of increasing importance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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