Short- and Long-Term Effects of Estrogen and Synthetic Anabolic Hormone in Postmenopausal Osteoporosis

B. Lawrence Riggs, Jenifer Jowsey, Ralph S. Goldsmith, Patrick J. Kelly, David L. Hoffman, and Claude D. Arnaud

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

Abstract In 29 women with postmenopausal osteoporosis, the proportion of total bone surface undergoing resorption or formation was evaluated by microradiography of iliac crest biopsy samples before and after short-term (2½–4 months) and long-term (26–42 months for estrogen and 9–15 months for anabolic hormone) treatment. After estrogen administration, values for bone-resorbing surfaces decreased, although less prominently after long-term than after short-term therapy. The magnitude of this decrease was positively correlated with the pretreatment value for bone-resorbing surfaces ($P < 0.001$). When the pretreatment value for bone-resorbing surfaces was used as a covariable, estrogen and anabolic hormone appeared to be equally effective. For bone-forming surfaces, short-term therapy with either hormone had no effect but long-term therapy significantly decreased the values. Serum immunoreactive parathyroid hormone (IPTH) increased significantly after estrogen therapy; the change in IPTH was inversely related to the change in serum calcium ($P < 0.001$, sign test). We conclude that the primary effect of sex hormones in postmenopausal osteoporosis is to decrease the increased level of bone resorption, perhaps by decreasing the responsiveness of bone to endogenous parathyroid hormone. However, this favorable effect, at least in part, is negated after long-term treatment by a secondary decrease in bone formation. Our data are consistent with the concept that the maximal benefit that can be derived from sex hormone therapy in postmenopausal osteoporosis is arrest or slowing of the progession of bone loss.

INTRODUCTION

In 1941 Albright, Smith, and Richardson (1) reported the use of sex hormones as treatment for postmenopausal osteoporosis. In the ensuing 30 years, estrogen has been the main therapy for this disease. Androgens were infrequently used in treatment until the introduction, in the 1950's, of synthetic analogs which had anabolic activity equal to that of testosterone, but markedly decreased virilizing properties (2). In spite of extensive clinical experience with sex hormone therapy in postmenopausal osteoporosis, the therapeutic value has not been completely established. Although short-term treatment with a sex hormone produces calcium retention in the majority of osteoporotic patients studied by metabolic balance methods (3) and a decrease in values for bone-resorbing surfaces without a change in values for bone-forming surfaces as assessed by microradiography (4), the failure to demonstrate an increase in skeletal radiodensity even after years of treatment (3) suggests that these short-term effects cannot be maintained indefinitely. Also, adequate studies comparing the therapeutic effectiveness of estrogen and synthetic anabolic hormones have not been made.

The present study evaluates short- and long-term effects of estrogen and a synthetic anabolic hormone on bone tissue and on calcium and phosphorus metabolism in postmenopausal osteoporosis and the possible role of parathyroid hormone in mediating these changes.

METHODS

Patients. 29 ambulatory women with progressive osteoporosis of sufficient severity to produce vertebral deformity were studied. None of the patients had any evident medical disease other than osteoporosis. All were postmenopausal, and the average age was 63.5 yr (range, 53–71). None of the patients had received previous treatment except three patients who had discontinued hormonal therapy 6 months, 10 months, and 4 yr before the study. All patients underwent iliac crest bone biopsy and biochemical studies before and after short-term treatment, and some were studied for a third time after long-term treatment.

17 patients received estrogen as conjugated equine estrogens (Premarin, Ayerst Laboratories, New York), 2.5 mg/day (a physiologic replacement dose [4]), administered cyclically. These patients were studied before and after

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short-term treatment (2½–4 months), and nine of them were studied for a third time after long-term treatment (26–42 months).[1] 12 patients received oxandrolone (Anavar, G. D. Searle & Co., Chicago, Ill.), a synthetic anabolic hormone, in divided doses of 10–20 mg daily. These patients were studied before and after short-term treatment (2½–4 months), and seven of them were restudied after long-term treatment (9–15 months); these seven patients also underwent radiocalcium kinetic studies at the time of the first and third examinations.

Laboratory studies. Bone from the anterior or posterior iliac crest was obtained by either open or trephine biopsy. Microradiographs were made and surfaces undergoing either active formation or resorption were quantitated as previously described (5). Eight of the patients received oral doses of 750 mg of tetracycline, to label bone-forming surfaces, at 8 days and 1 day before each biopsy so that the local rate of bone apposition could be estimated. The undecalcified bone section was transluminated with ultraviolet light and the average width between fluorescent tetracycline bands was measured microscopically with a calibrated eyepiece.

Radiocalcium kinetic data were analyzed according to the model of Aubert, Bronner, and Richelle (6). A tracer dose (usually 10 μCi) was given intravenously, and serum disappearance and urinary and fecal excretion were determined by radioassay using standard methods (7).

The patients were hospitalized on a metabolic ward and ate a diet providing 650 mg of calcium and 900 mg of phosphorus daily. All blood specimens for biochemical determinations were drawn by venipuncture without stasis at 8 a.m. For each patient, serum calcium, phosphorus, and alkaline phosphatase were determined, usually on four occasions, and serum proteins by paper electrophoresis and serum ultrafiltrable calcium were studied once. The 24 hr urinary excretion of calcium was determined on at least 3 successive days. On the next day, renal clearance studies were performed at 8 a.m. while the patient was fasting and hydrated. The seven patients who underwent radiocalcium kinetic studies ate a constant diet corresponding to their estimated home diet for calcium and phosphorus for the duration of the study.

Total and ultrafiltrable calcium were determined by atomic absorption spectrophotometry. Serum phosphorus (8), serum alkaline phosphatase (9), urinary calcium (10), inulin clearance (11), and percentage tubular reabsorption of phosphorus (TRP)[2] (12) were measured using standard methods. Serum immunoreactive parathyroid hormone (IPTH) concentration was determined before and after the administration of estrogen in eight patients and anabolic hormone in seven patients by the method of Arnaud, Tsao, and Littledike (13). The normal range using this method is from undetectable to 38 μl eq/ml. All serum IPTH measurements in this study were made in a single assay.

RESULTS

Microradiographic studies. The data from osteoporotic patients were compared with data from 23 persons without metabolic disease, matched as to age, sex, and biopsy site. For this normal group, the mean (±SD) and range were: bone-resorbing surfaces, 5.27±2.43%, 1.34 to 11.0%; bone-forming surfaces, 4.30±2.56%, 1.02 to 8.81%.

TABLE I

Results (Mean±SE) of Quantitative Microradiography

Treatment	Group*	Time	N	Bone-forming surfaces	Bone-resorbing surfaces
				%	%
Estrogen	A		9		
		Before		4.8±0.3	15.0±0.8
		After 2½–4 months		4.0±0.7	6.4±0.7‡
		After 26–42 months		0.6±0.2‡	10.6±0.8§
	A + B		17		
		Before		3.3±0.5	13.0±0.8
		After 2½–4 months		3.3±0.6	7.2±0.6‡
Anabolic hormone	A		7		
		Before		2.6±0.6	10.3±1.9
		After 2½–4 months		2.8±0.8	8.3±3.1
		After 9–15 months		1.6±0.4‖	8.7±1.3
	A + B		12		
		Before		3.1±0.4	10.0±1.2
		After 2½–4 months		2.2±0.5	8.7±0.8

* Group A refers to patients having both short- and long-term studies. Group B refers to patients having only short-term studies.
‡ For paired difference from before treatment, $P < 0.001$.
§ For paired difference from before treatment, $P < 0.01$.
‖ For paired difference from before treatment, $P < 0.05$.

The effect of sex hormone on bone turnover as assessed by quantitative microradiography is given in Table I. Before treatment, values for bone-resorbing surfaces exceeded the normal range in 13 of the 17 patients who subsequently received estrogen. These patients probably had more active disease than the patients who received anabolic hormone because only 5 of the 12 in this group had values for bone-resorbing surfaces that exceeded normal. For bone resorption, after short-term therapy with estrogen, there was a highly significant decrease in values for resorbing surfaces; after long-term therapy with estrogen, resorbing surfaces increased above values observed after short-term therapy, but remained significantly lower than pretreatment values. After either short- or long-term therapy with synthetic anabolic hormone, the decrease in values for resorbing surfaces was not significant.

For bone formation, after short-term therapy with either estrogen or synthetic anabolic hormone, bone-forming surfaces were unchanged; after long-term therapy with estrogen or synthetic anabolic hormone, however, there was a significant decrease in values for bone-forming surfaces. The local apposition rate (obtained by measuring the width between fluorescent tetracycline bands) did not change significantly with treatment.

In both groups, there was a significantly positive correlation between pretreatment values and posttreatment decreases in values for bone-resorbing surfaces (Fig. 1);

[1] Data from the first two studies of these nine patients have been previously reported (4).

[2] *Abbreviations used in this paper:* IPTH, immunoreactive parathyroid hormone; TRP, tubular reabsorption of phosphorus.

for estrogen the correlation coefficient (r) was 0.81 ($P < 0.001$) and for synthetic anabolic hormone, $r = 0.85$ ($P < 0.001$). The slope of the regression of these two variables on each other was not significantly different when the estrogen-treated group was compared with the anabolic hormone-treated group.

Radiocalcium kinetic studies. These data for seven patients studied before and after 9–15 months of treatment with synthetic anabolic hormone are summarized in Table II. Only three of these seven patients had relatively high pretreatment values for bone-resorbing surfaces or the parameter, Vo —. There was a significant decrease in the size of the exchangeable calcium pool and highly significant decreases in the parameters, Vo + (representing the total calcium inflow into bone) and Vo — (representing the total calcium outflow from bone).

Biochemical studies. After estrogen administration, serum calcium, phosphorus, and alkaline phosphatase and urinary calcium excretion decreased significantly. There was no significant change in TRP or inulin clearance. After anabolic hormone administration, serum calcium, serum phosphorus, TRP, and inulin clearance did not change significantly, but serum alkaline phosphatase and urinary calcium excretion decreased significantly. The ultrafiltrable component of the total serum calcium determined in seven patients did not change significantly after treatment with anabolic hormone.

Serum immunoreactive parathyroid hormone. IPTH was determined in 15 of the patients. Pretreatment values (mean ±SE) were 33.0±2.7 μl eq/ml for eight patients who received estrogen and 24.1±3.9 μl eq/ml for seven patients who received synthetic anabolic hormone. After 2½–4 months, IPTH increased significantly to

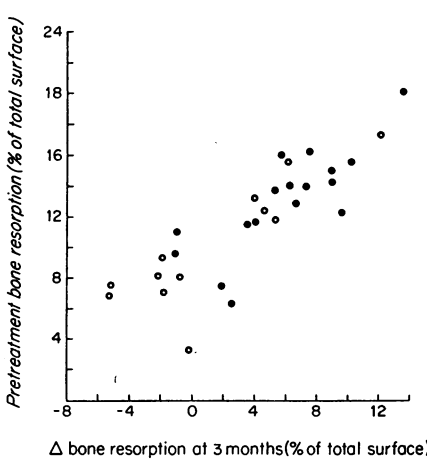

FIGURE 1 Relationship between pretreatment values for bone resorption and amount of decrease in these values as result of sex hormone therapy. Patients treated with estrogen are shown by solid circles and those treated with synthetic anabolic hormone are shown by open circles.

TABLE II

^{47}Ca Kinetic Studies in Seven Patients Treated with Anabolic Hormone (Mean±SE)

	Exchangeable Ca pool	Vo+	Vo−
	mg	*mg/day*	*mg/day*
Pretreatment	4,240±388	423±64	471±88
After 9–15 months	3,562±337	354±49	386±55
Difference		−69	−85
P of paired difference	<0.05	<0.001	<0.001

46.0±4.8 μl eq/ml ($P < 0.01$) after treatment with estrogen, but did not change significantly (23.4±1.8 μl eq/ml) after treatment with anabolic hormone. For individual values (Fig. 2), with one exception, IPTH increased after hormone therapy when serum calcium decreased and decreased when serum calcium increased. The inverse relationship was significant by the sign test ($P < 0.001$).

DISCUSSION

Henneman and Wallach (3) reported that long-term estrogen therapy resulted in cessation of both vertebral fractures and loss of height in 15 osteoporotic women. Lafferty, Spencer, and Pearson (14) studied four osteo-

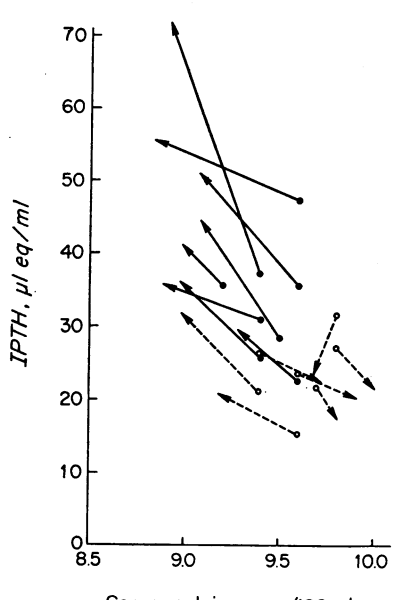

FIGURE 2 Relationship between IPTH and serum calcium concentration. For estrogen-treated patients, pretreatment value is shown by solid circle and posttreatment (after 2½–4 months) value is shown by arrow of solid line. For anabolic hormone-treated patients, pretreatment value is shown by open circle and posttreatment (after 2½–4 months) value is shown by arrow of broken line.

porotic patients and found that 2 months of sex hormone treatment did not affect ^{47}Ca skeletal accretion, but did produce calcium retention as judged by metabolic balance. They interpreted these data and the change in the shape of the plasma specific activity curve as indicating that bone formation was not affected, but that bone resorption had been decreased. When studies were repeated after 9–15 months, isotope accretion had decreased significantly in three of the four patients, and this decrease was accompanied by a diminution in calcium retention. Heaney (15) reported similar radiocalcium kinetic data.

Our microradiographic data clearly show that short-term administration of estrogen decreases bone-resorbing surfaces. This decrease occurred principally in those patients whose pretreatment values were increased; patients who had pretreatment values for bone-resorbing surfaces within the normal range for their age had minimal or no responses. It is not clear from our data whether estrogen decreases bone resorption by inhibiting induction of osteoclastic foci from bone mesenchyme, as has been suggested by Heaney (15), or by a direct effect on the osteoclast. Although after long-term therapy there was a partial return toward pretreatment values, the decrease in bone-resorbing surfaces resulting from estrogen administration was maintained for up to 42 months of therapy.

However, our data also show that long-term estrogen administration produces a secondary decrease in bone-forming surfaces to one-eighth of pretreatment values. The partial reversal of the initial inhibition of bone resorption combined with suppression of bone formation would be consistent with an inability to maintain the positive calcium balance observed by others after short-term estrogen therapy (when bone resorption is decreased but formation is unchanged); it would also explain the failure of 20 or more years of treatment to result in a roentgenographically demonstrable increase in bone density (3). In this regard, Davis, Strandjord, and Lanzl (16) found that women who had received estrogen replacement at the menopause had a higher phalangeal bone density, when assessed after 5–10 yr of therapy by a photon-absorption technique, than did women who did not receive hormones. Thereafter, the difference between the treated and untreated groups became progressively less and was not significantly different after 15–20 yr of therapy.

We believe that failure to observe a significant decrease in bone-resorbing surfaces after administration of synthetic anabolic hormone was due to the greater proportion of patients in this group who had pretreatment values for bone resorption within the normal range (and consequently responded poorly to therapy). When the pretreatment value for bone-resorbing surfaces was used as a covariable, both types of hormones appeared to be equally effective. However, additional studies utilizing larger groups of patients and including more with high levels of bone resorption in the anabolic hormone group will be needed to establish this point conclusively.

As with estrogen, long-term therapy with synthetic anabolic hormone decreased bone-forming surfaces. Radiocalcium kinetic data in these same patients showed a decrease in Vo + which was slightly less than the decrease in Vo —.

The increase in serum IPTH noted after estrogen therapy was probably related to the estrogen-induced decrease in serum calcium. Arnaud et al. (13) have previously reported that, in normal persons, IPTH is inversely correlated with serum calcium concentration. Because parathyroid hormone appears to be the major regulator of osteoclastic bone resorption (17), our finding that estrogen decreases bone resorption surfaces but increases serum IPTH suggests that one mechanism of its action is to decrease the responsiveness of bone to parathyroid hormone. This mechanism has been previously suggested by Heaney (18) and by Jasani, Nordin, Smith, and Swanson (19). In support of this conjecture, Nordin, Young, Bulusu, and Horsman (20) found that addition of stilbestrol diphosphate to the medium of cultured calvaria inhibited the bone-resorbing activity of parathyroid hormone in vitro.

Although therapy with sex hormones decreases bone resorption in most patients with postmenopausal osteoporosis, this favorable effect is negated at least in part after long-term treatment by a secondary decrease in bone formation. Consequently, our data are consistent with the concept that the maximal benefit that can be derived from sex hormone therapy is to arrest or slow the progression of bone loss.

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