CLINICAL STUDY

Increased risk of osteoporotic fractures in patients with Cushing's syndrome

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Abstract

Objective: To evaluate if fracture risk was increased in patients with Cushing's syndrome due to the increased endogenous cortisol production.
Design: Cohort.
Methods: A self-administered questionnaire was mailed to 125 patients with Cushing's syndrome diagnosed between 1985 and 1999 in Denmark. The response of each patient was compared with that of three age- and gender-matched control subjects randomly drawn among respondents to the same questionnaire from the background population.
Results: One hundred and four patients (83%) responded. The median age of the patients was 48 years (range 19–85 years). Sixty-eight had pituitary disease, 28 had adrenal disease, four had had both pituitary and adrenal surgery while four had not undergone surgery at the time of the study. The median time from diagnosis to surgery was 0.2 (range 0–3) years. Eighty-six percent were cured following surgery. There was an increased fracture risk within the last 2 years prior to diagnosis (incidence rate ratio 6.0, 95% confidence intervals (CI): 2.1–17.2). More than 2 years prior to diagnosis and following diagnosis there was no difference in fracture risk between patients and controls. The patients had more low-energy fractures than the controls (relative risk 5.4, 95% CI: 1.4–20.1). There was no difference in fracture risk between patients with adrenal or pituitary disease.
Conclusions: Patients with Cushing's syndrome had an increased fracture risk in a narrow time interval before diagnosis, while no increase in fracture risk could be demonstrated after diagnosis and treatment.

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Introduction

Glucocorticoid excess as in Cushing's syndrome is detrimental to bone (1). Subnormal bone mineral density (BMD) and osteoporosis have been found in patients with Cushing's syndrome (2–6). After cure of the hypercortisolism, an increase in BMD (6) even to normal levels (7) has been described.

At the cellular level, glucocorticoids may inhibit osteoblast maturation (8) and promote apoptosis (8). The formation of new collagen is inhibited (8) and the degradation of existing collagen is accelerated (8). Glucocorticoids also decrease insulin-like growth factor-I (IGF-I), growth hormone (GH) and sex steroid (8) levels. Moreover, intestinal calcium absorption is reduced and renal calcium excretion increased (8). An increased parathyroid function during glucocorticoid treatment has also been demonstrated (9). These mechanisms may lead to both a reversible and an irreversible loss of bone mineral and a weakening of the bone architecture.

Despite case reports on fractures and studies on biochemical markers of bone turnover (8) and bone mineral, no studies on fracture risk in patients with Cushing's syndrome have been published.

We therefore conducted a study of a cohort of patients with Cushing's syndrome in order to assess fracture risk before and after the diagnosis and to evaluate possible risk factors for fractures.

Subjects and methods

Eligible for the study were all patients treated at Danish hospitals for Cushing's syndrome between 1985 and 1995 ($n = 166$), and patients treated at Aarhus Kommunehospital, Odense University Hospital, and

Aalborg Hospital for Cushing's disease between 1996 and 1999 ($n = 19$). The patients were identified as previously described (10).

The diagnosis was made by an endocrinologist based on the clinical signs and symptoms and an inappropriately elevated excretion of free cortisol in the urine. Additional investigations included imaging of the pituitary and the adrenals, dexamethasone suppression and corticotrophin-releasing hormone (CRH) tests, determination of the peripheral plasma adrenocorticotrophic hormone (ACTH) concentration, sampling from the inferior petrosal sinus, etc. Cure of the disease was defined as (1) subnormal plasma cortisol concentration after a short ACTH test (< 500 nmol/l 30 min after i.v. injection of $250\,\mu g$ ACTH), and/or urinary free cortisol < 50 nmol/24 h measured 12–180 days after surgery, or (2) if plasma cortisol following the short ACTH test was > 500 nmol/l, but urinary free cortisol was < 250 nmol/l, cure was thought to have been achieved if the patients became panhypopituitary or if urinary free cortisol remained < 250 nmol/l more than 5 years following the initial surgery (10).

Of the 185 eligible patients, 49 had died, and 11 were lost to follow-up. The 125 surviving patients were contacted through a validated, self-administered questionnaire as previously reported (11). After 6 weeks the questionnaire was re-issued to non-respondents.

Each patient was age and gender matched to three control subjects selected from a random sample of the background population who had responded to the same questionnaire. Those contacted ($n = 4600$) were selected based on a random number system among inhabitants in the same region. The matching on age and gender was performed using the returned questionnaires ($n = 2634$ responded, of whom 312 were used). The questionnaires to patients and controls were issued at the same time. All patients with Cushing's syndrome in Denmark are treated at the participating centres, i.e. no patients with Cushing's syndrome were included in the background population.

Each control was subsequently assigned a dummy 'diagnosis date' corresponding to that of the patient that they were matched with. These dates formed the basis for subdividing the observation period into the time before and after diagnosis. The fracture rates in the control group were close to those of the population in general.

Variables covered by the questionnaire are shown in Table 1. When relevant, the participants were asked to describe in detail – in their own words – which bone(s) had fractured, and what had caused each fracture (e.g. a fall, an automobile accident, etc.). The questionnaire was specifically designed to study fracture occurrence in different time intervals before and after diagnosis to see if, for example, an incubation period with an increased fracture risk was present before diagnosis. The diagnosis of osteoporosis was based on bone mineral measurements and presence of low-energy fractures.

Based on the participants' account of the fractures, the energy (force) associated with each fracture was categorised in a blinded way by one of the investigators (PV) into: (1) low-energy fractures (i.e. fractures occurring after minor or no trauma); (2) medium-energy fractures (i.e. fractures occurring after a fall at the same level, dropping medium weight objects on or squeezing fingers or toes, etc.); and (3) high-energy traumas (i.e. fractures occurring after a fall from one level to another, car accidents, etc.) (Table 3). The blinded intra-observer kappa value for this classification was 0.87. A comparison of forearm BMD measurements (DEXA-scanning, Hologic, Waltham, MA, USA) in a consecutive series of 23 control patients with forearm fractures showed significantly higher BMD in the nonfractured forearm in those with high ($n = 8$, mean BMD 0.482 ± 0.076 g/cm^2) than in those with medium energy traumas ($n = 15$, mean BMD 0.380 ± 0.072 g/cm^2, two-tailed P-value $2P < 0.01$). This indicates that the classification reflects bone biomechanical competence. The validity of fracture reports was evaluated in an independent sample ($n = 2016$). Among these subjects 10 of 163 fracture reports could not be substantiated (6%, 95% confidence intervals (CI): 3–11%) upon review of files from hospitals, general practitioners, and departments of radiology.

The study had a power of 71% to detect a doubling of crude fracture incidence in 100 patients and 300 controls followed for a median of 10 years after diagnosis as in this study. Median and range were used as descriptive statistics.

As a first step in the statistical analysis strategy, incidence rates were calculated for fracture episodes (i.e. multiple fractures at the same time counted as one fracture episode) as number of fractures per 10 000 observation years. The incidence rates between cases and controls were compared by incidence rate ratios (RRs). The CI for the RR was calculated using the method described by Miettinen (12).

Mantel–Haenszel χ^2 statistics were used to determine if the RR was statistically significant, i.e. if the patients and controls differed with regards to fracture risk. This analysis was stratified into the time before and after diagnosis.

Poisson regression was used to compare RRs, i.e. to determine if one subgroup of patients deviated more from their controls than did another subgroup. This could be used to determine if the RR changed over time, i.e. to see if there was a significant increase in fracture risk in any time interval before or after diagnosis. The analysis was broken into the time intervals > 5 years, 2–5 years and < 2 years before and after diagnosis. The Poisson regression was subsequently used to determine if the relative fracture risk in patients compared with controls changed from before to after diagnosis, i.e. if there was any effect of treatment.

Numbers such as number of patients with or without a family history of fracture were compared by χ^2 for

Table 1 Baseline characteristics (median and range or actual number).

Variable	Patients ($n = 104$)	Normal controls ($n = 312$)	P
Age	48 (19−85)	48 (19−85)	
Gender			
Male	29 (28%)	87 (28%)	
Female	75 (72%)	225 (72%)	
Smoking			0.48[a]
Never smoker	34 (33%)	119 (39%)	
Current smoker	37 (36%)	99 (33%)	
Previous smoker	33 (32%)	85 (28%)	
Ever used corticosteroids			<0.01[a]
Yes	92 (89%)	33 (11%)	
No	12 (12%)	270 (89%)	
Age at first use of corticosteroids	35 (3−69) years	39.5 (10−58) years	0.46[b]
Duration of corticosteroid use			<0.01[a]
< 1 year	22 (24%)	19 (59%)	
> 1 year	70 (76%)	13 (41%)	
Ever diagnosed with osteoporosis			<0.01[c]
Yes	7 (7%)	1 (0%)	
No	97 (93%)	311 (100%)	
Family history of osteoporosis			0.86[a]
No	91 (88%)	268 (86%)	
Yes	9 (9%)	28 (9%)	
Do not know	4 (4%)	16 (5%)	
Family history of fractures			0.03[a]
No	64 (62%)	152 (49%)	
Yes	36 (35%)	153 (49%)	
Do not know	4 (4%)	7 (2%)	
Ever used oral contraceptives*			0.56[a]
Yes	57 (76%)	161 (73%)	
No	18 (24%)	61 (28%)	
Age at first use of oral contraceptives*	20 (14−40) years	19 (13−49) years	0.29[b]
Duration of oral contraceptive use*			0.04[a]
< 5 years	34 (60%)	71 (44%)	
> 5 years	23 (40%)	90 (56%)	
Premenopausal*	45 (60%)	135 (60%)	1.00[a]
Postmenopausal*	30 (40%)	90 (40%)	
Age at menopause in years*	49.5 (24−56) years	48 (35−55) years	0.74[b]
Use of HRT*			<0.01[a]
Yes	23 (31%)	33 (15%)	
No	52 (69%)	192 (85%)	
Age at first HRT use in years*	40 (24−53) years	49 (35−56) years	<0.01[b]
Duration of HRT use*			0.03[a]
< 5 years	8 (35%)	21 (64%)	
> 5 years	15 (65%)	12 (36%)	

HRT, Hormone replacement therapy.
*Only female respondents.
[a]χ^2 for contingency tables (P), [b]Mann−Whitney test (2P), [c]Fisher's exact test (P).

contingency tables, and if the number was too small for the χ^2 test by Fisher's exact test. Mann−Whitney statistics was used to compare continuous distributions such as age. Multivariate comparisons were made using logistic regression to adjust for potential confounders such as age, gender, type of Cushing's syndrome (pituitary or adrenal), and the presence of prior fractures. All calculations were performed using SPSS 6.1.3.

The study was approved by the regional ethics committees (no. 1999/4462).

Results

Of the 125 patients contacted, 104 (83.2%) responded. The respondents and non-respondents were similar concerning age ($2P = 0.82$), gender ($P = 0.45$), proportion with Cushing's disease ($P = 0.67$), and frequency of surgery ($2P = 1.00$). Tables 1 and 2 show the baseline characteristics of the patients and controls. The female patients had a shorter duration of oral contraceptive use than the controls due to the fact that more of the patients received substitution with female sex steroids due to pituitary insufficiency (Table 1). Among the patients a prior diagnosis of osteoporosis was more frequent than among the controls. Subjects with adrenal disease were younger than those with pituitary disease. As expected, patients with pituitary disease more frequently had deficiencies in other hormonal axes necessitating substitution (Table 2). None of the patients had received ketoconazole. It did not

Table 2 Baseline characteristics of the patients subgrouped according to pituitary or adrenal disease (median and range or actual number).

Parameter	Pituitary disease ($n = 68$)	Adrenal disease ($n = 28$)	P
Age (years)	50 (19–85)	43 (19–61)	0.02[a]
Age at diagnosis (years)	35 (7–69)	36.5 (3–53)	0.35[a]
Cured after surgery*			0.08[b]
Yes	40 (85%)	19 (100%)	
No	7 (15%)	0 (0%)	
Ever used corticosteroids			0.15[b]
Yes	59 (87%)	27 (96%)	
No	9 (13%)	1 (4%)	
Ever used GH			<0.01[b]
Yes	20 (29%)	0 (0%)	
No	48 (71%)	28 (100%)	
Ever used thyroid hormones			0.01[b]
Yes	20 (29%)	2 (7%)	
No	48 (71%)	26 (93%)	
Ever used female sex steroids†			0.01[b]
Yes	18 (42%)	3 (12%)	
No	25 (58%)	23 (89%)	
Ever used male sex steroids‡			0.49[b]
Yes	8 (32%)	0 (0%)	
No	17 (68%)	2 (100%)	
Ever used ADH			0.01[b]
Yes	13 (19%)	0 (0%)	
No	55 (81%)	28 (100%)	
Ever used vitamin D supplements			0.24[b]
Yes	7 (10%)	5 (18%)	
No	61 (90%)	23 (82%)	
Ever used calcium supplements			0.65[b]
Yes	14 (21%)	6 (21%)	
No	54 (79%)	22 (79%)	

ADH, anti-diuretic hormone (vasopressin).
[a]Mann–Whitney test, [b]Fisher's exact test.
* Only those with sufficient long-term follow-up data (>5 years), †Only female patients, ‡Only male patients.

change the results in the following to adjust for use of corticosteroids, use of oral contraceptives, use of hormonal replacement or family history of fractures.

Seventy-six of the respondents had Cushing's disease. Seventy-two of these had undergone pituitary surgery, while four had not had surgery at the time of the study. Four patients with Cushing's disease underwent additional adrenal surgery. Twenty-six had a benign adrenal adenoma and two had primary pigmented micronodular adrenocortical dysplasia. All 28 with adrenal disease had had surgery. The median time from diagnosis to surgery was 0.2 (range 0–3) years. In 77 patients more than 5 years had elapsed since surgery allowing for evaluation of late outcome (cure of the disease). Sixty-six (86%) were cured, while 11 (14%, including recurrences) were not.

Before the diagnosis of Cushing's syndrome was made, the patients reported a total of 27 fractures sustained during 3717 person years, while the controls suffered 110 fractures during 11 151 person years. After the diagnosis, the corresponding figures were 15 fractures during 1242 person years in the patients and 62 fractures during 3725 person years in the controls. There was a significant increase in overall crude fracture risk in the patients within the 2 years immediately

prior to diagnosis (RR = 6.0, 95% CI: 2.1–17.2), but no significant increase in fracture risk after diagnosis (Fig. 1). The RR in the 2 years immediately prior to diagnosis was significantly higher than it was more than 2 years before diagnosis and after diagnosis respectively ($2P < 0.01$ by Poisson regression). There was no difference in the increase in fracture risk in the last 2 years prior to surgery between patients with pituitary or adrenal disease ($P = 0.60$). Furthermore, patients with Cushing's syndrome had a higher risk of low-energy fractures (Table 3). At the time of the study, three patients (2.9%, 95% CI: 0.6–8.2%) were receiving treatment with bisphosphonates (two etidronate, one alendronate). Among the patients, 13% (95% CI: 7–20%) had ever used vitamin D, while 21% (95% CI: 14–30%) had ever used calcium supplementation before or after diagnosis.

Table 4 shows that a previous fracture was a strong risk factor for sustaining a new fracture after diagnosis. The male patients tended to have fewer fractures than the females. There was no significant difference in fracture risk between patients with pituitary and adrenal disease.

The number of fractures was too low to demonstrate any regional skeletal differences in fracture risk.
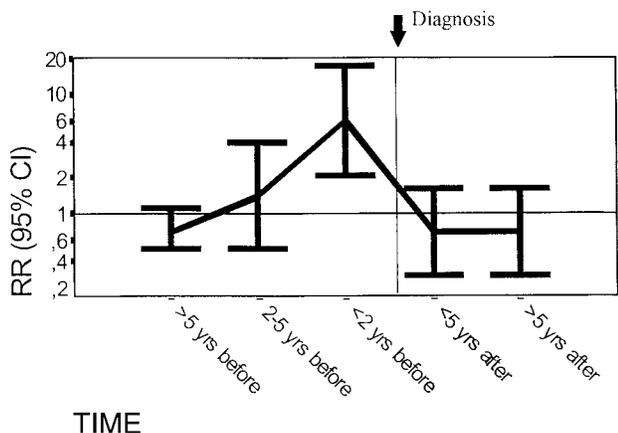
Figure 1 Fracture risk in patients compared with controls before and after the diagnosis (rate ratio (RR)) and 95% confidence interval (CI)). Note the log scale on the ordinate.

Discussion

Our data demonstrated an increased fracture risk in a large consecutive cohort of 104 patients with Cushing's syndrome. This increased fracture risk was confined to the last 2 years prior to diagnosis and therapy, and was reverted to normal following diagnosis and treatment. The narrow time window with an increased fracture risk prior to diagnosis might suggest that diagnosis was made within a few years after onset of the disease. The increased occurrence of low-energy fractures and the higher frequency of patients with a diagnosis of osteoporosis suggest a reduced biomechanical competence of the skeleton. A selection bias may have been present: a diagnosis of osteoporosis or an incident low-energy fracture in a young subject may have led to the diagnosis of Cushing's syndrome. However, this observation does not mean that the short time interval from onset to diagnosis was biased. Furthermore, the number of subjects with fractures, especially low-energy fractures, only accounted for a small proportion of all subjects, i.e. in most subjects the diagnosis was not made based on occurrence of fractures or a finding of osteoporosis.

The fracture risk was similar in pituitary disease and adrenal disease, indicating that although pituitary disease may cause a deficiency of bone anabolic hormones (e.g. sex steroids), the excess glucocorticoid is the main causative factor (8). This is in accordance with reports

Table 4 Risk factors for a fracture after the diagnosis was made among the patients, logistic regression with all variables entered into the equation.

Parameter	OR (95% CI)
Age (years)	1.03 (0.97–1.10)
Gender (male vs female)	0.15 (0.02–1.42)
Pituitary (n = 68) vs adrenal (n = 28) disease	1.20 (0.23–6.17)
Fracture prior to diagnosis (yes/no)	6.55 (1.64–26.12)*

OR: odds ratio.
* $P < 0.05$.

of pronounced clinical osteoporosis both in patients with pituitary (2) and adrenal disease (3). However, the number of patients with adrenal disease was limited, and small differences in fracture risk between patients with adrenal or pituitary disease (less than a doubling) may have been overlooked.

It is well recognised that exogenous glucocorticoids induce a prompt decrease in BMD (13) and that patients with Cushing's syndrome have a reduced BMD (5, 6). The rapid bone loss during exogenous glucocorticoid excess and the increase in BMD (14) and normalisation of fracture risk (1) following cessation of glucocorticoid therapy or cure of Cushing's syndrome (6, 7) indicate that at least part of the bone loss is reversible.

Although previous studies have suggested that the fracture threshold is reduced in osteoporosis induced by exogenous glucocorticoids (15), this notion was not supported by a recent major epidemiological study (16).

The normalisation of fracture risk following diagnosis and treatment stresses the importance of early diagnosis and treatment since irreversible bone changes with trabecular thinning and perforations may occur over time in the untreated state (17).

The decrease in fracture rate after diagnosis may be explained by the decrease in endogenous glucocorticoid secretion following surgery. Moreover, supplementation with vitamin D and calcium (9), treatment with sex steroids (18), and with bisphosphonates (19) may have contributed to reduce the risk of fractures.

The 49 patients who had died during the study period were not included. If these patients had died from their disease or complications to their disease, it is likely that they were more severely affected than the surviving patients and also may have had more fractures. The potential bias from excluding these patients will

Table 3 Fracture energies. Low-energy fractures: fractures occurring after minimal or no trauma; medium-energy fractures: fractures occurring after, for example, a fall at the same level; high-energy fractures: fractures occurring after a fall from one level to another or following, for example, a car accident.

Type	Low-energy fractures	Medium + high energy fractures
Cushing's syndrome	4 (9.5%)	38 (90.5%)
Controls	3 (1.8%)	167 (98.2%)

Fisher's exact test: $P = 0.004$.

therefore tend to reduce the difference between patients and controls and will not compromise the conclusion that fracture risk was increased before the diagnosis.

The fracture reports were reliable in accordance with observations from other studies (20), and bias from fracture reports does thus not seem to have affected the conclusions.

In conclusion, the present study has demonstrated an increased fracture risk in patients with Cushing's syndrome in the 2 years immediately prior to diagnosis, but not after the diagnosis and treatment.

Acknowledgement

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