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Bone Mineral Density Following Treatment of Hyperprolactinemia

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To investigate the effect of hyperprolactinemia (HPLN) on bone mineral density (BMD), 21 previously treated hyperprolactinemic amenorrheic women and 16 healthy, normally menstruating women were studied. Dualphoton absorptiometry was employed to specifically measure BMD at several sites in each of these women. Serum prolactin (PRL) along with LH, FSH, and estradiol (E_2) had been measured by radioimmunoassay before treatment. Although all measured sites (vertebral body, femur neck, Ward's triangle, and trochanter) showed lower BMDs in the study control group, only BMD at Ward's traingle, but no at the three other sites, was noted to be statistically significant in the study group compared with the control. There was no significant correlation between BMD and the patient's age, duration of amenorrhea, E_2, and prolactin levels. Difference in BMD according to therapeutic modality was analyzed in these patients after treatment: transsphenoidal adenodectomy (TSA) with or without subsequent bromocriptine (Bx) (TSA±Bx) proved better in preserving BMD than TSA combined with postoperative radiotheraphy (RT) and Bx (TSA+RT+Bx), or Bx alone.

Key Words: Hyperprolactinemia, bone mineral density, osteoporosis

HPLN is known to cause amenorrhea, galactorrhea, and infertility in women of reproductive age (Bohnet *et al.* 1976; Boyd *et al.* 1977). Thus, treatment has been mainly directed at managing these sequelae.

The problem of osteoporosis is usually associated with menopause, after which women's bone mass begin to decrease. Several reports have documented the evidence of osteopenia in HPLN, and now HPLN is considered to trigger osteopporosis (Klibanski et al. 1980; Schletchte *et al.* 1983; Koppelman *et al.* 1984). It is, however, not certain whether such osteoporosis would be a direct result of increased circulating prolacting or rather a phenomenon mediated by a hypoestrogenic state induced by HPLN.

The recent advent of advanced techniques of bone densitometry enabled us to measure BMD at various sites of the body, particularly those at a higher risk of clinical fracture usually due to postmenopausal osteoporosis. Osteoporosis caused by HPLN as well as by menopause is known to be type 1 osteoporsis (Genant *et al.* 1982; Riggs *et al.* 1983) in which trabecular bone loss is relatively greater than cortical bone loss. One can then assume that osteoporosis brought upon by HPLN would be conspicuous at the bony sites where trabecular bone density is comparatively high; the Ward's triangle of femur is one such site composed of about 90 percent of trabecular bone. We measured BMD of hyperprolactnemic and normal women at Ward's triangle, vertebral body, femur neck and trochanter—each with differing compositions of cortical and trabecular bones—to compare the osteoporotic effect of HPLN. Effort was also made to compare retrospectively the outcome of BMD subsequent to several different therapeutic modalities of HPLN. Although the number of study subjects recruited was short of being sufficient to permit assessment of the exact role of each modality, the attempt was worthwhile since no previous studies suggested the concept of intervening HPLN in a manner that would not only control HPLN, but would also effectively deter progression of osteoporosis.

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MATERIALS AND METHODS

The study group consisted of 21 women with HPLN with secondary amenorrhea; among them, two had empty sella syndrome, four were idiopathic and fifteen had pituitary adenoma. The control group had 16 healthy, normally menstruating women, in their 20s and 30s, without a history of hormone treatment within three months prior to study. The patients in the study group had previously been treated for HPLN; four received TSA+RT+Bx, six were treated with TSA±Bx, and eleven received Bx alone.

The patient and normal subjects all had normal renal and thyroid functions. There were no other accompanying endocrinopathies in all subjects. Sera for hormone assays were obtained in the morning after overnight fast in the each subject. Serum PRL was measured by Amersham RIA kit. Serum LH and FSH were also measured using Amersham RIA kit. Serum E_2 was measured by Abbot RIA kit.

Measurement of BMD was carried out in both the study and control groups using Dualphoton Absorptiometer (Lunar Radiation Corporation, Madison, Wisconsin) with 153Gd as the radionuclide source. Statistical analysis was made by the Student "t" test.

RESULTS

Table 1 shows the clinical data and basal hormonal profile before treatment in the study group. The mean age of the patients was 30.3±5.2 years with the mean duration of amenorrhagea 3.7±4.1 years. Serum PRL level averaged 447.2+518 ng/ml. The mean serum E_2, LH, and FSH levels were 51.6+37.4 pg/ml, 8.8+5.7 mIU/ml, and 6.7+4.1mIU/ml, respectively. Four of the patients were given treatment for hyperprolactinemia with TSA+RT+Bx; these four women apparently had pituitary adenoma. There were six patients with pituitary adenoma treated with TSA±Bx. Bx alone was instituted for treatment in eleven patients, of which two were with empth sella, four with idiopathic cases, and the remaining five with pituitary adenoma. All fifteen patients with pituitary adenoma were diagnosed as such after noting in each case the evidence of microadenoma on a CAT scan. Two empty sella cases were diagnosed with a CAT scan. The absence of CAT

Table 3. Correlation Coefficients between BMD and Age, Duration of Amenorrhea, and Hormonal Parameters

		Femur	
	Vertebra	Femur Neck	Ward's Triangle
Age	−0.1	−0.4*	−0.3*
Duration of Amenorrhea	−0.2	−0.3*	−0.3*
Time interval between onset of symptoms and treatment	−0.2	−0.1	−0.2
Estradiol	0.1	0.3*	0.2
Prolactin	−0.1	−0.03	−0.1

* $p<0.5$
\# $p<0.05$

Table 1. Clinical data and basal hormonal profile in study group

	Age (yrs.)	Duration of Amenorrhea (yrs.)	Prolactin (ng/ml)	E2 (pg/ml)	LH (mIU/ml)	FSH (mIU/m)
Mean±SD	30.3±5.2	3.7±4.1	447.2±518	51.6±37.4	8.8±5.7	6.7±4.1

Table 2. Comparison of BMD (g/cm^2 in study and control group (Mean±SD)

		Vertebra	Femur Neck	Ward's Triangle	Trochanter
Study Group	Mean	1.042	0.856	0.762	0.690
(N=16)	S.D.	0.247	0.028	0.145	0.082
Control Group	Mean	1.146	0.913	0.851	0.725
(N=16)	S.D.	0.09	0.079	0.100	0.067
p value		<0.1	<0.1	<0.05	<0.1

Table 4. Comparison of Bone Mineral Density (BMD) and Therapeutic Modality

Therapeutic Modality		BMD							
		Vertebra		Femur Neck		Ward's triangle		Trochanter	
		g/cm²	% of control	g/cm²	% of control	g/cm²	% of control	g/cm²	% of control
TSA+Rt+Bx	Mean	0.993	87	0.825	90	0.7025	82	0.715	99
(N=4)	S.D.	0.047		0.695		0.041		0.014	
TSA±Bx	Mean	1.158	101	0.970	106	0.910	106	0.715	99
(N=6)	S.D.	0.093		0.168		0.168		0.014	
Bx alone	Mean	0.095	87	0.085	88	0.704	83	0.651	90
(N=11)	S.D.	0.326		0.093		0.096		0.074	

TSA; transsphenoidal adenoidectomy
RT; radiation therapy
Bx; bromocriptine

findings of adenoma led to diagnosing four cases as idiopathic.

Comparison of BMD in the study and control groups (Table 2) revealed a lower BMD at all four sites; however, only BMD at Ward's triangle ($p<0.05$) was singificantly lower.

Table 3 lists the correlation coefficients between BMD and age, duration of amenorrhea, and other hormonal parameters. There seemed to be negative correlation between BMD and age, duration of amenorrhea, time interval between initial manifestation of HPLN and its treatment, and prolactin. None of the correlation coefficients, however, were statistically significant. Positive correlation, though not statistically significant, was observed between E_2 and BMD. BMD and the therapeutic modality of HPLN is compared in Table 4. There were, as described, three types of treatment employed. BMD was well preserved after treatment at all sites where BMD was measured. Both TSA+RT+Bx and Bx alone caused a decrease in BMD with the fall at Ward's triangle being especially significant. BMD at trochanter was similar after all of the three types of treatment modality.

DISCUSSION

Osteoporosis can be caused by a variety of conditions, among which HPLN is newly recognized but no extensively documented. Reports exist that demonstrate that osteoporosis brought upon by HPLN, as evidenced by decreased bone mineral content, is either the result of hypoestrogenism generated by HPLN (Klibanski *et al.* 1980) or the direct consequence of the impact of increased circulating PRL on bones (Schlechte *et al.* 1983).

It has been assumed that type I osteoporosis, thought to be typical of postmenopausal osteoporosis, occurs in HPLN as well. Our finding that the decrease in BMD at Ward's triangle, where trabecular bone is predominant, was conspicuous compared with the control is encouraging in that this region, the Ward's trangle, may then be used an alternative site to vertebral body for evaluation of this type of osteoporosis, particularly in HPLN.

Our observation seems to be in disagreement with that of Koppelman *et al.* (1984) since vertebral BMDs in our study, though low compared with control, still failed to show any statistical significance. Their patients, however, received no specific treatment for HPLN thus leaving bones exposed to persistent and uninterrupted osteoporotic insult. In our case, the treatment at one stage of the disease progression probably acted to mitigate, if not completely remove, such an effect. Bone mass is reported to have increased in HPLN after treatment in one study (Klibanski *et al.* 1986). Whether BMD actually increased after treatment of HPLN in the present analysis remains uncertain since BMD prior to treatment was not determined in this study. It would, nonetheless, be plausible to expect a less significant reduction in BMD in vertebra in our study. Absence of a significant correlation between BMD and the patient's age indicates that age-related osteoporosis probably contributed little in our study. This is believed largely because the mean age of the patients at the time of study was well below the age when physiologic osteoporosis is generally thought to initiate.

That the degree of BMD loss was found to be independent of duration of amenorrhea, initial E_2 and

prolaction levels needs to be elaborated. This may be one aspect of hyperprolactinemic osteoporosis that is different from postmenopausal osteoporosis. Postmenopausal osteoporosis, considered to be mediated by low estrogen (Nordin *et al.* 1966; Lindsay *et al.* 1966), is related to duration of amenorrhea since it occurs most sharply during the first few years of menopause but nonetheless continues as women's age advances, as previously reported. Castrated young females (Johansson *et al.* 1975; Aitken *et al.* 1973), no longer supplied by ovarian estrogen, experience osteoporosis and it is also related to duration of amenorrhea. Our results are somewhat similar to those of Schelechte *et al.* who suggested a direct effect of PRL on bone. That the degree of BMD loss was independent of PRL level brings into light the existence of several classes of PRL with different biioactivity (Suh and Frantz 1974; Whittaker *et al.* 1981). Difference in individual sensitivity to PRL may also be a possibility through which our result may be considered. The possibility of an unrecognized osteoporotic factor in HPLN may also be raised.

TSA±Bx proved superior to the other two modes of treatment for HPLN, TSA+RT+Bx or Bx alone, in preserving BMD. Here comparison can be made only between the first two because all 10 patients who were treated with either form of treatment had pituitary microadenoma. It was not known whether the patients who came to receive radiation after TSA tended to have the tumors incompletely removed or tended to have more persistent pre-or postoperative HPLN. Cranial irradiation alone, however, may cause hypogonadism. It is in this context that decreased BMD after postoperative radiotherapy may also be interpreted. A reasonable approach to controlling postoperative HPLN would thus be adjuvant use of Bx, since BMD in such cases was well maintained in our study. Bx alone fared poorly in preserving BMD in HPLN, though it is known to be effective in establishing normal estrogen levels and ovultory cycles in a majority of hyperprolactinemic women (Seppälä *et al.* 1977). The group of eleven patients given this form of treatment (Bx alone), however, encompassed three different categories of HPLN; empty sella, idiopathic and tumor. The drawing of any significant statistical conclusion from this group of patients, heterogeneous and small in number, would be premature and better dismissed until more patients are analyzed in each respective category. The BMD at trochanter, in which trabecular bone is less dense than at the three other sites, was not very different before and after treatment. This may support the theory that hyperprolactinemic osteoporosis is type I osteoporosis.

Detailed individual data before treatment was unavailable because most patients of this study were referred long after their clinical manifestation precluding longitudinal analysis on an individual basis.

Our results show that BMD was significantly reduced at Ward's triangle in the study group compared to control. There were no significant correlations between BMD and patient's age, duration of amenorrhea, initial E_2 and PRL levels. It is interesting that BMD was well preserved in patients treated with TSA±Bx, but was diminished markedly after TSA+RT+Bx or Bx alone. Realizing the morbidity and mortality of osteoporosis (Alffram *et al.* 1964), it now seems apt to stress the importance of preventing osteoporosis in HPLN.

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