

Bone Mineral Density and Bone Turnover before and after Surgical Cure of Cushing's Syndrome*

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ABSTRACT

We measured bone mineral density (BMD) using dual-energy x-ray absorptiometry in 20 patients with Cushing's syndrome (CS) (14 pre- and 2 postmenopausal women, 4 men) before and in 18 of them also at regular intervals after surgical cure (median duration of follow-up, 36 months). In addition, in the premenopausal women with CS, fasting blood samples and 2-h fasting urine samples for measurement of biochemical parameters of bone and collagen metabolism were collected before and in 9 of them also at regular intervals during the first 2 yr after surgery. Marked osteopenia was present in most patients with active CS (Z-scores: lumbar spine -1.45 ± 1.44 and femoral neck -1.50 ± 1.02 ; mean \pm SD). No consistent change in BMD was observed at 3 and 6 months after surgery. Thereafter BMD increased considerably in almost all patients. For the 15 patients with a follow-up of at least 1 yr, Z-scores at the last evaluation were -0.65 ± 1.27 for the lumbar spine and -0.98 ± 1.02 for the femoral neck (both $P < 0.002$ compared with pretreatment values). In the premenopausal patients, the increase in BMD both in the lumbar spine and in the femoral neck at 24 months was inversely correlated with age ($r = -0.733$, $P < 0.03$, and $r = -0.667$, $P < 0.05$, respectively). Serum levels of osteocalcin, bone alkaline phosphatase, carboxyterminal propeptide of type I pro-

collagen, aminoterminal propeptide of type III procollagen, and the cross-linked telopeptide of type I collagen were not significantly different between the group of 14 premenopausal patients with active CS and a control group of 18 age-matched healthy premenopausal women. However, the urinary hydroxyproline/creatinine ratio was significantly higher in patients with CS (24.6 ± 9.6 vs. 16.2 ± 3.5 $\mu\text{mol}/\text{mmol}$, $P < 0.01$). In all 9 premenopausal patients, serum levels of osteocalcin increased considerably between 0 and 3 months (from 1.04 ± 0.20 to 3.82 ± 0.30 nmol/L) (mean \pm SEM, $P < 0.0001$), indicating a prompt increase of osteoblast activity. Also serum levels of carboxyterminal propeptide of type I procollagen, aminoterminal propeptide of type III procollagen, and cross-linked telopeptide of type I collagen, and the urinary hydroxyproline/creatinine ratio increased significantly between 0 and 3 months. Thereafter these levels decreased gradually. We conclude that marked osteopenia in the lumbar spine and femoral neck is present in most patients with active Cushing's syndrome. Bone density does not consistently change in the first 6 months after cure, despite an apparently rapid restoration of osteoblast activity. Thereafter remarkable improvement of bone density can be observed in almost all patients. (*J Clin Endocrinol Metab* 80: 2859–2865, 1995)

IN HIS CLASSIC report on endogenous glucocorticoid excess attributable to ACTH-producing pituitary tumors, Harvey Cushing recognized osteoporosis as a serious consequence of hypercorticism (1). This type of bone loss is more marked in trabecular than in cortical bone and frequently leads to fractures of vertebrae, ribs, and pubic bones (2).

In recent years, accurate methods to assess bone mineral density (BMD) have become available, making it possible to study the reversibility of osteopenia after cure of Cushing's syndrome. However, only a small number of longitudinal observations on BMD in patients with treated Cushing's syndrome have been reported so far (3, 4). Pocock *et al.* (3) described two patients in whom lumbar and femoral BMD increased postoperatively. Unfortunately, in these patients no information on BMD before surgery was available. Lufkin *et al.* (4) followed nine patients for 3–66 months after surgery and observed a 20% increase in lumbar BMD. However, most

subjects had only a single follow-up measurement, and BMD in the proximal femur was not assessed.

In the present study BMD is evaluated in 20 patients with active Cushing's syndrome. In 18 of these patients BMD was also measured at regular intervals after surgical cure. Duration of follow-up in these patients ranged from 3–60 months. Fifteen patients were followed for at least 12 months after successful surgery. In addition, data are presented on serum levels of markers of osteoblastic activity and collagen synthesis and on serum and urine markers of bone resorption before and during the first 2 yr after surgical cure of Cushing's syndrome.

Patients and Methods

Patients

Twenty patients with Cushing's syndrome participated in this study. Informed consent was obtained from all patients. Relevant clinical data of the patients is given in Table 1. Patients 1–14 were premenopausal women (age 29 ± 9 yr, mean \pm SD), patients 15 and 16 were postmenopausal, and patients 17–20 were men.

Six patients (1–5 and 16) had a cortisol-producing adenoma, and 14 had pituitary-dependent Cushing's syndrome. Unilateral adrenalectomy was performed in the patients with an adrenal adenoma. Afterward they received substitution therapy with cortisone acetate, 37.5 mg

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TABLE 1. Clinical data of 20 patients with Cushing's syndrome

Patient number	Age (yr) ^a	Duration of symptomatic glucocorticoid excess (months) ^a	Duration of amenorrhea (months) ^a	Body mass index (kg/m ²) ^a	Mean 24-h plasma cortisol (μmol/L) ^{a,b}	Duration of follow-up after definitive surgery (months)
1	33	30	0	22.0	0.40	57
2	19	7	0	26.7	0.69	52
3	23	15	14	29.7	0.62	48
4	42	132	uterus extirpation	27.3	0.54	27
5	20	36	0	25.6	0.50	24
6	40	27	9	25.8	0.60	60
7	29	14	0	28.7	0.59	52
8	28	23	0	29.9	0.60	40
9	22	14	8	23.5	0.66	35
10	23	48	0	42.4	0.48	12
11	17	15	6	26.9	0.97	18
12	41	24	0	38.9	0.66	3
13	32	18	9	23.6	0.55	0
14	41	48	0	39.3	0.58	0
15	52	30	168	24.6	0.38	60
16	53	24	36	27.8	0.43	5
17	28	24		24.9	0.50	48
18	25	12		20.3	0.67	36
19	51	36		28.5	0.58	29
20	52	72		25.5	0.64	3

^a At the time of definitive surgery.

^b Mean value of plasma samples obtained at 0400, 0800, 1200, 1600, 2000, and 2400 h.

daily, which was tapered off in the year after surgery and stopped between 8 and 12 months postoperatively.

Six patients (6, 10–12, 15, and 20) with pituitary-dependent Cushing's syndrome were cured by pituitary microadenectomy via the transsphenoidal route. This operation caused transient hypocortisolism in patients 6, 10, 11, and 15, necessitating substitution therapy with cortisone acetate for 8–16 months, but did not induce other endocrine deficiencies. Patients 12 and 20 were also hypocortisolemic after pituitary microadenectomy, but the short follow-up after surgery does not permit conclusions with regard to permanent postoperative endocrine deficiencies. Patients 17–19 with pituitary-dependent Cushing's syndrome were cured by (sub-)total adenohipophysysectomy via the transsphenoidal route. This operation caused permanent secondary hypocorticism and hypothyroidism, necessitating substitution therapy with cortisone acetate and L-thyroxine. Postoperative secondary hypogonadism was present in patients 18 and 19, necessitating treatment with im injections of testosterone esters. In addition, postoperative growth hormone deficiency was present in all three patients. In patient 19 substitution therapy with recombinant human growth hormone was started 21 months postoperatively. Patients 7–9 were cured by bilateral adrenalectomy, necessitating substitution therapy with glucocorticoids and 9α-fluorohydrocortisone acetate. Previous unsuccessful pituitary surgery had not induced deficiencies of pituitary hormones in these patients. Patients 13 and 14 are awaiting pituitary surgery.

In all premenopausal patients who were amenorrheic before treatment, menses returned within a few months after definite surgical cure. At the time of the evaluation of BMD (and of biochemical parameters of bone metabolism) before definite surgical therapy, patients 12, 15, and 16 used a thiazide diuretic. None of the other patients used any drugs (at this time or in the preceding 3 months) that were known to influence bone metabolism, except for patients 5, 7, and 8, who used oral contraceptives, which were discontinued 4 weeks before the preoperative evaluation.

Methods

BMD measurements. BMD was measured two times before (on 2 consecutive days) and at 3, 6, 12, 18, 24, 36, 48, and 60 months after definitive surgical treatment. BMD was measured in the lumbar spine (L1–L4; anterior-posterior) and the left femoral neck using dual-energy x-ray absorptiometry (Hologic Inc., Waltham MA, model QDR-1000). The coefficient of variation (CV) for repeat measurements in our hospital is 1.0% in the lumbar spine and 1.7% in the femoral neck (5). In none of

the patients were fractures of lumbar vertebrae seen on radiographs made before and 24 months after surgery.

BMD measurements are expressed in g/cm². Furthermore, for each BMD measurement a Z-score was calculated according to the formula $Z\text{-score (SD)} = [\text{patient's value (g/cm}^2) - \text{mean of a reference group of age- and sex-matched healthy individuals (g/cm}^2)] \div \text{SD reference group (g/cm}^2)$.

Results of BMD measurements before and during the first 2 yr after surgical treatment in patients 1, 2, 3, 6, and 15 have been reported earlier (6).

Biochemical measurements. Before surgical therapy in the 14 premenopausal women with Cushing's syndrome, blood samples were drawn (between 0830 and 0930 h) and 2-h urine samples were collected (between 0800 and 1000 h) after an overnight fast for measurement of biochemical parameters of bone and collagen metabolism. In 9 of these premenopausal patients (1–9), the parameters (except for bone alkaline phosphatase) were also determined at 3, 6, 12, 18, and 24 months after definitive surgical treatment. Data were compared with those of a group of 18 age-matched healthy premenopausal women in the early follicular phase of the menstrual cycle.

Blood samples for measurement of serum bone alkaline phosphatase, osteocalcin, carboxyterminal propeptide of type I procollagen (PICP), aminoterminal propeptide of type III procollagen (PIIINP) and the cross-linked telopeptide of type I collagen (ICTP) were centrifuged immediately after collection. Thereafter, samples were kept at –20 C until analyzed. All samples were run in duplicate. Serum bone alkaline phosphatase was assayed by a direct immunoradiometric assay (Ostase, Hybritech, San Diego CA) using two monoclonal antibodies directed against the bone isoenzyme and with bone alkaline phosphatase purified from human osteosarcoma cells as a standard. Intra- and interassay CVs were 5% and 7.5%, respectively. Serum osteocalcin was measured by RIA (OSTK-PR, CIS, Gif-sur-Yvette Cedex, France; intraassay CV 6%, interassay CV 7%). Serum PICP was measured by RIA (PICP RIA-kit, Orion Diagnostica, Espoo, Finland). Intra- and interassay CVs using a reference serum sample were 3% and 5%, respectively. Serum PIIINP was determined by RIA (PIIINP RIA-kit, Orion Diagnostica). Intra- and interassay CVs using a reference serum sample were 4% and 6%, respectively. Serum ICTP was measured by RIA (ICTP RIA-kit, Orion Diagnostica; intraassay CV 4.5%, interassay CV 6%).

Urine samples were not acidified before analysis. Urinary creatinine was measured on a Cobas Bio automatic analyzer system (Roche, Basel, Switzerland). Urinary hydroxyproline was measured with the Hypronosticon kit (Organon Teknika, Boxtel, The Netherlands).

Statistical analyses

Statistical analyses were performed using the Wilcoxon signed rank test for paired observations (P values denoted as P), the Mann-Whitney U test for unpaired observations ($P = P^*$) and the Spearman rank correlation test ($P = P^{**}$). Unless otherwise stated, the mean values ± 1 sd are given.

Results

BMD in patients with active Cushing's syndrome

Marked osteopenia was present in most patients with active Cushing's syndrome (Table 2). The decrease in BMD was equally severe in the lumbar spine and femoral neck (Z-scores: lumbar spine -1.45 ± 1.44 and femoral neck -1.50 ± 1.02 ; $P > 0.10$). In 15 of 20 patients, BMD at one or both sites was lower than -1 sd and in about half of the patients even lower than -2 sd below the mean value when compared with the reference groups of age- and sex-matched healthy individuals. There was no significant difference in BMD between patients with pituitary-dependent Cushing's syndrome (Z-scores: lumbar spine -1.56 ± 1.32 and femoral neck -1.76 ± 0.85) and those with an adrenal adenoma (Z-scores: lumbar spine -1.19 ± 1.80 and femoral neck -1.39 ± 1.09).

In the group of 14 premenopausal women, BMD (Z-score) in the lumbar spine was significantly correlated with BMD in the femoral neck ($r = 0.553$, $P^{**} < 0.05$). BMD in the lumbar spine was also significantly correlated with the body mass index (kg/m^2) ($r = 0.644$, $P^{**} < 0.02$) in the group of premenopausal women, whereas there was no significant correlation between BMD in the femoral neck and body mass index ($r = 0.355$, $P^{**} > 0.10$). There was also no significant

correlation between BMD (Z-scores) at either site and age, duration of symptomatic glucocorticoid excess, duration of amenorrhea, or mean 24-h plasma cortisol in the group of premenopausal patients.

BMD after surgical cure of Cushing's syndrome

After surgery no consistent change in BMD was observed at 3 and 6 months (Fig. 1). In fact, BMD was lowered by 2% or more in comparison with pretreatment values at one or both time points in 6 of 17 patients at the lumbar spine and in 11 of 16 patients at the femoral neck. In the group of premenopausal women, there was a highly significant inverse correlation between age and increase in BMD in the lumbar spine in the first 6 months after surgery ($r = -0.925$, $P^{**} < 0.0005$).

From 6 months onward BMD increased considerably in most patients (Fig. 1). For the 15 patients with a duration of follow-up of at least 1 yr, Z-scores at the time of the last evaluation are given in Table 2. At the last evaluation Z-scores in these 15 patients were -0.65 ± 1.27 for the lumbar spine and -0.98 ± 1.02 for the femoral neck (both $P < 0.002$ compared with pretreatment values). When compared with pretreatment values, BMD at the last measurement had increased in the lumbar spine in 12 of 15 patients (in 7 of them by more than 15%; increase $22.1\% \pm 4.8\%$, $n = 7$) and in the femoral neck in 11 of 15 patients (in 5 of them by more than 15%; increase $22.0\% \pm 4.0\%$, $n = 5$). However, at the last measurement, BMD in the lumbar spine was still lower than -1 sd in 6 of 15 patients and in the femoral neck in 7 of 15 patients. In the group of premenopausal patients, the in-

TABLE 2. Bone mineral density (BMD; g/cm^3) in the lumbar spine (L1-L4) and left femoral neck in 20 patients with Cushing's syndrome before and after surgical cure

Patient number	BMD lumbar spine in g/cm^2 (Z-score in sd)		BMD femoral neck in g/cm^2 (Z-score in sd)		Time between definitive surgery and last measurement of BMD (months)
	Before definitive surgery ^a	Last measurement after definitive surgery ^b	Before definitive surgery ^a	Last measurement after definitive surgery ^b	
1	0.700 (-3.18)	0.861 (-1.57)	0.633 (-2.54)	0.632 (-2.29)	48
2	0.791 (-2.08)	0.989 (-0.41)	0.661 (-2.31)	0.802 (-0.93)	48
3	1.024 (-0.10)	1.288 (+2.22)	0.684 (-2.12)	0.876 (-0.14)	48
4	0.937 (-0.70)	0.933 (-0.63)	0.664 (-1.77)	0.691 (-1.38)	24
5	0.723 (-2.70)	0.931 (-0.89)	0.731 (-1.64)	0.858 (-0.36)	24
6	0.918 (-0.99)	0.986 (-0.11)	0.737 (-1.15)	0.760 (-0.65)	60
7	0.949 (-0.79)	0.927 (-1.06)	0.722 (-1.76)	0.716 (-1.59)	48
8	0.708 (-3.07)	0.707 (-3.08)	0.545 (-3.44)	0.573 (-3.10)	36
9	0.869 (-1.48)	1.031 (-0.09)	0.811 (-0.83)	0.973 (+0.80)	24
10	1.014 (-0.15)	1.067 (+0.26)	0.815 (-0.80)	0.821 (-0.73)	12
11	0.800 (-1.90)	0.942 (-0.67)	0.720 (-1.76)	0.767 (-1.28)	18
12	1.061 (+0.39)		0.779 (-0.66)		
13	0.757 (-2.62)		0.673 (-2.09)		
14	0.934 (-0.80)		0.811 (-0.37)		
15	0.671 (-2.50)	0.771 (-1.25)	0.637 (-1.43)	0.651 (-0.96)	60
16	1.120 (+1.60)		0.763 (-0.15)		
17	0.743 (-3.17)	0.863 (-2.07)	0.623 (-2.98)	0.767 (-1.42)	48
18	0.828 (-2.40)	0.925 (-1.51)	0.802 (-1.40)	0.782 (-1.44)	36
19	1.130 (+0.74)	1.158 (+1.04)	0.955 (+0.99)	0.919 (+0.74)	24
20	0.710 (-3.05)		0.649 (-1.75)		
Mean \pm SD	0.869 ± 0.147 (-1.45 ± 1.44)	0.959 ± 0.143 (-0.65 ± 1.27)	0.721 ± 0.093 (-1.50 ± 1.02)	0.773 ± 0.109 (-0.98 ± 1.02)	

In parentheses BMD is expressed as positive or negative standard deviations from the age- and sex-specific normal mean (Z-score, see text).

^a Mean of two determinations.

^b Values of patients with a duration of follow-up of at least 12 months after definitive surgery are given.

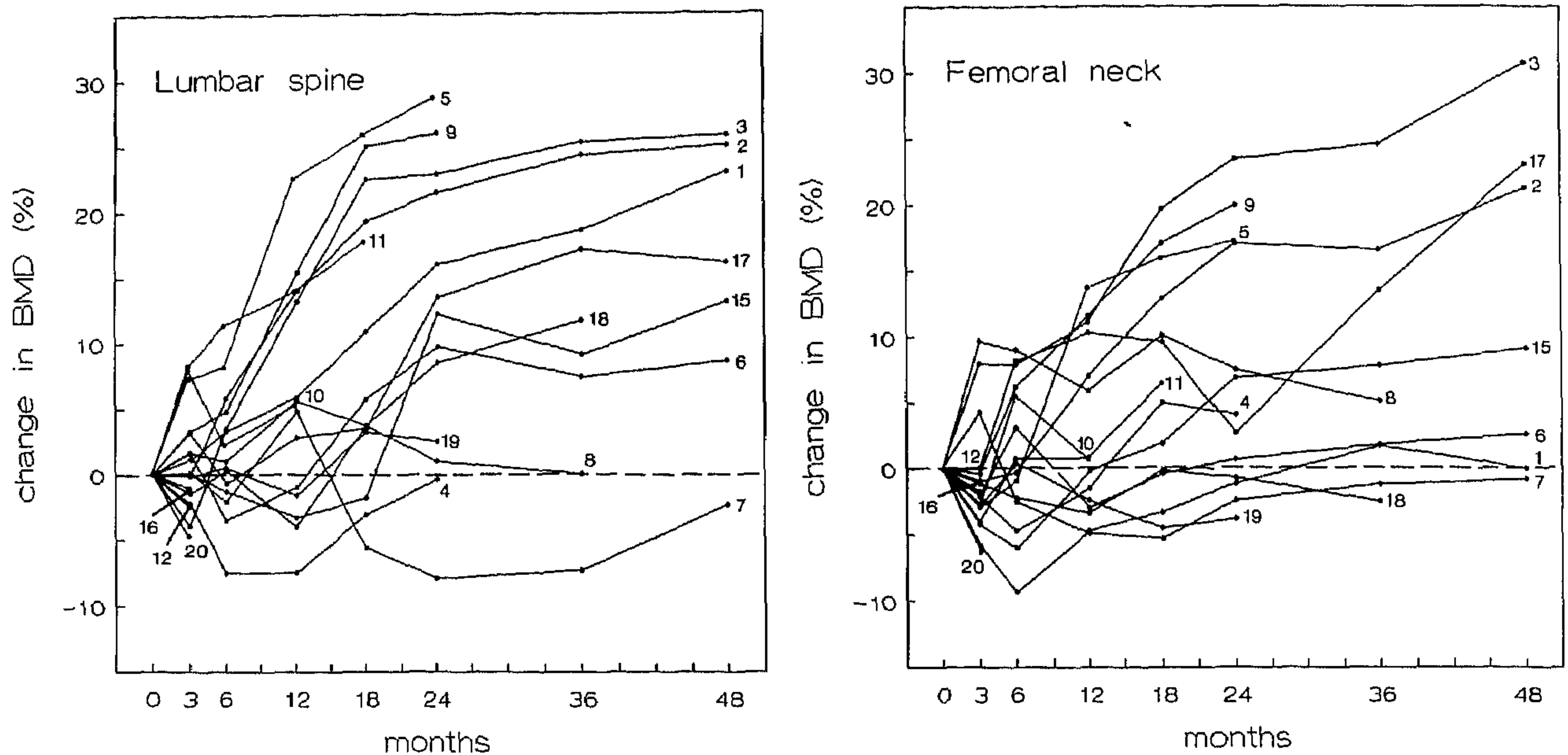


FIG. 1. Percentage change in BMD in the lumbar spine (L1-L4) and femoral neck after surgical cure of 18 patients with Cushing's syndrome. The individual values at seven time points after surgery were compared with the pretreatment value ($t = 0$ months; mean of two determinations). Note that the improvement of BMD in the lumbar spine in patients 7 and 8 is less than that in the other patients. Both patients used glucocorticoids in doses that were higher than the normal substitution dose, and patient 7 was treated for a malignant midline granuloma 9 months after bilateral adrenalectomy.

crease in BMD in the lumbar spine at 24 months was inversely correlated with age ($r = -0.733$, $P^{**} < 0.03$) and positively correlated with the increase in BMD in the femoral neck at 24 months ($r = 0.767$, $P^{**} < 0.03$) and with the increase in BMD in the lumbar spine at 6 months ($r = 0.867$, $P^{**} < 0.005$). The increase in BMD in the femoral neck at 24 months was also inversely correlated with age ($r = -0.667$, $P^{**} < 0.05$).

Biochemical parameters of bone and collagen metabolism in premenopausal patients with active Cushing's syndrome

Serum levels of parameters of osteoblast activity and collagen synthesis (osteocalcin, bone alkaline phosphatase, PICP, PIIINP) were not significantly different between the group of 14 premenopausal patients with active Cushing's syndrome and the group of 18 age-matched healthy premenopausal women (Table 3). Of the parameters of bone resorption, the urinary hydroxyproline/creatinine ratio was significantly higher in patients with Cushing's syndrome,

whereas serum levels of ICTP were not different between both groups.

In the patients with Cushing's syndrome, serum osteocalcin levels were significantly correlated with those of PICP ($r = 0.645$, $P^{**} < 0.03$) and those of bone alkaline phosphatase ($r = 0.639$, $P^{**} < 0.05$). No other significant correlations were observed between the above-mentioned biochemical parameters in the group of premenopausal patients with Cushing's syndrome. Z-scores in the lumbar spine or the femoral neck did not correlate significantly with any of the biochemical parameters of bone and collagen metabolism.

In the group of healthy premenopausal women, serum osteocalcin levels were significantly correlated with those of PICP ($r = 0.602$, $P^{**} < 0.01$) and of bone alkaline phosphatase ($r = 0.783$, $P^{**} < 0.0001$), as they were in the patients with Cushing's syndrome. In the healthy women, serum PICP levels were also correlated with serum levels of bone alkaline phosphatase ($r = 0.737$, $P^{**} < 0.0003$). Unlike the serum levels of ICTP in the patients with Cushing's syndrome, serum levels of ICTP in the healthy premenopausal women were

TABLE 3. Serum and urine levels of parameters of bone and collagen metabolism in 14 premenopausal patients with active Cushing's syndrome and in 18 age-matched healthy premenopausal women

	Cushing's syndrome	Healthy women	P-value ^a
Serum osteocalcin (nmol/L)	1.05 ± 0.60	1.28 ± 0.42	NS
Serum bone alkaline phosphatase (μg/L)	12.6 ± 6.5	9.9 ± 3.7	NS
Serum PICP (μg/L)	190 ± 99	128 ± 53	NS
Serum PIIINP (μg/L)	3.9 ± 2.8	2.6 ± 0.8	NS
Serum ICTP (μg/L)	3.8 ± 1.6	3.7 ± 1.1	NS
Urine hydroxyproline/creatinine (μmol/mmol)	24.6 ± 9.6	16.2 ± 3.5	<0.01

PICP, Carboxyterminal propeptide of type I procollagen; PIIINP, aminoterminal propeptide of type III procollagen; ICTP, cross-linked telopeptide of type I collagen.

^a Mann-Whitney *U* test (NS, not significant).

significantly correlated with those of osteocalcin ($r = 0.504$, $P^{**} < 0.05$), PICP ($r = 0.608$, $P^{**} < 0.01$), and bone alkaline phosphatase ($r = 0.740$, $P^{**} < 0.0003$).

Biochemical parameters of bone and collagen metabolism after surgical cure of premenopausal patients with Cushing's syndrome

In nine premenopausal patients with Cushing's syndrome we determined the above-mentioned parameters, except for bone alkaline phosphatase, at regular intervals during the first 2 yr after surgical cure (Fig. 2). In all patients, serum levels of osteocalcin increased considerably between 0 and 3 months [from 1.04 ± 0.20 to 3.82 ± 0.30 nmol/L (mean \pm SEM), $P < 0.0001$], indicating a prompt increase of osteoblast activity. Also serum levels of PICP and PIIINP increased significantly between 0 and 3 months [PICP from 173 ± 32 to 250 ± 35 μ g/L (mean \pm SEM), $P < 0.05$, and PIIINP from 3.14 ± 0.89 to 14.80 ± 1.75 μ g/L (mean \pm SEM), $P < 0.0001$]. Thereafter PICP levels decreased gradually (24 months vs. 3 months, $P < 0.05$; 24 months vs. healthy controls, $P^* > 0.10$). Serum osteocalcin and PIIINP levels also decreased gradually from 3 months after surgery onward (24 months vs. 3 months, both $P < 0.05$), but at 24 months after surgery these levels were still elevated when compared with levels in healthy women ($P^* < 0.04$ for PIIINP and $P^* < 0.006$ for osteocalcin). Of the parameters of bone resorption, the urinary hydroxyproline/creatinine ratio and serum levels of

ICTP increased in all patients between 0 and 3 months [ICTP: from 4.07 ± 0.65 to 14.09 ± 2.30 μ g/L (mean \pm SEM), $P < 0.05$; urinary hydroxyproline/creatinine ratio: from 27.36 ± 2.85 to 70.73 ± 7.45 μ mol/mmol (mean \pm SEM), $P < 0.0001$]. Thereafter the urinary hydroxyproline/creatinine ratio decreased gradually (24 months vs. 3 months, $P < 0.005$; 24 months vs. healthy controls, $P^* > 0.10$). Serum ICTP levels also decreased gradually from 3 months after surgery onward (24 months vs. 3 months, $P < 0.05$), but at 24 months after surgery these levels were still elevated when compared with levels in healthy women ($P^* < 0.05$).

Discussion

In the present study, marked osteopenia, equally severe in the lumbar spine and in the femoral neck, was demonstrated by dual-energy x-ray absorptiometry in most patients with active Cushing's syndrome. In a preliminary report, Mercado-Asis *et al.* (7), using the same technique as that used in our study, emphasized that the decrease in BMD was more severe in pediatric than in adult patients with Cushing's syndrome [in agreement with the observation that young patients receiving glucocorticoid therapy lose bone more rapidly than do older patients (8)]. In our group of 14 adult premenopausal patients with Cushing's syndrome, we could not demonstrate a significant correlation between BMD and age, nor between BMD and estimated duration of symptom-

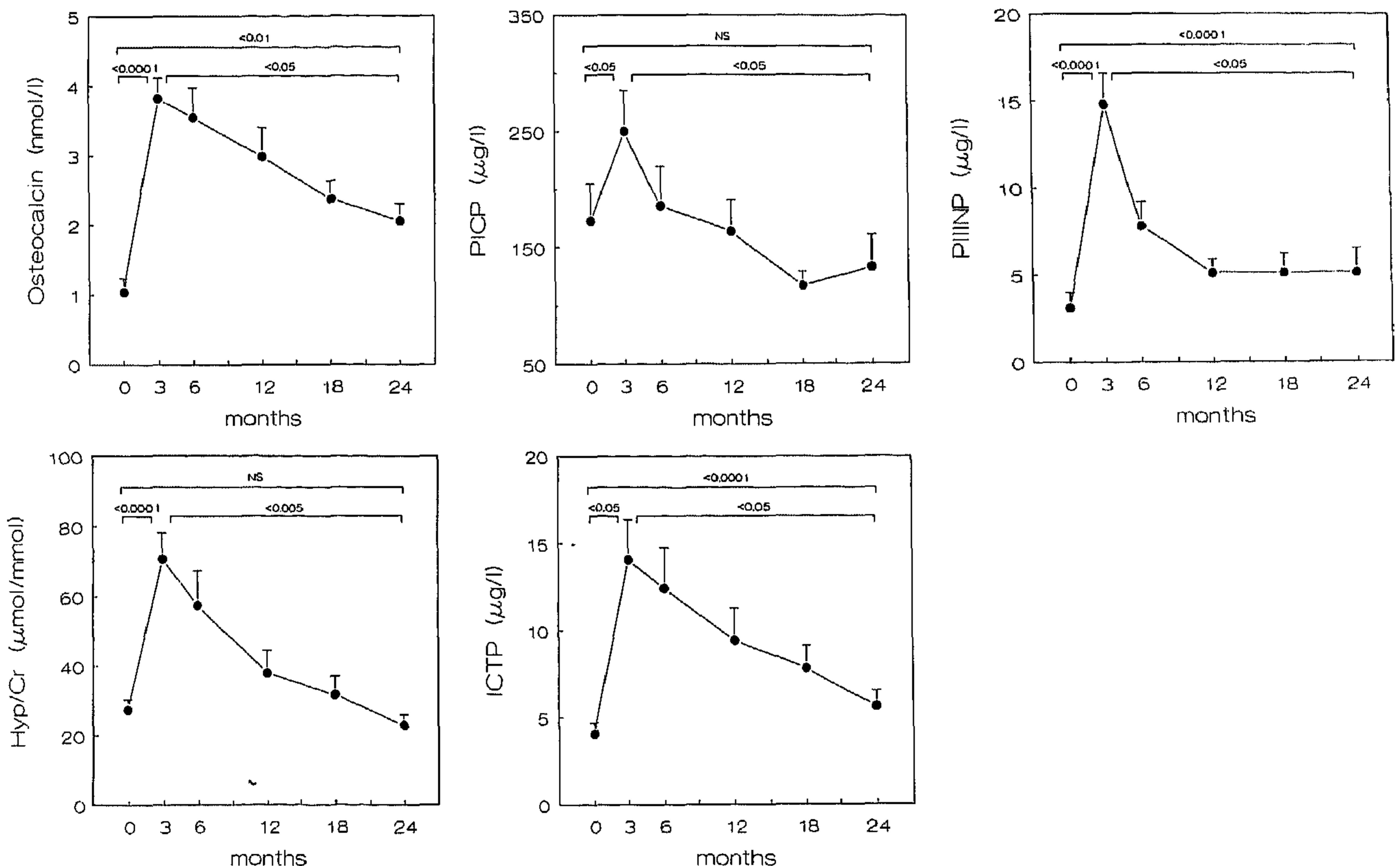


FIG. 2. Serum levels (mean \pm SEM) of osteocalcin, PICP, PIIINP and ICTP, and the urinary hydroxyproline/creatinine ratio in nine premenopausal women with Cushing's syndrome before ($t = 0$ months) and at 3, 6, 9, 12, 18, and 24 months after surgical cure (blood was sampled between 0830 and 0930 h, and urine was collected between 0800 and 1000 h after an overnight fast).

