J Endocrinol Invest (2014) 37:957–965
DOI 10.1007/s40618-014-0126-1

ORIGINAL ARTICLE

Fracture risk assessment before and after resolution of endogenous hypercortisolism: Is the FRAX® algorithm useful?

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Received: 28 April 2014 / Accepted: 19 June 2014 / Published online: 11 July 2014

Abstract
Purpose Fracture risk data following curative treatment of Cushing's syndrome (CS) are scarce and the role of bisphosphonates in bone recovery after remission is controversial. We evaluated the effects of hypercortisolism remission in bone recovery in CS. Then, we assessed if the FRAX® algorithm calculated before the cure can predict fracture risk after cure.
Methods Thirty-six patients with CS were retrospectively investigated. Bone turnover markers, bone mineral density (BMD) at the lumbar spine (L1–L4) and left femur (both neck and total hip were considered), and fracture risk using FRAX® algorithm with femoral neck BMD were evaluated at diagnosis and after a median follow-up of 24 months (range 12–108 months) from hypercortisolism remission. Data about bone active therapy were analyzed.
Results Hypercortisolism remission was associated with the improvement of all densitometric parameters and with the reduction of fracture risk. The percentage change in BMD and the fracture risk were not significantly different in bisphosphonate-treated vs. untreated patients. During follow-up, three fractured patients at baseline exhibited a new vertebral fracture. A baseline 10-year probability of major osteoporotic fractures (FRAX® Major) of 17 % was able to predict the occurrence of a new vertebral fracture during follow-up after cure with 100 % sensitivity, 77 % specificity, 81 % positive predictive value and 100 % negative predictive value.
Conclusions Osteoporosis and fracture risk may be reversible after curative treatment of CS, regardless of bisphosphonate therapy. We suggest applying the FRAX® algorithm to all active CS patients using a baseline FRAX® Major of 17 % as "intervention threshold".

Keywords Cushing's syndrome · Fracture risk · FRAX® algorithm · Bone complications

Introduction

Chronic glucocorticoid excess is accompanied by a wide range of signs and symptoms, known as Cushing's syndrome (CS). Endogenous glucocorticoid excess in patients with CS may arise from ACTH-secreting pituitary tumor, ectopic (non-pituitary) ACTH production, or adrenal tumor [1].

Osteoporosis is a major complication of CS leading to an increased risk of fragility fractures [1, 2]. The prevalence of osteoporosis among patients with CS has been reported to be about 40 % [3], with 21 % of these patients developing non-traumatic bone fractures [4]. Hypercortisolism exerts both direct and indirect effects on bone. Direct effects include reduction of osteoblast function, increase of bone resorption, and impairment of enteral calcium absorption; indirect effects include impaired hormonal secretion and action (in particular gonadal steroids and growth hormone), and reduction of muscle volume and strength [2, 5].

The trabecular bone is the most affected by glucocorticoid excess, with a consequent increased risk of vertebral osteoporotic fractures that frequently represent the first

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manifestation of CS and can occur even when the bone mineral density (BMD) is normal [2, 6]. It is suggested that the development of endogenous glucocorticoid-induced osteoporosis (GIO) and bone fractures depends on age at onset, duration and severity of hypercortisolism, and individual susceptibility to glucocorticoids, which is genetically determined [2, 7]. Bone loss induced by glucocorticoids is potentially reversible after curative treatment of the glucocorticoid excess; a few studies reported an improvement of BMD up to complete normalization in some cases after remission of hypercortisolism [8–12].

Despite the large literature on exogenous GIO, data on fracture risk after curative treatment of CS are retrospective and very limited probably as a consequence of the rarity of CS [3]. In fact, the only study that evaluated this aspect collected information on fracture history via a self-administered questionnaire. As well as limitations with the study methodology, the study showed that fracture risk seemed to revert to normal in the first few years after treatment [13].

Various agents have been evaluated for the treatment of GIO. Currently, several bisphosphonates (alendronate, risedronate, and zoledronic acid) and PTH (teriparatide) are widely approved for the management of GIO, but studies on their efficacy are mainly addressed in glucocorticoid-treated patients [14]. Data in patients with endogenous hypercortisolism are very scarce and the role of antiresorptive therapy with bisphosphonates in the recovery of bone mass after treatment of CS is unclear. The study by Di Somma et al. [15] of 11 patients suggested that alendronate may induce a more rapid improvement in BMD than cortisol normalization alone, probably by restoring the balance between bone formation and resorption. On the contrary, more recent data from 20 patients with CS (five of them treated with bisphosphonates) showed that spontaneous improvement of osteoporosis is independent of basal conditions and unaffected by treatment with bisphosphonates [12].

In a recent review article, Tóth and Grossman, emphasized the importance of detailed fracture risk assessment not only in patients with exogenous GIO but also in patients with endogenous hypercortisolism although it is difficult to translate glucocorticoid dosage to different degrees of endogenous hypercortisolism [16]. More recently, Scillitani et al. discussed who, when, and how the patient with endogenous hypercortisolism should be treated with bone active therapy. The authors point out that although there are no data on validation of FRAX® stratification method in patients with endogenous hypercortisolism, this algorithm could be applied to CS to identify the patients to treat before and after hypercortisolism remission [17].

Considering this aspect and the lack of guidelines for the management of endogenous GIO, the aim of the present study was to retrospectively evaluate the effect of the remission of hypercortisolism following curative surgery on bone mass, bone turnover markers, and fracture risk using FRAX® algorithm with femoral neck BMD; and to investigate the possible additional role of antiresorptive therapy with bisphosphonates in the recovery of bone metabolism alterations in patients with CS.

Then, we assessed if the FRAX® algorithm calculated before the cure can predict fracture risk after cure.

Subjects and methods

Subjects

Thirty-six consecutive CS patients referred to our specialized centre were retrospectively investigated. Eligible criteria were a diagnosis of active CS followed by hypercortisolism remission after curative surgery for at least 12 months at the time of data analysis.

The differential diagnosis between Cushing's disease (CD), ectopic ACTH secretion (EAS), and adrenal CS (ACS) was made based on clinical features and laboratory assessments, according to the consensus statement and clinical practice guidelines [1, 18].

Disease duration was estimated considering the date of onset of signs and symptoms of hypercortisolism. In all patients, pathological findings and clinical remission of hypercortisolism after surgery confirmed the diagnosis.

Remission of hypercortisolism was defined on the basis of regression of clinical signs/symptoms of hypercortisolism, and normalization of biochemical and hormonal parameters [urinary-free cortisol (UFC) normalization, normal cortisol suppression after low dose of dexamethasone, and cortisol rhythm restoration]. Substitutive steroid supplementation with cortisone acetate at a mean dosage of 37.5 mg/day was started just after surgery and tapered off until discontinuation; median duration 6 months postoperatively (range 3–12 months).

Outcome measurements

Patients have been evaluated at diagnosis and after a median follow-up of 24 months (range 12–108 months) from hypercortisolism remission. Bone profile was investigated by evaluating biochemical markers of bone turnover, densitometric parameters, prevalence of vertebral fractures, and fracture risk.

We calculated the percentage change in densitometric parameters and fracture risk from baseline to the last follow-up after hypercortisolism remission as: %

change = [(follow up values − baseline values)/baseline values] × 100.

Hormonal evaluations

Hormonal evaluations included measurements of midnight serum cortisol (after 24-h hospitalization), 24-h UFC (the average of two collections was used for all patients), and serum cortisol levels after 1-mg dexamethasone suppression test. Serum cortisol was measured by chemiluminescent immunometric assays (Advia Centaur; Bayer Diagnostics, Newbury, UK). Method sensitivity was 0.4 μg/dl; intra-assay and inter-assay variation coefficients (CVs) were 4.4 and 6.0 %, respectively. 24-h UFC was assessed by high-performance liquid chromatography (intra-assay CV 7.73 %; normal range 9.2–45.2 μg/24 h).

Biochemical and bone turnover markers

In all patients, we evaluated biochemical parameters of calcium and phosphorus metabolism, and bone turnover markers. We considered serum C-terminal telopeptides of type I collagen (s-CTX) as a marker of bone resorption and serum osteocalcin (s-OC) as a marker of bone apposition. s-CTX and s-OC were measured using electrochemiluminescence immunoassay on a Roche Modular Analytics E170 Analyzer (F. Hoffman-La Roche Ltd, Basel, Switzerland). The measuring range for s-CTX was 10–6,000 pg/ml (normal range: <570 pg/ml for premenopausal women, <1,000 pg/ml for postmenopausal women, and <700 pg/ml for men aged 50–70 year) and for s-OC was 0.500–300 ng/ml (normal range 13–48 ng/ml). All hormone determinations were performed in the same laboratory.

BMD measurements

BMD was measured by dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L1–L4) and left femur (both neck and total hip were considered) using a Lunar Prodigy® densitometer (GE Healthcare, Madison, WI, USA) equipped with Lunar Prodigy® enCore software. BMD values were expressed as g/cm^2. All DXA evaluations were performed by the same radiologist technician. *T*- and *Z*-scores were expressed as the increase in relative risk of fracture per unit SD decrease in BMD measurements and calculated according to the manufacturer's normative data. Quality control was guaranteed by scanning of anthropometric spine phantom every other day. Fractured vertebrae were excluded from BMD measurements in all patients and the site with the lowest *T*- or *Z*-score of the three skeletal sites was used to make a diagnosis.

The World Health Organization (WHO) criteria were used to define the conditions of normal mineralization, osteopenia, and osteoporosis (*T*-score ≥ −1.0 SD; −2.5 SD < *T*-score < −1.0 SD; and *T*-score ≤ −2.5 SD, respectively) in postmenopausal women and in men aged >50 year. In fertile women and in men aged ≤50 year, the diagnosis was made based on *Z*-scores relative to the expected BMD values of healthy individuals matched for age and sex. The diagnosis of osteoporosis was made when *Z*-scores were ≤ −2.5 SD, with the addition of a secondary cause of osteoporosis (for example CS). The presence of vertebral or femoral fractures, regardless of *Z*-scores, was also a criterion to define osteoporosis in this group of patients [19].

Vertebral fractures

To detect vertebral fractures, all patients underwent morphometric X-ray absorptiometry followed by morphometric radiography which uses conventional lateral thoracolumbar spine radiographs to analyze vertebral body shape. According to the Genant visual semiquantitative method [20], vertebral fractures were defined as reductions on lateral spine radiographs of >20 % in one vertebral body's height.

Fracture risk assessment

Fracture risk was evaluated using FRAX® algorithm with femoral neck BMD. FRAX® is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the WHO Collaborating Centre for Metabolic Bone Diseases [21–23]. The algorithm integrates clinical risk factors and femoral neck BMD, and calculates the 10-year probability of hip (FRAX® Hip) and major osteoporotic fractures (clinical spine, hip, humerus, or wrist fracture; FRAX® Major).

FRAX® models have been developed from studying population-based cohorts from Asia, Europe, the Middle East and Africa, North America, Latin America, and Oceania [21–23]. They are based on age, sex, weight, height, and dichotomized clinical risk factors such as: previous fracture, family history of hip fracture, current smoking, alcohol consumption, use of long-term oral glucocorticoids, rheumatoid arthritis, or secondary osteoporosis (such as type 1 diabetes, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease). Femoral neck BMD can be optionally input to enhance fracture risk prediction [24]. FRAX® algorithm can be used to evaluate fracture risk in patients with exogenous GIO [25], but it is not designed to be used in patients with endogenous hypercortisolism due

to the rarity of the disease and the lack of available data for the FRAX® cohorts. However, CS is a well-recognized secondary cause of osteoporosis characterized by a state of hypercortisolism similar to that of patients treated with exogenous glucocorticoids for various disorders. Considering these facts, we used FRAX® algorithm in patients with CS, entering "yes" in both the "secondary osteoporosis" and "glucocorticoids" fields of the algorithm for patients with active disease, and "no" in the same fields after hypercortisolism remission.

Finally, it should be noted that FRAX® algorithm is designed for patients aged 40–90 year; for younger patients, the program computes probabilities as for a patient aged 40 year.

Statistical analysis

The Kolmogorov–Smirnov test was applied to assess the normal distribution of quantitative variables. According to data distribution, comparison of continuous variables between two groups of patients was performed using Student's *t* test or the Mann–Whitney rank sum test. Continuous variables were expressed as mean ± SD. Categorical variables were analyzed by the χ^2 test or Fisher's exact test if appropriate and expressed as percentages.

Receiver operating characteristic (ROC) curve analyses were used to determine the optimal cutoff value for the 10-year probability of major osteoporotic fracture for discriminating CS patients with and without fracture as well as to evaluate the predictive value of baseline FRAX® Major for the occurrence of a new vertebral fracture during follow-up after cure. ROC curves were generated by plotting the relationship of true positivity (sensitivity) and false positivity (1 − specificity) at various cutoff points of the tests. An AUC of 1.0 is characteristic of an ideal test, whereas 0.5 indicates a test of no diagnostic value.

Logistic regression analysis was used to assess the association between the occurrence of a new vertebral fracture during follow-up after cure (dependent variable) and independent variables such as age, gender, duration of follow-up, cumulative dose of substitutive steroid supplementation and bone active therapy.

A P value <0.05 was considered significant. All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

All 36 patients were white (30 female and 6 male; mean age 43.6 ± 13.5 year). Twenty-two patients were diagnosed with CD, ten patients with ACS due to a cortisol hypersecreting adrenal adenoma, and four patients with EAS. Mean disease duration was 44.6 ± 48.0 months. No patients had a past or current history of diseases known to affect bone metabolism other than CS.

At the time of diagnosis, 18 women were premenopausal and 12 postmenopausal. One patient became postmenopausal during the study period. All male patients at baseline presented subnormal serum testosterone levels (range 8.5–12.3 nmol/l).

Six patients (four with CD, one with ACS, and one with EAS) were under antiresorptive therapy with a bisphosphonate (four patients with alendronate 70 mg/week and two patients with risedronate 35 mg/week), and calcium (1,000 mg/day) and vitamin D (800 IU/day) supplementation. All the patients with vitamin D deficiency were under adequate supplementation.

Bone mass measurements and fracture evaluation

At baseline, 22 of 36 patients (61 %; 13 of 22 with CD, 7 of 10 with ACS, and two of four with EAS) showed alterations of bone mass (BMD below the expected range for age and sex, osteopenia, or osteoporosis). Vertebral fractures were present in 8 of 36 patients (22 %; 5 of 22 with CD, 2 of 10 with ACS, and 1 of 4 with EAS). Only four fractured patients (4 of 8) were treated with a bisphosphonate. Baseline characteristics of fractured vs. unfractured patients are presented in Table 1. Compared with unfractured patients, fractured patients exhibited more compromised spine and femoral neck densitometric parameters (Table 1).

According to ROC curve analysis, a cutoff value of 17 % for the FRAX® Major was able to discriminate fractured patients from those without fractures, with sensitivity (SE) and specificity (SP) of 100 % (AUC FRAX® Major 1.00; 95 % confidence interval 1.00–1.00; $P = 0.001$).

Bisphosphonate therapy assessment

Baseline characteristics of the six patients treated with bisphosphonates compared with the 30 untreated patients are reported in Table 2. No differences were found in age, gender distribution, hypercortisolism degree, and disease duration between the two groups. The densitometric parameters of the bisphosphonate-treated patients were significantly lower, fracture prevalence was higher, and FRAX® Hip and FRAX® Major were increased, compared with the untreated patients (Table 2).

Follow-up after curative surgery

In total, 35 of 36 patients with CS improved their bone mass. One patient, whose gonadal status changed from

Table 1 Baseline characteristics of Cushing's syndrome patients with and without vertebral fractures

	CS unfractured ($n = 28$)	CS fractured ($n = 8$)	P	All CS ($n = 36$)
Age (years)	43.39 ± 12.71	44.38 ± 17.25	0.86	43.61 ± 13.57
Age range (years)	17–66	25–70		17–70
BMI (kg/m^2)	28.09 ± 6.02	28.06 ± 2.67	0.99	28.08 ± 5.33
Female sex	24 (86 %)	6 (75 %)	0.40	30 (83 %)
Disease duration (months)	46 ± 50	39 ± 41	0.79	44 ± 48
Midnight serum cortisol (nmol/l)	541.52 ± 178.57	618.24 ± 112.05	0.42	552.82 ± 170.29
UCF (nmol/24 h)	906.44 ± 1,855.79	1,083.37 ± 1,085.80	0.85	932.63 ± 1,747.65
1 mg-DST (nmol/l)	557.24 ± 467.26	675.37 ± 94.39	0.69	574.08 ± 434.42
s-CTX (pg/ml)*	481.02 ± 288.07	485.95 ± 252.17	0.97	481.96 ± 275.55
s-OC (ng/ml)**	5.33 ± 7.21	5.15 ± 2.74	0.95	5.29 ± 6.57
Lumbar (L1–L4) BMD (g/cm^2)	1.061 ± 0.140	0.936 ± 0.192	<0.05	1.032 ± 0.159
Lumbar (L1–L4) *T*-score (±SD)	−1.02 ± 1.18	−1.99 ± 1.44	0.06	−1.26 ± 1.29
Lumbar (L1–L4) *Z*-score (±SD)	−1.01 ± 1.18	−1.77 ± 1.49	0.13	−1.18 ± 1.27
Femoral neck BMD (g/cm^2)	0.849 ± 0.139	0.715 ± 0.177	<0.05	0.815 ± 0.158
Femoral neck *T*-score (±SD)	−1.18 ± 1.02	−2.27 ± 1.42	<0.05	−1.45 ± 1.21
Femoral neck *Z*-score (±SD)	−1.03 ± 1.04	−2.01 ± 1.14	<0.05	−1.28 ± 1.13
Total hip BMD (g/cm^2)	0.971 ± 0.158	0.799 ± 0.271	0.09	0.928 ± 0.199
Total hip *T*-score (±SD)	−0.33 ± 1.17	−1.76 ± 2.39	0.08	−0.69 ± 1.62
Total hip *Z*-score (±SD)	−0.40 ± 1.02	−1.71 ± 1.90	0.06	−0.72 ± 1.36
Bone mass alterations	14 (50 %)	8 (100 %)	<0.05	22 (61 %)
FRAX® Major (%)	8.75 ± 3.59	35.83 ± 14.21	<0.05	18.90 ± 16.07
FRAX® Hip (%)	1.53 ± 1.51	19.83 ± 14.63	<0.05	8.39 ± 12.51

Data are expressed as mean ± SD or absolute number (percentage in parentheses)

BMD bone mineral density, *BMI* body mass index, *CS* Cushing's syndrome, 1 mg-DST serum cortisol after 1-mg dexamethasone suppression test, *s-CTX* serum C-terminal telopeptides of type I collagen, *s-OC* serum osteocalcin, *UFC* urinary-free cortisol

* s-CTX values excluding patients treated with bisphosphonates were: 475.88 ± 296.72 pg/ml (unfractured patients) vs. 447.17 ± 293.87 pg/ml (fractured patients); $P = 0.94$; 471.35 ± 288.23 pg/ml (all CS)

** s-OC values excluding patients treated with bisphosphonates were: 5.56 ± 7.47 ng/ml (unfractured patients) vs. 5.48 ± 3.03 ng/ml (fractured patients); $P = 0.52$; 5.54 ± 6.97 ng/ml (all CS)

premenopausal to postmenopausal during the study period, had a lower bone mass compared with baseline. The six patients under antiresorptive treatment at baseline were all still treated at follow-up evaluation. The overall median duration of bisphosphonate treatment was 42 months (range 24–96 months).

Follow-up data regarding bone turnover markers and densitometric parameters in patients treated and untreated with bisphosphonates are reported in Tables 3 and 4, respectively. In both groups of patients, BMD, *T*- and *Z*-scores at lumbar spine and *Z*-scores at femoral neck significantly improved after hypercortisolism remission. A significant increase leading to a normalization of s-OC levels was also observed in untreated patients (Table 4).

Figure 1 shows the changes in 10-year fracture risk. In both groups (patients treated and untreated with bisphosphonates), the FRAX® Major significantly decreased at follow-up (Fig. 1a). Untreated patients also showed a significant reduction of the FRAX® Hip (Fig. 1b).

The percentage increase in lumbar spine and femoral neck BMD, as well as the percentage decrease in the 10-year probability of hip and major osteoporotic fractures is not significantly different in patients treated with bisphosphonates compared with those untreated (Table 5). No correlations were observed between the percentage change in BMD and fracture risk and the following parameters: basal densitometric parameters, degree and duration of hypercortisolism, duration and cumulative dose of steroid replacement taken, duration of follow-up.

During follow-up, none of the patients unfractured at baseline developed new vertebral and/or non-vertebral fractures. In contrast, three of the fractured patients at baseline each exhibited a new vertebral fracture. Considering the eight fractured patients at baseline, no significant differences were found between those who worsened at follow-up (three of eight) and those who remained unchanged (five of eight). However, it is worth noting that fractured patients who worsened at follow-up were all untreated with bisphosphonates.

ROC curve analysis was performed to assess if baseline FRAX® values may predict the occurrence of new vertebral fractures during follow-up after cure. A cutoff value for baseline FRAX® Major of 17 % was able to predict the occurrence of a new vertebral fracture after cure with

Table 2 Baseline characteristics of Cushing's syndrome patients treated with and without bisphosphonates (data for all CS patients are the same as in Table 1)

	CS untreated ($n = 30$)	CS treated ($n = 6$)	P
Age (years)	43.40 ± 13.29	44.67 ± 16.25	0.83
BMI (kg/m^2)	28.20 ± 5.81	27.57 ± 2.42	0.81
Female sex	25 (83 %)	5 (83 %)	1.00
Disease duration (months)	45 ± 48	43 ± 51	0.95
Midnight serum cortisol (nmol/l)	542.89 ± 165.60	615.48 ± 135.24	0.43
UCF (nmol/24 h)	914.13 ± 1,814.07	1,080.67 ± 1,350.62	0.88
1 mg-DST (nmol/l)	567.73 ± 454.84	612.72 ± 339.48	0.85
s-CTX (pg/ml)	471.35 ± 288.23	582.75 ± 27.64	0.60
s-OC (ng/ml)	5.54 ± 6.97	3.54 ± 2.04	0.57
Lumbar (L1–L4) BMD (g/cm^2)	1.060 ± 0.149	0.896 ± 0.148	<0.05
Lumbar (L1–L4) *T*-score (±SD)	−1.02 ± 1.26	−2.31 ± 0.87	<0.05
Lumbar (L1–L4) *Z*-score (±SD)	−0.97 ± 1.23	−2.21 ± 1.05	<0.05
Femoral neck BMD (g/cm^2)	0.837 ± 0.152	0.699 ± 0.151	<0.07
Femoral neck *T*-score (±SD)	−1.27 ± 1.17	−2.44 ± 0.98	<0.05
Femoral neck *Z*-score (±SD)	−1.10 ± 1.09	−2.20 ± 1.03	<0.05
Total hip BMD (g/cm^2)	0.956 ± 0.184	0.767 ± 0.245	0.13
Total hip *T*-score (±SD)	−0.40 ± 1.43	−2.34 ± 1.92	<0.05
Total hip *Z*-score (±SD)	−0.45 ± 1.16	−2.25 ± 1.67	<0.05
Bone mass alterations	17 (57 %)	5 (83 %)	0.22
FRAX® Major (%)	12.15 ± 7.71	33.76 ± 20.48	<0.05
FRAX® Hip (%)	3.12 ± 3.68	19.98 ± 17.57	<0.05

Data are expressed as mean ± SD or absolute number (percentage in parentheses)

BMD bone mineral density, *BMI* body mass index, *CS* Cushing's syndrome, 1 mg-DST, serum cortisol after 1-mg dexamethasone suppression test, *s-CTX* serum C-terminal telopeptides of type I collagen, *sOC* serum osteocalcin, *UFC* urinary-free cortisol

Table 3 Changes in bone turnover markers and densitometric parameters after hypercortisolism remission following curative surgery in patients with Cushing's syndrome treated with bisphosphonates

	Baseline ($n = 6$)	Follow-up[a] ($n = 6$)	P
s-CTX (pg/ml)	582.75 ± 27.64	310.50 ± 318.90	0.41
s-OC (ng/ml)	3.54 ± 2.04	28.97 ± 32.66	0.45
Lumbar (L1–L4) BMD (g/cm^2)	0.896 ± 0.148	1.062 ± 0.111	<0.05
Lumbar (L1–L4) *T*-score (±SD)	−2.31 ± 0.87	−1.04 ± 0.90	<0.05
Lumbar (L1–L4) *Z*-score (±SD)	−2.21 ± 1.05	−0.66 ± 1.55	<0.05
Femoral neck BMD (g/cm^2)	0.699 ± 0.151	0.754 ± 0.141	<0.05
Femoral neck*T*-score (±SD)	−2.44 ± 0.98	−2.02 ± 0.95	<0.05
Femoral neck *Z*-score (±SD)	−2.20 ± 1.03	−1.40 ± 0.99	<0.05
Total hip BMD (g/cm^2)	0.767 ± 0.245	0.781 ± 0.222	0.61
Total hip T-score (±SD)	−2.34 ± 1.92	−2.03 ± 1.50	0.35
Total hip *Z*-score (±SD)	−2.25 ± 1.67	−1.70 ± 1.15	0.23

Data are expressed as mean ± SD

BMD bone mineral density, s-*CTX* serum C-terminal telopeptides of type I collagen, *s-OC* serum osteocalcin

[a] Median 24 months

100 % SE, 77 % SP, 81 % positive predictive value (PPV) and 100 % negative predictive value (NPV).

Logistic regression analysis showed that the occurrence of a new vertebral fracture during follow-up after cure was independent from age, sex, duration of follow-up, cumulative dose of substitutive steroid supplementation and bone active therapy.

Discussion

Our study confirms that patients with CS present a high prevalence of osteoporosis and fractures; in particular, bone mass alterations were detected in 61 % and vertebral fractures in 22 % of patients investigated. Moreover, fractures occurred even in patients presenting a normal BMD value. These results are in line with previously published studies [4, 7].

We evaluated fracture risk in patients with CS using the FRAX® algorithm with BMD; to our knowledge, this is the first time this has been done. This available worldwide algorithm allows the calculation of population-specific individualized fracture risk based on the principle that the use of clinical risk factors in conjunction with BMD measurement improves global fracture risk prediction [24, 26].

Table 4 Changes in bone turnover markers and densitometric parameters after hypercortisolism remission following curative surgery in patients with Cushing's syndrome untreated with bisphosphonates

	Baseline ($n = 30$)	Follow-up[a] ($n = 30$)	*P*
s-CTX (pg/ml)	481.02 ± 288.07	430.16 ± 167.26	0.80
s-OC (ng/ml)	5.33 ± 7.21	16.37 ± 8.15	<0.05
Lumbar (L1–L4) BMD (g/cm^2)	1.061 ± 0.140	1.156 ± 0.186	<0.05
Lumbar (L1–L4) *T*-score (±SD)	−1.02 ± 1.18	−0.19 ± 1.54	<0.05
Lumbar (L1–L4) *Z*-score (±SD)	−1.01 ± 1.18	0.15 ± 1.73	<0.05
Femoral neck BMD (g/cm^2)	0.849 ± 0.139	0.867 ± 0.124	0.22
Femoral neck *T*-score (±SD)	−1.18 ± 1.02	−0.97 ± 0.98	0.14
Femoral neck *Z*-score (±SD)	−1.03 ± 1.04	−0.48 ± 0.88	<0.05
Total hip BMD (g/cm^2)	0.971 ± 0.158	0.994 ± 0.176	0.98
Total hip *T*-score (±SD)	−0.33 ± 1.17	−0.15 ± 1.23	0.67
Total hip *Z*-score (±SD)	−0.40 ± 1.02	−0.45 ± 1.17	0.20

Data are expressed as mean ± SD

BMD bone mineral density, *s-CTX* serum C-terminal telopeptides of type I collagen, *s-OC* serum osteocalcin

[a] Median 24 months

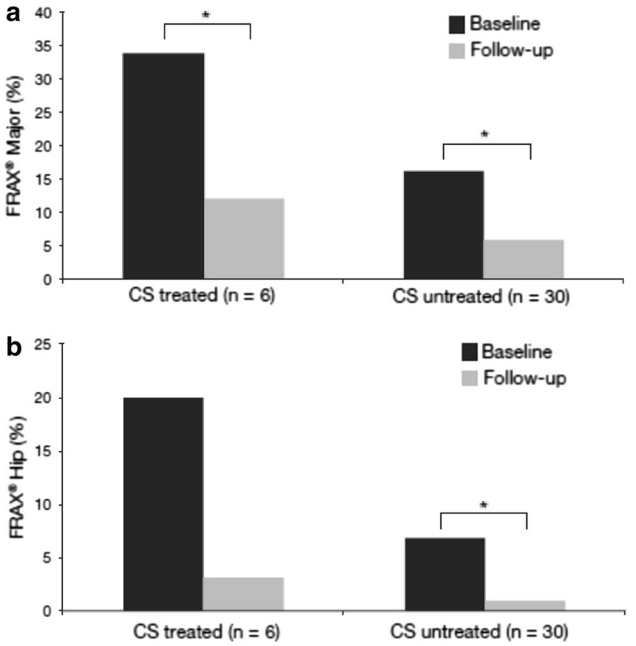

Fig. 1 Changes in the 10-year probability of: **a** major osteoporotic fracture (FRAX® Major); and **b** hip fracture (FRAX® Hip) after curative surgery of hypercortisolism in patients with Cushing's syndrome (CS), treated with and without bisphosphonates (*$P < 0.05$)

Table 5 Percentage change in BMD and fracture risk from baseline to the last follow-up after hypercortisolism remission in patients with Cushing's syndrome, treated with and without bisphosphonates

% Change (from baseline to follow-up)	CS treated ($n = 6$)	CS not treated ($n = 30$)	*P*
Lumbar (L1–L4) BMD	11.24 ± 5.66	6.91 ± 8.71	0.30
Femoral neck BMD	8.44 ± 5.55	2.12 ± 6.16	0.07
FRAX® Major	−48.21 ± 19.04	−47.67 ± 10.97	0.94
FRAX® Hip	−59.68 ± 29.82	−56.44 ± 16.95	0.79

Data are expressed as mean ± SD

CS Cushing's syndrome, *BMD* bone mineral density

Our results show that fracture risk in patients with CS significantly reduced after hypercortisolism remission following curative surgery. In this context, the remission of hypercortisolism represents the major determinant for the recovery of bone health in patients with CS. Previous studies have demonstrated that endogenous GIO is reversible after treatment of glucocorticoid excess [8–12] and that fracture risk decreases after remission of CS [13]. Our data confirm these findings and show that cure of endogenous hypercortisolism is followed by a significant improvement in BMD, both at spine and femoral neck sites, independent of densitometric parameters and follow-up duration. In fact, almost all patients (35 of 36) improved their bone mass; only one patient worsened probably because she changed her gonadal status from premenopausal to postmenopausal during the study period.

The role of bisphosphonates in the recovery of bone mass after cure of CS is controversial [12, 15]. Our data suggest that the use of bisphosphonates in patients with CS does not induce a more rapid improvement in BMD than cortisol normalization alone. This finding is in line with recent data of Randazzo et al. [12].

The reduction in osteoblast number and function has a central role in the pathogenesis of GIO leading to suppression of bone formation, identified by a decrease of s-OC. The latter represents the more specific bone apposition marker in patients with endogenous hypercortisolism, whereas data about other markers of bone turnover are discordant [21, 22, 27, 28].

In line with previously published literature [8–10], our patients with CS exhibit, at diagnosis, s-OC levels below the normal range with a rapid restoration after cure of endogenous hypercortisolism. In this context, bisphosphonates could theoretically exert an unfavorable effect by decreasing bone turnover and osteoblast number, thereby preventing reversion of the suppressive mechanism [12].

To our knowledge, no data are available regarding the role of bisphosphonates in promoting the reduction of fracture risk after cure of CS. Our study is the first to focus on this topic, finding no difference between the percentage reduction of the 10-year probability of hip and major osteoporotic fractures after hypercortisolism remission in patients treated and untreated with bisphosphonates. Based on this result, clinical improvement due to hypercortisolism remission seems to be sufficient to reduce or "normalize" fracture risk in patients with CS.

However, three fractured patients exhibited a new vertebral fracture during follow-up.

As many guidelines consider a prior fragility fracture sufficient for starting treatment [29–31], the intervention threshold in patients without a prior fracture can be set at fracture probability equivalent to individuals with a prior fragility fracture.

In the present study, a 10-year probability of major osteoporotic fracture of 17 %, determined by the FRAX® algorithm with BMD, was able to discriminate fractured from unfractured patients and to predict the occurrence of a new vertebral fracture during follow-up after cure with a good prognostic profile (SE 100 %, SP 77 %, PPV 81 %, NPV 100 %). This "fracture threshold" might so represent the "intervention threshold" in patients with CS. It should also be noted that the threshold value of 17 % found in our study is substantially in line with that of 20 % proposed by the current guidelines of exogenous GIO [14, 25]. Based on these results, we suggest using the FRAX® algorithm with BMD in all patients with CS, to stratify fracture risk and to identify patients who could benefit from therapy.

The major limitations of the present study are the retrospective data analysis, the relatively short duration of follow-up for assessing incident fractures and the relatively small number of patients with CS investigated. However, CS is a rare disease with an annual incidence of 0.7–2.4 per million people [32], which makes it difficult to obtain exhaustive data on many aspects of this potentially lethal disorder. Therefore, many controversial issues of CS still wait to be clarified from large-scale studies [18, 33]. However, the cohort of patients in the present study is the largest compared with previous studies addressing BMD recovery after cure of hypercortisolism [8–12]. The numbers of patients receiving bisphosphonate treatment are also very limited, but similar to those reported in the two previous studies investigating the role of bisphosphonates in the recovery of bone mass after CS remission [12, 15].

FRAX® algorithm presents also some limitations associated with its use. In particular, in exogenous hypercortisolism, the use of glucocorticoids is entered as a dichotomous risk factor (yes or no) and does not take into account both the dose and the duration of glucocorticoid treatment. Therefore, FRAX® may underestimate fracture risk in patients taking higher doses, and overestimate risk in those taking lower doses. For this reason, Kanis et al. [34] recently formulated a simple arithmetic adjustment of conventional FRAX® to modulate the risk assessment with knowledge of the dose of glucocorticoid. Considering the lack of standardized criteria to define severity in patients with CS and the lack of available data to compare the doses of glucocorticoids with the degree of endogenous hypercortisolism, we assessed fracture risk in patients using the conventional FRAX® algorithm without any adjustment.

Finally, it should be noted that FRAX® algorithm is not validated for morphometric vertebral fractures and that it is not designed to assess fracture risk during bone active therapy.

The main strength of the present study is that, for the first time, the effect of hypercortisolism cure, calcium and/or vitamin D supplementation and bisphosphonate therapy, both on bone mass and particularly on fracture risk evaluated by the FRAX® algorithm with BMD, was evaluated in patients with CS. As the FRAX® algorithm is not validated for use in patients with CS, its application could be questionable. However, based on the results reported in this study, we believe that it could be a useful tool in clinical practice for the management of osteoporosis induced by endogenous hypercortisolism.

In conclusion, fracture risk induced by CS seems to be reversible after treatment, regardless of bisphosphonate therapy. We suggest the use of the FRAX® algorithm with BMD in all active CS patients to identify patients at high-fracture risk who will benefit from bone active therapy. A "fracture threshold" of 17 % for the 10-year probability of major osteoporotic fracture could be suggested as an "intervention threshold".

Acknowledgments The authors would like to thank Mihaela Voinea, PhD, of Excerpta Medica, who provided editorial assistance and styling prior to submission. This research was partially supported by PRIN (grant number 201098WFZ2_006).

Conflict of interest The Authors have no conflict of interest to declare. The authors received editorial/writing support in the preparation of this manuscript provided by Excerpta Medica, funded by Novartis Oncology Region Europe. The authors did not receive honoraria related to the preparation of this manuscript.

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