# Effects of Cushing Disease on Bone Mineral Density in a Pediatric Population

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**Objective** To evaluate bone mineral density (BMD) in children with Cushing disease before and after transphenoidal surgery (TSS).

**Study design** Hologic dual-energy x-ray absorptiometry (DXA) scans of 35 children with Cushing disease were analyzed retrospectively. Sixteen of the 35 patients had follow-up DXA scans performed 13 to 18 months after TSS. BMD and bone mineral apparent density (BMAD) for lumbar spine (LS) L1 to L4 and femoral neck (FN) were calculated.

**Results** Preoperatively, 38% and 23% of patients had osteopenia of the LS and FN, respectively. Both BMD and BMAD Z-scores of the LS were worse than those for the FN (–1.60 ± 1.37 versus –1.04 ± 1.19, $P = .003$), and (–1.90 ± 1.49 versus –0.06 ± 1.90, $P < .001$); postoperative improvement in BMD and BMAD were more pronounced in LS than in the FN (0.84 ± 0.88 versus 0.15 ± 0.62, $P<.001$; and 0.73 ± 1.13 versus –0.26 ± 1.21, $P = .015$). Pubertal stage, cortisol levels, and length of disease had no effect on BMD.

**Conclusions** In children with Cushing disease, vertebral BMD was more severely affected than femoral BMD and this effect was independent of degree or duration of hypercortisolism. BMD for the LS improved significantly after TSS; osteopenia in this group may be reversible. *(J Pediatr 2010;156:1001-5)*.

Cushing disease is rare in children.[1] Osteopenia has been reported in adults with Cushing disease.[2-7] Although exposure to excess glucocorticoids is a frequent cause of osteoporosis or osteopenia in both children and adults, limited data are available about bone mineral density (BMD) in children with Cushing disease.[7-12] Hypercortisolism is known to be associated with loss of skeletal mass and can lead to increased vertebral fracture risk.[13] Impaired BMD has been shown at the time of diagnosis in adults with a variety of causes of Cushing syndrome (CS), including Cushing disease.[2-7]

Similarly impaired BMD at the time of diagnosis has been seen in 3 studies involving as many as 14 patients with childhood-onset Cushing disease.[7,10,11] BMD has been shown to improve after cure in adult patients; however, limited follow-up data exist for children.[2,4,5,9,14,15] One longitudinal study in 6 children demonstrated that BMD impairment in childhood-onset Cushing disease could be partially reversed 2 years after normalization of cortisol levels.[9] Another study looked at Hologic dual-energy x-ray absorptiometry (DXA) scans performed in 11 children at a mean of 4.5 years after cure of Cushing disease; however, information on BMD before surgery in these patients was not available.[10] A prospective study of 14 patients with CS showed that most had major increases in bone mass after normalization of cortisol secretion; by the third year of remission, BMD at the spine and hip had returned to the reference range in most patients, compared with low pretreatment values.[11]

Multiple factors contribute to decreased BMD in Cushing disease, including a direct effect of glucocorticoids on osteoclasts and osteoblasts, both enhancing bone resorption and impairing bone formation.[16,17] Glucocorticoids also act to decrease gastrointestinal calcium absorption and renal calcium reabsorption.[18] Children with Cushing disease often have musculoskeletal weakness and can have decreased weight-bearing activity that may contribute to impaired BMD. In addition, patients with Cushing disease are at risk for other pituitary hormone deficiencies, including central hypogonadism and growth hormone (GH) deficiency, both of which have the potential to contribute to osteopenia.[1] Because

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| BMAD | Bone mineral apparent density |
| BMD | Bone mineral density |
| CS | Cushing syndrome |
| DXA | Dual-energy x-ray absorptiometry |
| FN | Femoral neck |
| GH | Growth hormone |
| GHD | Growth hormone deficiency |
| LS | Lumbar spine |
| TSS | Transphenoidal surgery |
| UFC | Urinary free cortisol |

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childhood and adolescence is a time of high bone mass accrual, one might expect that disordered bone formation and remodeling during this critical period may impair the achievement of peak bone mass.[19] Whether poor peak bone mass accrual in childhood leads to an increased risk of osteoporosis later in life is being debated.[20] In this study, we analyzed BMD data at the spine and hip before and as long as 18 months after transphenoidal surgery (TSS) in children with Cushing disease and examined whether BMD in these patients was associated with the degree of hypercortisolism.

## Methods

All patients were admitted to the National Institutes of Health Warren Magnuson Clinical Center in the last 10 years. Studies were performed under clinical protocol 97-CH0076, which was approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Institutional Review Board. Informed consent from the patients' parents (and assent from older children) was obtained for all patients. A total of 35 patients underwent TSS; 16 patients had follow-up DXA scans performed 13 to 18 months after TSS. Cure of hypercortisolism was achieved in 34 of the patients by TSS alone; 1 patient required a second TSS and radiation therapy. None of the patients had fractures.

Patients were examined for pubic hair and breast or testicular development and were grouped in Tanner stages 1, 2, and 3 (pre-pubertal to mid-puberty) versus Tanner 4 and 5 (late puberty).

Dual-energy x-ray absorptiometry (DXA) scans (Hologic, Inc, Bedford, Massachusetts) were obtained in 35 children with Cushing disease and were retrospectively analyzed (20 females; mean age, 12.8 ± 3.1 years; **Table**). DXA scans were performed on the Hologic (Hologic Inc., Bedford, Massachusetts) densitometers QDR2000, QDR4500, and DelphiA. From measurement of an anthropomorphic spine phantom, the coefficient of variation for determination with the QDR2000 instrument was <0.5%, and for the QDR4500 and DelphiA instruments, the values were <0.4% for 6 months. Comparison of a spine phantom scanned on both the QDR2000 and QDR4500 instruments and another phantom on both the QDR4500 and Delphi instruments gave bone mineral density determinations that were within 1.0%. Femoral neck (FN) and lumbar spine (LS) Z-scores were calculated by using the National Institute of Child Health and Human Development Children's Reference Database, which provides age-, race-, and sex-specific reference curves.[21] Low bone density for chronological age was defined as a Z-score ≤–2.00.[22] Our cohort of patients with Cushing disease included those with short stature caused by hypercortisolemia. Because BMD calculations may be underestimated in shorter patients, we normalized the BMD to a derived reference volume by correcting BMD values to adjust for differences in bone size by using bone mineral apparent density (BMAD), an estimation of volumetric bone mass (g/cm$^3$).[23,24] BMAD for FN and LS anterior posterior 2 to 4 were calculated as previously described.[23] Z-scores for BMAD were calculated by using the Stanford University Bone Mineral Density website (http://www-stat-class.stanford.edu/pediatric-bones/#applet).

**Table. Demographic and clinical characteristics in patients with Cushing disease**

| | Cushing disease |
|---|---|
| Female (%)/male (%) n = 35 | 20 (57.14) / 15 (42.86) |
| Age at surgery, years (n = 35) | 12.8 (3.07) |
| ***Race (%) n = 35*** | |
| Asian | 1 (2.86) |
| Black | 1 (2.86) |
| White | 25 (71.43) |
| Other/Unknown | 8 (22.86) |
| ***Ethnicity (%) n = 35*** | |
| Latino or Hispanic | 8 (22.86) |
| Not Latino or Hispanic | 27 (77.14) |
| ***Tanner Stage (%) n = 35)*** | |
| 1, 2, or 3 | 23 (65.71) |
| 4 or 5 | 12 (34.29) |
| Initial height SD score (n = 35) | −1.19 ± 1.12 |
| Height SD score at follow-up (n = 16) | −0.81 ± 1.17 |
| BMI Z-score (n = 35) | 2.02 ± 0.76 |
| Midnight cortisol, μg/dL (n = 35) | 21. 7 ± 21.6 |
| Urinary free cortisol, μg/m$^2$ (n = 35) | 304.5 ± 325.4 |
| Length of disease, months (n = 35) | 27.2 ± 15.3 |
| Duration to follow-up, months (n = 16) | 14.7 ± 1.5 |

Data are preoperative values and are mean ± SD, unless otherwise specified.

Cortisol hypersecretion was demonstrated in all patients with 24-hour urinary free cortisol (UFC) measurements and diurnal cortisol measurements. Diurnal plasma cortisol was obtained by placing an intravenous line at least 2 hours before the test; midnight cortisol levels were drawn at 11:30 p.m. and 12:00 a.m., while the patient was asleep. Plasma cortisol level was measured with chemiluminescence immunoassay. UFC was averaged from 2 separate preoperative measurements and was calculated per square meter of body-surface area, as previously described.[25] After TSS, 24-hour UFC was measured on postoperative days 5 to 9. Serum cortisol level was measured beginning on postoperative day 5 and was repeated daily until postoperative day 10. During this postoperative period, dexamethasone was administered to patients who required replacement. Patients were defined as cured of disease with postoperative measurements of UFC <10 μg/24 hours, plasma cortisol levels of <1 μg/dL, and/or adrenocortical insufficiency for which they received replacement.

### Statistical Analysis

Paired *t* tests, or its non-parametric parallel (Wilcoxon signed-rank test only for the change in height SD score that was not normally distributed), were used to compare paired continuous data. A 2-sample *t* test was used for comparing continuous data from distinct groups. Dichotomous data from independent groups were compared with the $\chi^2$ and Fisher exact tests, whereas paired data were compared with McNemar tests. Because the preoperative LS and FN prevalences of osteopenia were from patients with and without follow-up, their comparison with the 1-year postoperative