Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma

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Abstract

Objective: Patients with secondary adrenal insufficiency (AI) have an excess mortality. The objective was to investigate the impact of the daily glucocorticoid replacement dose on mortality in patients with hypopituitarism due to non-functioning pituitary adenoma (NFPA).

Methods: Patients with NFPA were followed between years 1997 and 2014 and cross-referenced with the National Swedish Death Register. Standardized mortality ratio (SMR) was calculated with the general population as reference and Cox-regression was used to analyse the mortality.

Results: The analysis included 392 patients (140 women) with NFPA. Mean $\pm$ s.d. age at diagnosis was 58.7 ± 14.6 years and mean follow-up was 12.7 ± 7.2 years. AI was present in 193 patients, receiving a mean daily hydrocortisone equivalent (HCEq) dose of 20 ± 6 mg. SMR (95% confidence interval (CI)) for patients with AI was similar to that for patients without, 0.88 (0.68–1.12) and 0.87 (0.63–1.18) respectively. SMR was higher for patients with a daily HCEq dose of >20 mg (1.42 (0.88–2.17)) than that in patients with a daily HCEq dose of 20 mg (0.71 (0.49–0.99)), $P=0.017$. In a Cox-regression analysis, a daily HCEq dose of >20 mg was independently associated with a higher mortality (HR: 1.88 (1.06–3.33)). Patients with daily HCEq doses of ≤ 20 mg had a mortality risk comparable to patients without glucocorticoid replacement and to the general population.

Conclusion: Patients with NFPA and AI receiving more than 20 mg HCEq per day have an increased mortality. Our data also show that mortality in patients substituted with 20 mg HCEq per day or less is not increased.

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Introduction

Patients with hypopituitarism have increased morbidity and mortality (1, 2). Along with factors such as young age at diagnosis, female gender, underlying pituitary disease and pituitary radiation therapy, it has been suggested that the current hormone replacement regimes may contribute to the adverse outcome (2, 3, 4, 5, 6, 7, 8).

The traditional glucocorticoid (GC) replacement dose used in patients with adrenal insufficiency (AI) is considerably higher than the estimated endogenous cortisol production rate in healthy subjects (10–15 mg/day) (9, 10). Excess GC exposure over time may contribute to an increased risk of adverse metabolic profile and

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premature death (4, 11, 12, 13). Previous studies have shown increased mortality in hypopituitary patients with acromegaly using daily hydrocortisone (HC) replacement doses of ≥ 25 mg (12) and in patients with NFPA with daily HC doses of ≥ 30 mg (13). HC clearance depends largely on body weight and a weight-adjusted GC replacement dose has therefore been suggested (14). Zueger *et al.* demonstrated that body weight-adapted HC doses of ≥ 0.35 mg/kg are associated with increased mortality (4). Our group has, in a previous study, shown that patients with hypopituitarism and AI using a daily hydrocortisone dose ≥ 20 mg per day had a worse cardiometabolic risk profile than hypopituitary patients without GC replacement therapy (11).

The aim of this study was to investigate the impact of GC dose on mortality in a large and unselected population of NFPA patients. Our main hypothesis was that patients receiving daily HC doses higher than 20 mg have the worst outcome.

Subjects and methods

Study design

This was a cohort study including all patients treated or followed for NFPA in the western region of Sweden between Jan 1, 1997 and Dec 31, 2011. To be certain that all patients with NFPA from the western region of Sweden were included, we also searched the Swedish National Patient Register (Patient Register). The Patient Register achieved a national coverage in 1987 and contains information from every patient visit within the Swedish hospital system using a unique identification number.

Medical charts for all patients were manually reviewed to ensure that the diagnosis of NFPA was correct and in order to collect information on medical history and clinical characteristics, including hormonal replacement therapy. In total, 405 patients with a confirmed NFPA were identified. Of these, 13 patients were excluded due to GC treatment for non-endocrine diseases (ten of these patients died during the study period). Thus, 392 patients were included in the final analysis.

For each patient start of follow-up was defined as either the time point when NFPA was diagnosed or the start of the study (January 1, 1987). All patients were followed to Dec 31, 2014 or until death. Current replacement therapy was defined as the treatment the patients received at their last clinical visit before the end of study. Information on

mortality was obtained from the Swedish National Cause of Death Register.

Secondary AI was diagnosed according to local clinical practice. The majority of patients have, however, been diagnosed and followed at Sahlgrenska University Hospital, using morning serum cortisol measurements and a Synacthen test. If inconclusive, these tests were followed by an insulin tolerance test.

For patients with secondary AI, and not receiving HC ($n=7$, all receiving cortisone acetate), a HC equivalent (HCeq) dose was calculated (15, 16). Patients with GC replacement were divided into three groups according to their daily HCeq dose (<20 , 20 or >20 mg/day). The patients were also grouped according to their daily HCeq dose per kg body weight (≤ 0.25 , >0.25 – 0.30 and >0.30 – 0.55 mg/kg/day).

Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and by the National Board of Health and Welfare, Sweden.

Statistics

Person-years at risk were calculated from study inclusion to death, or end of study, and stratified according to gender, 5-year age groups and 1-year calendar periods. The expected number of deaths for each stratum was calculated using the general Swedish population for every calendar year and 5-year age group as reference. The observed number of deaths among patients with NFPA was compared to that expected by standardised mortality ratios (SMRs). Ninety-five percent confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed numbers. Subgroup analyses for absolute daily HCeq dose and daily HCeq dose per kg were performed. SMRs for non-overlapping subgroups were compared to each other (17).

Multivariable Cox-regression models were used to calculate hazard ratio (HR) of mortality, adjusted for: age at the start of the study, gender and treatment with radiotherapy, as well as absolute- or weight-adjusted HCeq dosage. HR was also calculated for patients with secondary AI and compared to patients with intact hypothalamic–pituitary–adrenal function. The level of significance was set to $P < 0.05$. IBM SPSS (version 24) and STATA SE (version 14) software was used to perform the statistical analyses.

Table 1 Characteristics of patients with non-functioning pituitary adenoma included in the study.

	Total (n=392)
Gender, n (%)	
Men	252 (64)
Women	140 (36)
Age at diagnosis, years, mean $\pm$ s.d.	58.7 $\pm$ 14.6
Men, mean $\pm$ s.d.	58.9 $\pm$ 13.9
Women, mean $\pm$ s.d.	58.3 $\pm$ 15.9
Hypopituitarism, n (%)	313 (80)
Diabetes insipidus, n (%)	46 (12)
Hormonal replacement, n (%)	
- None	75 (19)
- Levothyroxine	272 (69)
- Glucocorticoids ^a	193 (49)
- Sex steroids	186 (47)
- Growth hormone	160 (41)
Mean follow-up time, years (range)	12.7 (0.1–28)
Patient-years at risk in the study	4961
Treatment with surgery, n (%)	287 (73)
Treatment with radiotherapy, n (%)	78 (20)

Patients treated with glucocorticoids due to non-endocrine chronic disorders were excluded (n=13).

^aIncludes replacement with hydrocortisone (n=186) and cortisone acetate (n=7).

Results

Patient characteristics

In total, 392 patients with NFPA were included in the analysis, 252 men and 140 women (Table 1). The mean

age at diagnosis was 58.7 $\pm$ 14.6 years and the mean follow-up time was 12.7 $\pm$ 7.2 years. Of the 392 patients, 287 (73%) underwent surgical treatment, of whom 76 (19%) also received pituitary radiation therapy. Two patients received treatment with radiation therapy alone, and the remainder (n=103, 26%) did not receive any targeted therapy for their NFPA.

The prevalence of growth hormone, levothyroxine, sex hormones and anti-diuretic hormone replacement therapy in the cohort are shown in Table 1. The number of patients with any form of hypopituitarism was 313 (80%). Secondary AI was recorded in 193 patients (49%). The vast majority received HC (n=186) and the remainder received cortisone acetate (n=7). The mean $\pm$ s.d. daily HCeQ dose was 20 mg $\pm$ 6 and the mean HCeQ dose per kg was 0.25 $\pm$ 0.09. The most common dosing frequency of GC replacement was BID (n=159), followed by OD (n=27) or TID (n=7).

Mortality

In the whole group of 392 patients, 106 deaths were recorded. The most frequent cause of death in all subgroups was diseases of the circulatory system (ICD-10 Chapter 9) (Table 2). Only two patients died due to infectious diseases (ICD-10 Chapter 1). Patients with secondary AI had an SMR similar to that for patients

Table 2 Characteristics of non-functioning pituitary adenoma patients with and without glucocorticoid (GC) replacement therapy.

	Without GC	With GC	With GC		
			<20 mg/day	20 mg/day	>20 mg/day
No. of patients (%)	199 (51)	193 (49)	43 (11)	113 (29)	37 (9)
Gender, men/women (%)	113/86 (57/43)	139/54 (72/28)	25/18 (58/42)	88/25 (78/22)	26/11 (70/30)
Age at diagnosis (years, mean $\pm$ s.d.)	57.6 $\pm$ 15.5	59.8 $\pm$ 13.6	57.6 $\pm$ 12.7	59.1 $\pm$ 12.9	64.6 $\pm$ 15.7
Body weight at the end of follow-up (kg, mean $\pm$ s.d.)	81.2 $\pm$ 16.0	84.1 $\pm$ 18.0	83.1 $\pm$ 20.6	84.9 $\pm$ 16.3	82.6 $\pm$ 19.8
Growth hormone replacement therapy (%)	61 (31)	99 (51)	24 (56)	61 (54)	14 (38)
Comorbidities, n (%) ^a					
Type 2 diabetes mellitus	22 (11)	20 (10)	6 (14)	11 (10)	3 (8)
Hyperlipidaemia	74 (37)	67 (35)	14 (33)	44 (39)	9 (24)
Hypertension	107 (54)	111 (58)	20 (47)	73 (65)	18 (49)
Cause of death (ICD-10 Chapters), n (%) ^b					
Total number of deaths	42	64	10	33	21
Neoplasms (2)	14 (33)	13 (20)	3 (30)	5 (15)	5 (24)
Diseases of the nervous system (6)	4 (10)	2 (3)	0 (0)	2 (6)	0 (0)
Diseases of the circulatory system (9)	15 (36)	28 (44)	5 (50)	16 (48)	7 (33)
Diseases of the respiratory system (10)	2 (5)	4 (6)	2 (20)	1 (3)	1 (5)
Diseases of the digestive system (11)	2 (5)	4 (6)	0 (0)	2 (6)	2 (10)
External causes of morbidity and mortality (20)	3 (7)	4 (6)	0 (0)	3 (9)	1 (5)

^aComorbidities have been registered throughout the follow-up period. ^bAll chapters with more than 5 deaths are shown.

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Table 3 Standardised mortality ratio in non-functioning pituitary adenoma patients with and without glucocorticoid replacement therapy using the general population as reference.

Outcome	Expected no. of deaths	Observed no. of deaths	Standardised mortality ratio (95% CI)	P
Analysed using HCeq dose/kg				
Patients without HC	48.3	42	0.87 (0.63–1.18)	0.41
Patients with >0–0.25 mg/kg	32.2	23	0.72 (0.45–1.07)	0.12
Patients with >0.25–0.30 mg/kg ^a	24.5	16	0.65 (0.37–1.06)	0.091
Patients with >0.30–0.55 mg/kg ^a	16.1	25	1.56 (1.01–2.30)	0.047
Analysed using HCeq dose/day				
Patients without HCeq	48.3	42	0.87 (0.63–1.18)	0.41
Patients with <20 mg	11.4	10	0.88 (0.42–1.62)	0.84
Patients with 20 mg ^b	46.6	33	0.71 (0.49–0.99)	0.046
Patients with >20 mg ^b	14.8	21	1.42 (0.88–2.17)	0.15

^aSignificant difference between the groups ($P=0.011$); ^bSignificant difference between the groups ($P=0.017$).

NFPA, non-functioning pituitary adenoma; HCeq, hydrocortisone equivalents have been calculated as previously described (15, 16).

without, 0.88 (95% CI: 0.68–1.12) and 0.87 (95% CI: 0.63–1.18) respectively. Also, when separately analysing women, there was no difference in SMR between patients with and without secondary AI, 1.01 (95% CI: 0.60–1.59) and 0.86 (95% CI: 0.50–1.38) respectively. SMR for patients with an HCeq dose of >20 mg per day was higher (1.42; 95% CI: 0.88–2.17) than that for patients with a daily HCeq dose of 20 mg (0.71; 95% CI: 0.49–0.99) ($P=0.017$) (Table 3). Furthermore, SMR was also higher for patients receiving a daily HCeq dose of >0.30–0.55 mg/kg (1.56; 95% CI: 1.01–2.30) compared with patients receiving a daily HCeq dose of >0.25–0.30 mg/kg (0.65; 95% CI: 0.37–1.06) ($P=0.011$).

Internal analyses were also performed in order to adjust for confounding factors. Cox-regression, adjusted for age at the start of study, gender and radiotherapy, showed that patients receiving a daily HCeq dose of >20 mg had

a significantly increased mortality compared to patients without GC replacement (HR: 1.88; 95% CI: 1.06–3.33; $P=0.032$). In contrast, patients with a daily HCeq dose of 20 mg and patients with <20 mg had mortality similar to patients without GC replacement (Fig. 1A). These results were consistent for weight-adjusted doses where patients receiving >0.30 mg/kg of daily HCeq had an increased mortality (HR: 1.97; 95% CI: 1.13–3.41; $P=0.016$) (Fig. 1B) compared to patients without GC replacement. Neither treatment with radiotherapy, nor gender had a significant effect on mortality. The HR for women was 1.5 (95% CI: 0.92–2.63) in the Cox-regression investigating the total daily HCeq dose and 1.4 (95% CI: 0.86–2.34) in the Cox-regression investigating the weight-adjusted dose.

Discussion

In this study on an unselected population of 392 NFPA patients, we have shown that daily HC replacement doses above 20 mg or 0.30 mg/kg in patients with secondary AI were associated with increased mortality compared to patients with lower doses and to patients without secondary AI. Patients with NFPA with daily doses of ≤20 mg had, however, a mortality risk comparable to patients without GC replacement and to the general population.

This study is the first to show that daily HC doses already at >20 mg or >0.30 mg/kg are associated with increased mortality. Previous studies have shown that patients with secondary AI receiving higher GC replacement doses conferred an independent risk of death in studies conducted among patients with acromegaly (>25 mg/day) and NFPA (≥30 mg/day) (4, 12, 13). Zueger *et al.* reported increased mortality with a RR of 4.0 (95% CI: 1.07–14.85) for patients receiving daily HC

Figure 1

Hazard ratio with 95% confidence intervals for mortality in patients with non-functioning pituitary adenoma (NFPA) and secondary adrenal insufficiency. Treatment groups were based on absolute (A) and weight-adjusted (B) hydrocortisone equivalent (HCeq) replacement doses and were compared to NFPA patients without secondary adrenal insufficiency. The analysis was adjusted for age at start of study, gender and radiotherapy.

doses of ≥ 30 mg (4). A more recent study by O'Reilly *et al.* reported similar results with a RR 3.79 (95% CI: 1.49–9.67) for hypopituitary patients receiving HC doses of ≥ 30 mg (13). These findings support that higher doses for replacement may contribute to increased cardiovascular morbidity and mortality such as that seen in patients with Cushing's syndrome (18). O'Reilly *et al.* concluded that secondary AI (HR: 2.26; 95% CI: 1.15–4.47), independent from dose, had a negative impact on mortality (13). However, we could not see an overall increased mortality in patients with secondary AI, only in those with higher GC replacement doses.

Several studies have demonstrated an excess mortality in hypopituitary patients, especially in women (2, 5). Due to the heterogeneity of the disease, the exact cause of this increased mortality is difficult to study. Risk of death is largely influenced by the underlying condition such as craniopharyngioma, a disease with mortality rate nearly 4 times that of other more benign causes of hypopituitarism (2, 19). Previous data are inconsistent in terms of the impact of pituitary radiation therapy on mortality (20, 21). This may, however, be influenced by the size and behaviour of the underlying tumour. Also, secondary AI, untreated gonadotropin deficiency, untreated growth hormone deficiency and the presence of diabetes insipidus have all been identified as independent factors of mortality in some but not all studies (2, 7, 12, 13, 22, 23).

The previously demonstrated excess mortality in patients with AI has been mainly attributable to cardiovascular, respiratory and infectious diseases as well as cancer (1, 2, 24). It is likely that the degree of AI is of importance for outcome and that patients who are completely insufficient may be more vulnerable to intercurrent illness, whereas patients with partial ACTH deficiency may be over-treated under normal unstressed conditions using conventional replacement doses (25). Hence, inadequate treatment of hypocortisolism remains a significant cause of death during stressful events and intercurrent illness in patients with hypopituitarism (26). A possible explanation for the poor outcome in patients with AI receiving overly high doses of GC replacement is that excess GC exposure over time induces independent risk factors for cardiovascular disease such as diabetes mellitus, hypertension and obesity (27, 28, 29).

A major strength of this study is the unselected cohort of patients diagnosed with NFPA within the same geographical area. To the best of our knowledge, this is the first study where SMR was compared between patients on different GC replacement doses in a cohort

of patients without a high inherent excess mortality such as acromegaly or craniopharyngioma. In addition, the follow-up period was extensive with a mean observation time of more than 10 years. Also, patients were not only compared to the general population, but also to a group with the same underlying pituitary disease without GC replacement. Furthermore, all patients with high doses of GC due to non-endocrine diseases were excluded from the analysis. The limitations of this study are its retrospective design and that cumulative GC exposure over time was not available. Additionally, due to the limitations of the study size, effects of gender and radiotherapy on mortality cannot be ruled out.

In conclusion, we can show that NFPA patients with secondary AI with a daily HCeq replacement dose already higher than 20 mg or 0.30 mg/kg have an increased mortality both when compared to patients with HCeq doses ≤ 20 mg per day and in comparison with the background population. Our study also shows that daily replacement doses of 20 mg HCeq or less do not result in any premature mortality. Previous studies together with our data highlight the importance of using replacement treatment that results in a physiological cortisol exposure to prevent an excess mortality.

Declaration of interest

D S O has been a consultant for Sandoz, Ipsen, Novartis and Pfizer. A G N has received lecture fees from Shire and Pfizer. G J has received speaker's honorarium from Eli Lilly, Merck Serono, Novartis, Novo Nordisk, Pfizer, Otsuka and Shire and has been a consultant for AstraZeneca, Merck Serono, Pfizer and Shire. C H, T H, E A, T S and O R have nothing to disclose.

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Author contribution statement

All authors took part in the design of the study. C H and D S O performed the patient selection process. C H and D S O have reviewed all the patient medical records. All authors contributed to the data interpretation and analysis and in writing and revision of the report. All authors are responsible for the integrity of the data and accuracy of the analysis, and all approved the final report.

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