ORIGINAL ARTICLE

Cushing's syndrome and bone mineral density: lowest Z scores in young patients

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ABSTRACT

Background: Patients with Cushing's syndrome have a high prevalence of osteoporotic fractures. Little is known about factors determining bone mineral density (BMD) in these patients.

Objective: To evaluate which factors influence BMD at the time of diagnosis of Cushing's syndrome.

Methods: In 77 consecutive patients with Cushing's syndrome with a median age of 41.1 (interquartile range 31.1 to 52.2) years we measured BMD of the lumbar spine and the femoral neck at the time of diagnosis. From the medical records we obtained information on possible predictors of BMD. We compared BMD with a reference population by means of the Z score. Adjustment for other variables than age and sex was made with linear regression models.

Results: Patients with Cushing's syndrome had a low Z score in both the lumbar spine (–1.07 SD (95% CI –1.43 to –0.71 SD)) and in the femoral neck (–0.81 SD (95% CI –1.06 to –0.55 SD)). 82% of patients had osteopenia at one or both sites (T score lower than –1 SD), including 31% with osteoporosis (T score –2.5 SD or lower).

The main determinant of the Z score at both sites and for both sexes was age. Z score increased by about 0.4 SD per decade. 81% of patients <40 years had osteopenia at one or both sites, including 31% with osteoporosis. For patients ≥40 years these percentages were 83 and 32%, respectively. Origin of Cushing's syndrome, average 24-hour serum cortisol, duration of symptomatic glucocorticoid excess, sex, body mass index, menstrual status and duration of amenorrhoea did not influence the Z score.

Conclusions: At the time of diagnosis, BMD in patients with Cushing's syndrome is low compared with sex- and age-matched controls. The prevalence of osteopenia and osteoporosis at the time of diagnosis of Cushing's syndrome is independent of age. Treatment with bisphosphonates should be considered in patients of all ages with Cushing's syndrome who have a decreased BMD.

KEYWORDS

Cushing, endogenous glucocorticoid excess, bone mineral density, Z score, age, osteoporosis

INTRODUCTION

The association between hypercorticism and loss of skeletal mass was first described by Harvey Cushing.[1] It is most likely that several factors act together in causing bone loss in Cushing's syndrome. Glucocorticoids impair bone formation through direct effects on cells of osteoblastic lineage and they enhance bone resorption due to direct effects on osteoclasts.[2,3] So, the coupling between bone resorption and bone formation, crucial to the normal process of bone remodelling, appears to be lost in active Cushing's syndrome.[4] Furthermore, there is a decrease in intestinal calcium absorption and in renal calcium reabsorption.[5,6] Glucocorticoid-induced inhibition of gonadotropin and growth hormone secretion may also play a role, as well as glucocorticoid-induced decrease in muscular strength, leading to impaired physical activity.[6,7] Bone loss due to treatment with pharmacological doses of glucocorticoids is more profound in trabecular than in cortical bone.[5,8] This is supposedly related to the greater surface-to-volume ratio of trabecular bone compared with cortical bone. Since bone remodelling takes place at bone surfaces, trabecular bone responds more rapidly to either positive or negative changes in bone balance.[9] In patients with endogenous hypercortisolism, bone loss in the lumbar spine, consisting mainly of trabecular bone, also seems to be more profound than bone loss in the femoral neck, consisting mainly of cortical bone.[4,10-12]

So far, little is known about factors that determine bone mineral density (BMD) in patients with untreated Cushing's syndrome. The aim of the present study was to evaluate which factors influence BMD at the time of diagnosis of Cushing's syndrome.

PATIENTS AND METHODS

Between 1989 and 2003, all patients newly diagnosed with Cushing's syndrome referred to the Department of Endocrinology of the Radboud University Nijmegen Medical Centre in Nijmegen, the Netherlands underwent measurement of BMD of both the lumbar spine (L1-L4, posterior-anterior) and the right femoral neck. Before treatment of hypercortisolism, BMD was measured by dual-energy X-ray absorptiometry (DEXA, Hologic Inc., Waltham MA, before 1998 QDR-1000, thereafter QDR-4500 Elite). The scanner was calibrated daily by means of phantom measurements. Vertebrae that showed artefacts due to fracture, spinal deformation and/or degenerative disease were excluded from the analysis. For each measured value of BMD (g/cm²) a T score and a Z score were calculated. A Z score of 0 SD means that the BMD is average for age and sex. From the medical records we also derived information on possible predictors of BMD.

To assess the effect of endogenous hypercortisolism on BMD we used the Z score, which implicitly means comparison with a reference group. To assess determinants of BMD within the group of Cushing patients we also used the Z score as measure of BMD, which means that comparisons are adjusted for age and sex. The comparisons were made by calculating mean differences in Z score between subgroups with corresponding 95% confidence intervals (95% CI). Adjustment for other variables than age and sex were made with linear regression models. To assess correlations between variables, we used Pearson correlation coefficients. To evaluate the risk for osteoporotic fractures we used the T score.

RESULTS

A total of 58 patients with untreated pituitary-dependent and 21 patients with untreated adrenal-dependent Cushing's syndrome were seen during the study period. For unknown reasons, BMD measurements were not carried out in two patients with pituitary-dependent Cushing's syndrome. Furthermore, we excluded patients with ectopic ACTH secretion from our analysis. Thus, BMD values of 56 patients with pituitary-dependent and 21 patients with adrenal-dependent Cushing's syndrome (15 adrenal adenoma, 4 adrenal carcinoma, and 2 bilateral macronodular hyperplasia) were available. The group consisted of 19 men and 58 women, median age 41.1 (interquartile range 31.1 to 52.2) years. The average level of serum cortisol in blood samples taken over 24 hours at four hourly intervals was median 0.578 (interquartile range 0.498 to 0.668) μmol/l. Of the women, 21 were oligomenorrhoeic or eumenorrhoeic, whereas 31 women were postmenopausal or had been amenorrhoeic for at least six months secondary to the Cushing's syndrome.

Two patients had undergone extirpation of the uterus, and four women were on oral contraceptive agents. Median body mass index was 27.7 (interquartile range 25.2 to 32.5) kg/m². The characteristics of patients of different ages, and patients with Cushing's syndrome of different origins, did not differ with respect to the variables used in our analyses, except of course that older female patients were more often amenorrhoeic. None of the patients had previously taken drugs known to interfere with bone metabolism.

BMD at diagnosis of Cushing's syndrome

Before treatment, patients with Cushing's syndrome had a low mean BMD. The decrease in BMD seemed to be more severe in the lumbar spine than in the femoral neck, although the difference was not statistically significant. In the lumbar spine we found a mean BMD of 0.89 g/cm² (95% CI 0.85 to 0.93 g/cm²), corresponding to a mean Z score of −1.07 SD (95% CI −1.43 to −0.71 SD), whereas in the femoral neck a mean BMD of 0.76 g/cm² (95% CI 0.73 to 0.79 g/cm²) was found with a mean Z score of −0.81 SD (95% CI −1.06 to −0.55 SD). In 73% of the patients, the Z score at one or both sites was lower than −1 SD, including 16% who had a Z score of −2.5 SD or lower. A total of 82% had osteopenia at one or both sites, including 31% with osteoporosis according to World Health Organisation criteria. There was no significant difference in Z score between patients with Cushing's syndrome of different origins. For patients with pituitary-dependent Cushing's syndrome we found mean Z scores in the lumbar spine of −1.08 SD (95% CI −1.52 to −0.63 SD) and in the femoral neck of −0.66 SD (95% CI −0.99 to −0.33 SD), whereas for those with adrenal-dependent Cushing's syndrome we found Z scores in the lumbar spine of −1.14 SD (95% CI −1.82 to -0.46 SD) and in the femoral neck of −1.14 SD (95% CI −1.55 to −0.74 SD).

Factors predictive of BMD

Table 1 shows the relative influence of various variables on the Z score at the time of diagnosis of Cushing's syndrome. Variables related to Cushing's syndrome, such as origin of Cushing's syndrome, average 24-hour serum level of cortisol and duration of symptomatic glucocorticoid excess, did not exert an influence on Z scores. In females, BMD of the femoral neck was lower than in males. When correcting for the other variables analysed, femoral neck BMD in females was 0.13 g/cm² (95% CI 0.05 to 0.21) lower than in males. Interestingly, in males as well as in females, age correlated positively with Z score at both the lumbar spine and the femoral neck. Z scores increased by about 0.4 SD per decade (*figure 1*). Of female patients <40 years, 82% had a T score lower than −1 SD at one or both sites and 27% had a T score of -2.5 SD or lower. For female patients ≥40 years these percentages were 86 and 31%, respectively. Percentages for male patients were comparable. Of male patients under the age of 40 years, 79% had a T score lower

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Table 1. *Influence of variables on Z score (SD) of the lumbar spine (L1-L4) and the femoral neck at the time of diagnosis of Cushing's syndrome*

Lumbar spine	Linear regression coefficient univariate (95% CI)	Linear regression coefficient multivariate[a] (95% CI)
Origin of Cushing's syndrome (adrenal versus pituitary)	-0.08 (-0.85 to 0.70)	0.25 (-0.96 to 1.45)
Average 24h serum cortisol (μmol/l)[b]	-1.61 (-3.89 to 0.67)	-0.62 (-3.27 to 2.04)
Age (years)	0.04 (0.02 to 0.06)[**]	0.04 (0.003 to 0.07)[*]
Sex (male *vs.* female)	-0.69 (-1.47 to 0.09)	-0.34 (-1.52 to 0.84)
Body mass index (kg/m²)	0.03 (-0.03 to 0.09)	0.01 (-0.05 to 0.08)
Secondary amenorrhoea *vs* oligo-/eumenorrhoea[c]	0.17 (-0.55 to 0.88)	0.58 (-0.50 to 1.66)
Length of period of secondary amenorrhoea before DEXA measurement (years)[c]	0.04 (-0.02 to 0.11)	0.10 (-0.12 to 0.33)
Femoral neck	**Linear regression coefficient univariate (95% CI)**	**Linear regression coefficient multivariate[a] (95% CI)**
Origin of Cushing's syndrome (adrenal *vs.* pituitary)	-0.47 (-1.03 to 0.09)	0.14 (-0.64 to 0.92)
Average 24h serum cortisol (μmol/l)[b]	0.35 (-1.29 to 1.99)	1.32 (-0.37 to 3.01)
Age (years)	0.03 (0.01 to 0.05)[**]	0.04 (0.02 to 0.06)[**]
Sex (male *vs.* female)	0.47 (-0.12 to 1.06)	0.70 (-0.08 to 1.47)
Body mass index (kg/m²)	0.00 (-0.05 to 0.04)	0.00 (-0.05 to 0.04)
Secondary amenorrhoea *vs* oligo-/eumenorrhoea[c]	0.32 (-0.26 to 0.91)	-0.41 (-1.39 to 0.57)
Length of period of secondary amenorrhoea before DEXA measurement (years)[c]	0.01 (-0.04 to 0.06)	0.03 (-0.14 to 0.21)

[*]$p<0.05$; [**]$p<0.01$. [a] Adjusted for age, sex, body mass index, origin of Cushing's syndrome, and average 24-hour serum cortisol; [b]Average of serum cortisol in blood samples taken at 0.00 h, 4.00 h, 8.00 h, 12.00 h, 16.00 h, and 20.00 h; [c]Secondary amenorrhoea is defined as postmenopausal or amenorrhoeic for at least 6 months secondary to Cushing's syndrome.

than –1 SD at one or both sites including the 36% who had a T score of -2.5 SD or lower. For male patients ≥40 years these percentages were 60 and 40%, respectively.

DISCUSSION

The main finding of the present study is that in male as well as in female patients with Cushing's syndrome, age correlated positively with Z scores, both in the lumbar spine and in the femoral neck. In Cushing patients of either sex the prevalence of osteopenia as well as of osteoporosis at either the lumbar spine or the femoral neck or at both sites was the same in patients <40 years compared with patients of ≥40 years. This explains why also young patients with Cushing's syndrome have a considerable fracture risk.

We found that in patients with newly diagnosed endogenous Cushing's syndrome, the mean Z score is approximately 1 SD below control values, consistent with previous reports.[4,11,13-17] The decrease in BMD seems to be more severe in the lumbar spine than in the femoral neck; however, as in previous reports[10,11] the difference was not statistically significant.

Our data do not show a significant difference in BMD between patients with adrenal-dependent and pituitary-dependent Cushing's syndrome, neither in the group as a whole, nor in male or female patients separately. This confirms the findings in a very recent study by Tauchmanovà *et al.*[15] In contrast, Ohmori *et al.*[18] did find a lower BMD in females with adrenal-dependent

Cushing's syndrome than in females with pituitary-dependent Cushing's syndrome, both in the lumbar spine and in the femoral neck. In their study body mass index was significantly higher in patients with a pituitary origin of the disease than in those with an adrenal origin, which may explain their findings. Minetto *et al.*[16] also found that lumbar spine BMD, but not femoral neck BMD, was lower in patients with adrenal-dependent than in patients with pituitary-dependent Cushing's syndrome.

In our study severity of Cushing's syndrome, expressed as average 24-hour cortisol levels in serum, and duration of symptomatic glucocorticoid excess, did not influence Z scores. These findings are in line with observations in patients treated with pharmacological doses of glucocorticoids. In patients treated with glucocorticoids the daily dose does not correlate with BMD,[19] and bone loss occurs particularly during the first months of treatment.[19,20] At diagnosis of Cushing's syndrome, the duration of glucocorticoid excess is usually more than a year, so it is not surprising that we did not observe a correlation between duration of symptomatic glucocorticoid excess and BMD. In our group of patients neither body mass index nor menstrual status showed a relation with Z scores. This is in line with observations published in a very recent report,[15] but is in contrast with the situation in healthy subjects, where body mass index and menstrual status strongly influence BMD.[21]

The calculation of Z scores for BMD as measured by the two types of DEXA scanners used in our study was based on the same reference population, i.e. NHANES reference

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Figure 1: *Influence of age on Z score of the lumbar spine (L1-L4; A and C) and the femoral neck (B and D) at the time of diagnosis of Cushing's syndrome in both sexes*
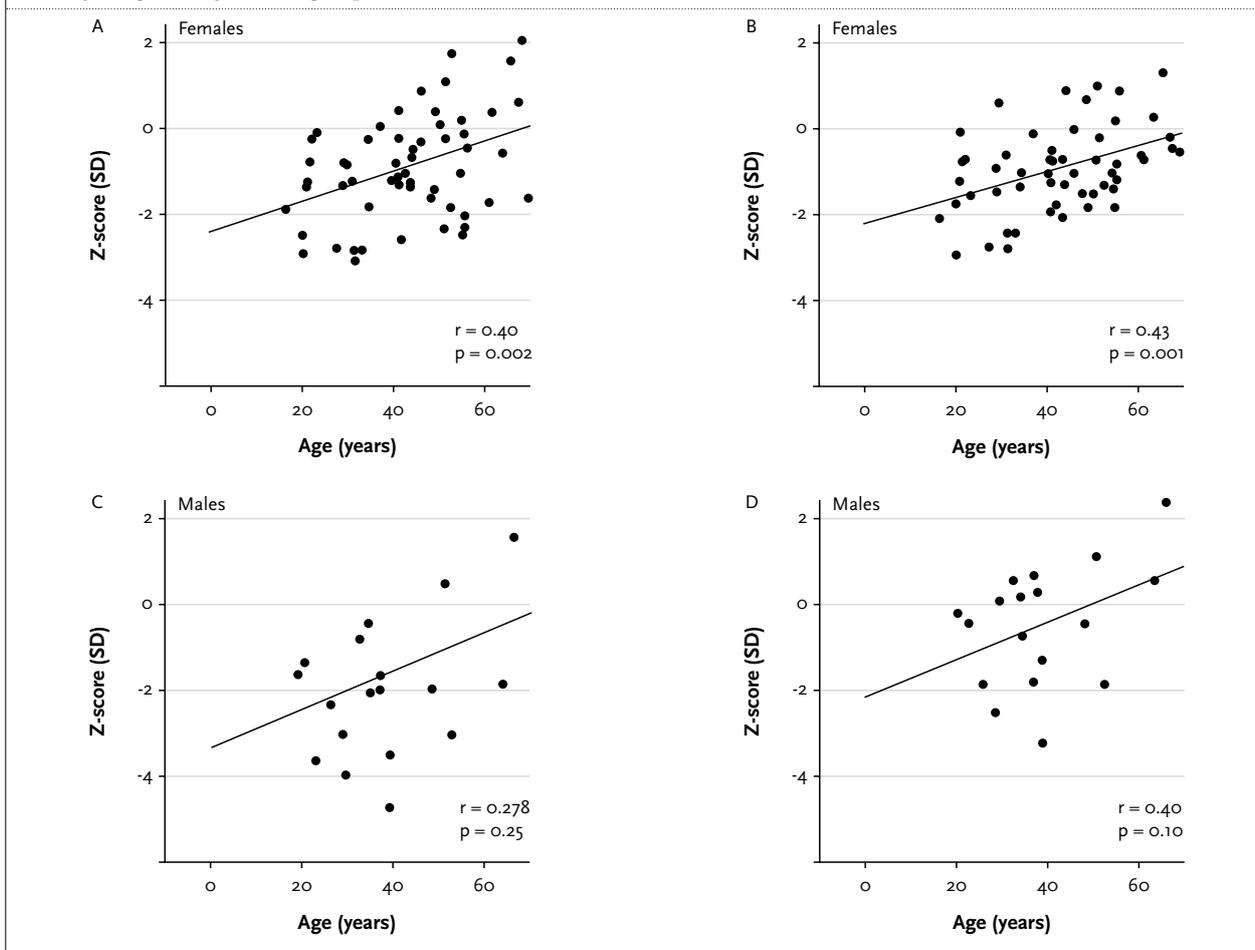
population. Besides presenting Z-scores, for the purpose of clinical interpretation we pooled BMD values obtained by two types of DEXA scanners. This pooling is justified by the results of a study in which Litaker *et al.* compared repeatedly measured values of BMD within 219 individuals, as obtained by Hologic QDR-1000/W and 4500W DXA scanners. The difference between the mean values as measured by the two types of machines was only 0.02 g/cm² in white females and 0.05 g/cm² in white males. The differences found by Litaker *et al.* clearly pose a problem for the interpretation of longitudinal follow-up studies, measuring the gradual effect of the course of disease or cure within individuals. For cross-sectional studies, in contrast, describing a point estimate for the large effect of a situation such as the presence of Cushing's syndrome, the disagreement between the machines is negligible. Indeed, the difference between the machines is far smaller than the difference we found between white, mostly female, patients with Cushing's syndrome and the NHANES reference population (i.e. a decrease of 1.07 SD ≈ 0.11 g/cm² in lumbar spine and a decrease of 0.81 SD ≈ 0.08 g/cm² in femoral neck).[22] The low R² values we found using multivariate regression (0.145 for lumbar spine and 0.315 for femoral neck)

indicate that there is a lot of variation in BMD that cannot be explained by the variables we used for our analyses. Therefore, one or more as yet undetermined (e.g. genetic) factors exert a strong influence on BMD in Cushing patients.

Osteoporosis is a well-known side effect of treatment with glucocorticoids. For patients in whom prednisone treatment is started with an intended treatment duration of at least three months at a dose of ≥7.5 mg per day, it is advised to add bisphosphonates.[23] Although results in one nonrandomised study on alendronate therapy in patients treated for Cushing's disease are promising,[12] at present there is no consensus that patients with endogenous Cushing's syndrome should start on bisphosphonates as soon as hypercortisolism has been demonstrated. One of the reasons for not giving bisphosphonates is the fact that BMD after cure of Cushing's syndrome recovers spontaneously.[4,11,13] However, normalisation of BMD in Cushing's syndrome may last approximately ten years and it is not certain whether complete recovery occurs in every patient. At the time of diagnosis, 82% of our patients had a T score lower than –1 SD, and 31% had a T score of –2.5 SD or lower, consistent with a previous report.[17]

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Other authors found even higher prevalences.[12,18] As a T score lower than −1 SD is associated with a 1.5- to 2-fold increase of the risk of fractures and a T score of −2.5 SD or lower is associated with a 3.5- to 4.5-fold increase of fracture risk in eucorticoid postmenopausal persons,[24,25] Cushing patients have a considerable fracture risk. Moreover, at comparable levels of BMD, patients treated with glucocorticoids have a higher risk of fractures than nonusers, probably reflecting glucocorticoid-induced deterioration of bone quality.[15,19,26-28] Indeed, the prevalence of osteoporotic fractures in patients with endogenous Cushing's syndrome (30 to 76%) is higher than expected on the basis of BMD alone, particularly at the vertebral level.[15,16,29-31]

In summary, 82% of patients with untreated Cushing's syndrome had a T score lower than −1 SD, including the 31% of patients who had a T score of −2.5 SD or lower. Surprisingly, we found that the prevalence of osteopenia and osteoporosis at the time of diagnosis of Cushing's syndrome was independent of age. As recovery of bone loss after treatment of Cushing's syndrome may last many years, treatment with bisphosphonates should be considered in patients with Cushing's syndrome who have a decreased BMD, independent of age. A randomised trial with sufficient power and duration of follow-up is needed to definitively prove that treatment with bisphosphonates accelerates the recovery of bone loss after successful treatment of Cushing's syndrome and that treatment with bisphosphonates prevents fractures in patients with this disorder.

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