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SPINAL BONE LOSS AND OVULATORY DISTURBANCES

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Abstract *Background.* Osteoporosis develops in women with estrogen deficiency and amenorrhea who lose bone at an accelerated rate. It is not known to what extent bone loss differs between ovulatory women with regular menstrual cycles who are training intensely and those who are sedentary.

Methods. We measured the density of cancellous spinal bone from the 12th thoracic vertebra to the 3rd lumbar vertebra by quantitative computed tomography on two occasions one year apart in 66 premenopausal women 21 to 42 years of age. All the women had two consecutive ovulatory cycles immediately before entering the study. Twenty-one women were training for a marathon, 22 ran regularly but less intensively, and 23 had normal levels of activity. The lengths of the women's menstrual cycles and luteal phases, diet, exercise levels, and hormonal levels were also determined. We defined ovulatory disturbances as anovulatory cycles and cycles with short luteal phases.

Results. The mean (±SD) spinal bone density in the 66 women decreased 3.0±4.8 mg per cubic centimeter per year (2.0 percent per year) ($P<0.001$). Amenorrhea did not develop in any woman during the year of observation (only 2.7 percent of the cycles were >36 days long). Ovulatory disturbances occurred in 29 percent of all cycles, however. Bone loss was strongly associated with these disturbances ($r = 0.54$, 24 percent of the variance). The 13 women who had anovulatory cycles lost bone mineral at a rate of 6.4±3.8 mg per cubic centimeter per year (4.2 percent per year). The women training for a marathon had menstrual cycles similar to those of the women in the other two groups.

Conclusions. Decreases in spinal bone density among women with differing exercise habits correlated with asymptomatic disturbances of ovulation (without amenorrhea) and not with physical activity. (N Engl J Med 1990; 323:1221-7.)

ACCELERATED bone loss occurs with the cessation of menstruation at the time of menopause[1] and in women who have amenorrhea as a result of prolactin-producing pituitary tumors,[2] anorexia nervosa,[3] or intense long-distance running associated with undernourishment.[4] These situations are all accompanied by estrogen deficiency, which is likely to be a major determinant of the accelerated bone loss. Bone loss also occurs when estrogen therapy is withdrawn.[5,6]

Although "exercise-associated amenorrhea" is now accepted as an entity, all reports of its occurrence are based on cross-sectional studies. Women studied prospectively who were training to run a marathon had irregular menstrual cycles and decreases in serum estradiol levels within the normal range, but their cycles did not cease.[7,8] Several subsequent prospective studies have confirmed that amenorrhea does not develop during exercise training, but the cycle length becomes irregular.[9-11] In addition, prospective studies during exercise training document changes in ovulatory function,[12] including decreases in the endogenous production of progesterone during cycles with insufficient and short luteal phases (<10 days) and anovulatory cycles.[9-11,13-15]

Like estrogen, progesterone is now known to be active in bone metabolism.[16] Estrogen acts to prevent bone resorption and decrease remodeling, whereas progesterone appears to promote bone formation and accelerate remodeling.[17] Therefore, we postulated that ovulating women runners would have accelerated bone loss if disturbances of ovulation or cycle length developed during training for a marathon.

Ovulation has not been documented in previous prospective studies of bone density in premenopausal women whose spinal bone density has been reported to decrease from 1 to 3 percent per year.[18-23] Because of the evidence that progesterone is active in bone metabolism,[16] we conducted this prospective one-year study to determine whether spinal bone loss occurred in ovulatory premenopausal women. A second purpose was to determine to what extent menstrual cycles were altered in such women during intense exercise

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training and whether the reported premenopausal bone loss correlated with weight loss, abnormal cycles, or physical activity.

Methods

Subject Selection and Study Design

We initially evaluated 245 women who responded to notices about a study of the effects of running and the menstrual cycle on bone density. Among these 245 women, 132 were excluded after an initial interview on the basis of the following criteria: use of an oral contraceptive, glucocorticoid, or other bone-active drug during the preceding six months; obesity; low weight for height[24]; a change in weight of more than 2.5 kg in the preceding year; and shift work (which would interfere with the accuracy of basal-temperature measurements). We also excluded women if the interview indicated that they had an eating disorder or were compulsive exercisers (people whose emotional stability depended on running). At this interview we also obtained information about lifestyle, previous health, and family health, including any history of osteoporosis. The remaining 113 women were asked to measure their basal temperature daily for two consecutive menstrual cycles.

The 81 women who had had menstrual cycles and luteal phases of normal length during the two cycles immediately after the interview were enrolled in the study. The length of the normal cycle was considered to range from 21 to 36 days,[25] and that of the normal luteal phase to range from 10 to 16 days on the basis of basal-temperature measurements.[26,27] Amenorrhea was defined as the cessation of menstrual flow for six or more months (≥180 days).[25]

After enrollment, the women were seen at approximately three-month intervals and were contacted frequently by telephone between visits. Spinal bone density, body morphometric indexes, and serum hormone levels were measured in the first and final cycles of the yearlong study period. Data on menstrual cycles, basal temperatures, and characteristics of exercise were recorded daily. The total intake of nutrients for seven days was recorded every three months.

Subjects

The 81 enrolled women were all healthy and between 20 and 42 years of age (mean age, 34), and none abused alcohol or smoked heavily. (All but two were white — one woman was Chinese and another Filipino.) Sixty-six women completed the one-year study period. In the case of the others, the reasons for dropping out of the study were pregnancy (four women), a move (four), illness or injury (two), and occupational or personal reasons (five). All the women gave informed written consent to this study, which was approved by the Clinical Screening Committee for Research Involving Human Subjects of the University of British Columbia.

Prospective Documentation of Exercise

For each woman, the estimated distance, time, and intensity of running were recorded daily. For each session, the average heart rate during exercise was determined as the mean of three 10-second counts of the pulse of the radial artery, as recorded by each woman 10 minutes into the exercise session, halfway through, and at the end of the session. From the mean heart rate during exercise, the weekly basal heart rate, the maximal heart rate (estimated by subtracting the woman's chronologic age from 220 beats per minute), and the duration of exercise, an assessment was made of the relative work performed. This individual measure of exercise intensity, adjusted for a person's fitness, is called a training impulse (TRIMP).[28] Exercise in forms other than running was recorded according to type (e.g., aerobics, walking, cycling, swimming, cross-country skiing), duration in minutes, and exercise heart rate. The results of the exercise documentation were expressed per menstrual cycle, since more than 95 percent of all cycles were four weeks long.

The 81 women initially grouped themselves into three exercise-related categories, as follows: women training for a marathon (28 runners who planned to intensify their running over a six-to-nine-month period in preparation for a recreational marathon), consistent runners (25 recreational runners who ran for more than one hour per week at a constant pace but were not training for a specific race or to improve their running), and women with a normal level of activity (28 sedentary or minimally active women who performed less than one hour per week of aerobic exercise [exercise in which their heart rates were raised above 140 beats per minute]).

The 66 women who completed the study were divided into three categories according to the extent of their running activity over the year, expressed as the mean number of kilometers run per menstrual cycle. There were 21 marathon runners, who ran ≥80 km per cycle, 22 consistent runners, who ran from ≥24 to 79 km per cycle, and 23 normally active women, who ran <24 km per cycle. All the women remained in the exercise groups they had initially selected, except for two women who ran in a marathon race during the first few months of the study and then became consistent runners for the rest of the year. The 15 women who dropped out before the completion of the study were distributed equally among the three groups.

Menstrual-Cycle Data

The women measured their oral temperature immediately on awakening each morning using a low-reading thermometer (Becton Dickinson, No. 4009) that could be read to the nearest 0.05°C. They recorded the temperature and date on a form on which the first day of menstrual flow (day 1 of the cycle) was listed at the top. They were instructed to include comments about such factors as late rising and illness opposite the temperature measurement.

The normal characteristics of the menstrual cycle were defined on the basis of the literature.[25,26] The presence or absence of ovulation and the length of the luteal phase were determined by the quantitative method of least-squares analysis of basal temperature.[27] This analysis has been validated in a double-blind study of 24 cycles against the peak serum concentration of luteinizing hormone at midcycle ($r = 0.88$, $P<0.001$).[27] The onset of the luteal phase, as defined by a shift ($P<0.05$) to an increased mean temperature, follows the day of the peak serum concentration of luteinizing hormone by two to three days. The end of the luteal phase is the day before the onset of menstrual flow. The luteal-phase index, the proportion of time spent in the luteal phase by each woman, was expressed as a ratio of the length of the luteal phase to the length of the total menstrual cycle, for each cycle during the year. It is reported as a decimal — e.g., a 14-day luteal phase in a 28-day cycle would yield a luteal-phase index of 0.5. Ovulatory disturbances were defined as including both anovulatory cycles and cycles with short luteal phases.

Dietary and Morphometric Data

Each woman kept seven-day records of her chosen diet at three-month intervals. The records were analyzed for total energy (in kilojoules) and nutrient and mineral intake per day.[29] The results are reported as the means of all seven-day records for each nutrient category.

The women's height and weight were measured during the follicular phase of the first and last menstrual cycles of the study year, and the body-mass index was calculated from the weight in kilograms divided by the square of the height in meters.[27] At the same times, skin-fold thickness was measured in four sites (abdomen, anterior thigh, triceps, and suprailiac crest) with a constant-tension Harpenden caliper. The amount of subcutaneous fat was calculated with a formula validated for athletic women.[30]

Measurements of Bone Density

The cancellous-bone density of the spine (from the 12th thoracic vertebra to the 3rd lumbar vertebra) was measured by single-energy quantitative computed tomography (QCT). The original quantitative method, which was modified for this study,[31] measured an elliptical region of interest in the center of each of the four vertebral bodies as identified by an edge-detection program.[32] The coefficient of variation (for the mean of the four vertebral bodies) was 0.8 percent in 74 premenopausal women who had two scans on the same day, with repositioning between the scans.[33] The measure-

ments were made with a Siemens DR2 instrument at 96 peak kilovolts, 300 milliampere-seconds, with 8-mm slices. The results were expressed in milligrams of mineral equivalents of dibasic potassium phosphate per cubic centimeter. The radiation doses at each session were estimated to be 200 mrem in the QCT slices and 10 mrem to the gonads.

The mean (±SD) interval between the two measurements of bone density was 12.0±1.8 months (range, 6 to 16). Because of technical and personal difficulties, 15 of the 66 women were tested <11 or ≥13 months after their first test. All results were annualized.

Hormone Analyses

Serum samples were obtained for hormonal analysis during the first and last menstrual cycles of the study year. Equal volumes of single samples obtained from each woman during the early-follicular and mid-luteal phases of the cycle were pooled and the results reported as one value per cycle. These samples were collected in the afternoon, when the women were rested and had not run for 12 to 24 hours. The specimens were stored at −70°C. All samples from a given woman were analyzed at the same time in duplicate in each assay.

Serum levels of luteinizing hormone, follicle-stimulating hormone, estradiol, progesterone, prolactin, cortisol, testosterone, and triiodothyronine were measured by standard radioimmunoassay methods.[34] The normal ranges for premenopausal women were as follows: luteinizing hormone, <33 IU per liter; follicle-stimulating hormone, 4 to 15 IU per liter; estradiol, 40 to 730 pmol per liter (follicular phase) and 180 to 570 pmol per liter (luteal phase); progesterone, 0.3 to 4.8 nmol per liter (follicular phase) and 19 to 90 nmol per liter (luteal phase); prolactin, <15 μg per liter; cortisol, 50 to 660 nmol per liter; testosterone, 0.5 to 3.8 nmol per liter; and triiodothyronine, 1.2 to 2.8 nmol per liter. An estimated value for luteal-phase progesterone was derived by adjusting for the dilution of the luteal-phase sample by the follicular-phase sample and subtracting the mean follicular-phase progesterone level in normal women (2 nmol per liter).

Statistical Analysis

The Biomedical Database program was used in the statistical analysis.[35] The parametric tests used included analysis of variance, multiple and stepwise linear regression, and tests of slope. Chi-square analysis and Fisher's exact test were used for categorical variables. All levels of significance were determined on the basis of two-tailed testing. P values below 0.05 were considered significant. Results are expressed as means ±SD, with ranges shown in parentheses.

Table 1. Mean (±SD) Demographic, Dietary, and Exercise Data Obtained during the Study in 66 Normal Premenopausal Women, According to Exercise Group.*

Variable	All	Normally Active	Consistent Runners	Marathon Runners	P Value†
No. of women	66	23	22	21	—
Age (yr)	33.7±7.1	35.2±5.7	33.6±5.1	32.7±5.9	0.359
Weight (kg)	58.2±6.5	59.6±8.2	59.8±4.0	54.9±6.4	0.267
Height (cm)	162.0±6.4	161.3±7.0	164.6±5.0	160.0±6.0	0.056
Body fat (%)	19.6±4.5	22.8±5.0	19.0±3.4	17.2±3.8	0.001
Dietary intake per day					
Calories (kJ)	6981±1455	6575±1179	7148±1797	7198±1237	0.214
Carbohydrate (kJ)	199±46	179±34	200±56	219±40	0.015
Calcium (mg)	912±307	766±243	1000±356	975±271	0.020
Exercise per cycle					
Running distance (km)	65.2±66.3	4.7±7.9	54.2±17.4	142.2±60.0	0.001
Other (min)	116±146	67±100	129±113	156±198	0.110

*The women were grouped according to the number of kilometers they ran in one menstrual cycle, as follows: normally active women, <24 km; consistent runners, ≥24 to <80 km; and marathon runners, ≥80 km.

†By analysis of variance among all three exercise groups.

Results

The mean age of the 66 women who completed the study was 33.7±5.6 years (range, 21 to 42) at the start of the study. Table 1 shows demographic, dietary, and exercise data for these women. Their mean height was 2 cm above the population average, and their mean weight was within the ideal range, after adjustment for age and height (Metropolitan Life tables, 1976). The median distance run for all 66 women was 49 km per cycle (range, 0 to 283), and the median time spent in other forms of exercise was 64 minutes per cycle (range, 0 to 854).

The mean menstrual-cycle characteristics of the 66 women during the one-year study period were a cycle length of 28.2±2.6 days and a luteal phase of 10.1±2.0 days (Table 2). Only 13 of the 66 women (20 percent), however, had normal menstrual cycles, as defined by the presence of luteal phases of normal length, consistently during the year. Forty women had one or more short luteal phases — 12 having one short luteal phase and 28 more than one such phase. Thirteen women had at least one anovulatory cycle (besides having one or more cycles with short luteal phases) (Table 2). The mean serum estradiol level was normal, and the mean estimated serum progesterone value in the luteal phase (≥19 nmol per liter) indicated the presence of ovulatory cycles. Although luteal function was disturbed in 29 percent of the menstrual cycles, few cycles were abnormal in length, and in 97 percent of all cycles the length was normal (21 to 36 days[24]). None of the anovulatory cycles were abnormal in length.

The mean initial spinal bone density was 154.1±21.7 mg of dibasic potassium phosphate equivalents per cubic centimeter (range, 105.0 to 209.5) (Table 3), and the mean change in spinal bone density was −3.0±4.8 mg per cubic centimeter per year (−2.0±3.1 percent per year) (P<0.001). Although there was great variability in the change in bone density over the year, the reproducibility of the QCT measurement was excellent. The results in the 51 women who had the two measurements at an interval of 12±1 months and in the 15 who had the measurements at intervals of <11 or ≥13 months were similar (−2.9±4.9 vs. −3.1±4.7 mg per cubic centimeter per year; P = 0.93).

Exercise Categories

The three exercise groups were well matched in age (Table 1) and equivalent with respect to sociologic and economic characteristics (data not shown). The three groups did not differ in their daily intake of calories (Table 1), protein, or fat (data not shown)

during the study. Both groups of runners (the marathon runners and the consistent runners) had a significantly lower percentage of subcutaneous fat and a higher calcium intake than the group with normal levels of activity. The marathon runners consumed more carbohydrates per day (Table 1) and had a significantly lower body-mass index ($P<0.03$, data not shown) than the normally active group.

Table 3. Mean (±SD) Spinal Bone Density, as Measured by Single-Energy QCT in 66 Normal Premenopausal Women, According to Exercise Group, Initially and after One Year.

Characteristic	All	Normally Active	Consistent Runners	Marathon Runners	P Value*
No. of women	66	23	22	21	—
Bone density (units†)					
Initial	154.1±21.7	154.4±22.2	153.3±23.6	154.8±19.9	0.973
Change in 1 year	−3.0±4.8	−4.1±3.8	−1.7±5.4	−3.0±4.8	0.248

*Differences between groups were tested by analysis of variance.

†Bone density was measured in milligrams of dibasic potassium phosphate equivalents per cubic centimeter.

The exercise results during the one-year study period are shown in Table 1. By definition, the distance run in each menstrual cycle differed significantly among the three groups. The number of minutes per cycle spent in other exercise varied considerably among women, but the mean values in the three groups were not significantly different.

The women in training for a marathon had menstrual-cycle patterns similar to those in the other two groups (Table 2). Specifically, amenorrhea did not develop in any, and none had an anovulatory cycle that was abnormally long. The mean luteal-phase length, luteal-phase index, and hormone levels also did not differ among the three groups (Table 2).

Neither the initial values for spinal bone density nor the changes in bone density after one year differed among the three groups (Table 3). The mean decrease in bone density of 3.0±4.8 mg per cubic centimeter per year was significant ($P<0.001$). The annual percentage decrease in bone density was also not different among the three exercise groups; it was 2.7 percent, 1.1 percent, and 1.9 percent in the marathon runners, consistent runners, and normally active women, respectively ($P = 0.308$).

Factors Relating to the Change in Spinal Bone Density

Univariate relations between the values for demographic characteristics, diet, exercise, menstrual cycle, and hormone measurements and the change in spinal bone density were sought. The strongest univariate relation was between the change in bone density and the luteal-phase index ($r = 0.54$, $P<0.001$) (Fig. 1). Mean annual luteal-phase length ($r = 0.48$, $P<0.001$) and mean estimated serum luteal-phase progesterone level ($r = 0.25$, $P<0.05$) were also significantly related to the one-year change in bone density. In addition, total caloric intake ($r = 0.29$, $P = 0.02$) and family history of osteoporosis were associated with the change in bone density (chi-square = −4.27, $P = 0.04$). Linear regression analysis revealed no association between the change in bone density over the year and the number of kilometers run per cycle ($r = -0.077$), the mean length of each run, the number of kilometers run per day, the relative workload (as measured in TRIMPs to adjust for level of fitness), or the number of minutes of other exercise per cycle. In addition, cycle length ($r = 0.05$), age ($r = -0.01$), serum estradiol level ($r = 0.06$), serum testosterone level ($r = 0.13$), serum triiodothyronine level ($r = -0.04$), and serum cortisol level ($r = 0.002$) were not correlated with the change in bone density over the year of the study.

According to multiple regression analysis, the luteal-phase index was the strongest explanatory variable for the change in spinal bone density (Table 4), with caloric intake contributing minimally and family history of osteoporosis contributing about 4 percent. No variable related to age, morphometric measurements, exercise, or hormonal status was significant in the multiple regression model (Table 4).

Table 2. Mean (±SD) Menstrual-Cycle and Hormonal Characteristics during the Year of Study, According to Exercise Group.

Characteristic*	All	Normally Active	Consistent Runners	Marathon Runners	P Value†
No. of women	66	23	22	21	—
Cycle length (days)	28.2±2.6	27.9±2.2	28.9±2.8	27.9±2.8	0.377
Luteal-phase length (days)	10.1±2.0	10.4±1.9	10.3±1.9	9.7±2.0	0.401
Luteal-phase index	0.359±0.073	0.371±0.058	0.360±0.073	0.346±0.088	0.459
Serum estradiol (pmol/liter)	275±112	279±122	301±93	245±115	0.290
Luteal-phase serum progesterone (nmol/liter)	26.9±15.3	30.0±18.1	28.0±15.8	22.8±11.4	0.293
			no. of women		
Luteal-phase analysis					
Normal cycles	13	7	4	2	—
Short luteal phases					
1	12	1	6	5	—
>1	28	10	8	10	—
Anovulatory cycles‡	13	3	6	4	—
Cycle length (days)					
Long (>36)	13	5	5	3	—
Short (<21)	3	2	0	1	—

*The normal length of the menstrual cycle is 21 to 36 days, and that of the luteal phase 10 to 16 days. The luteal-phase index is the mean ratio of the length of the luteal phase to that of the menstrual cycle. The serum estradiol levels shown are the results of measurements in pools of single early-follicular-phase and midluteal-phase samples, whereas the progesterone levels are estimated midluteal values from two cycles from the same pools (see text).

†Analysis of variance was used, except in the analysis of luteal phase and cycle length, for which Fisher's exact test was used. There were no significant differences among groups for these two characteristics.

‡All women with anovulatory cycles also had cycles with short luteal phases.

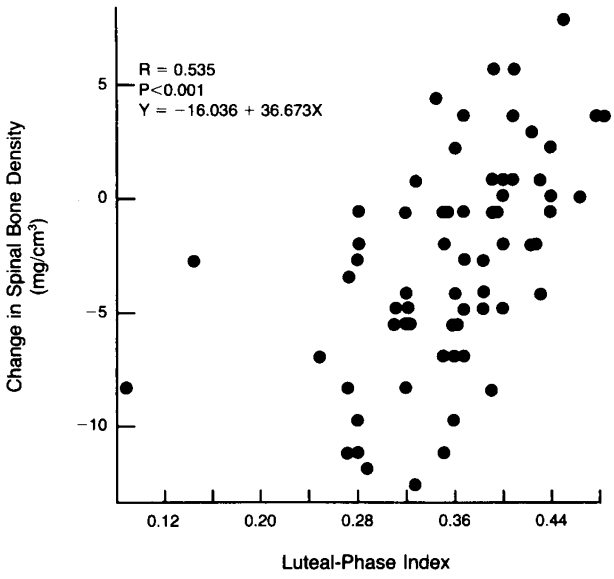

Figure 1. Relation between the Mean Luteal-Phase Index and the Change in Spinal Bone Density over a Period of One Year in 66 Normal Premenopausal Women, as Measured by Single-Energy QCT.

Spinal bone density was measured in milligrams of dibasic potassium phosphate equivalents per cubic centimeter. The luteal-phase index is the ratio of the length of the luteal phase to the length of the cycle. The length of the luteal phase was determined by a quantitative basal-temperature method validated by the determination of the midcycle peak of the serum luteinizing hormone concentration.[27] The two outlier values to the left of the cluster were included in the calculation of the correlation coefficient.

To understand the effect of luteal-phase length on the change in bone density, the women were grouped according to their menstrual-cycle experience over the year (Fig. 2). The 13 women with normal cycles tended to have increases in spinal bone density (1.5±3.9 mg per cubic centimeter per year, P = 0.2). The 28 women who had more than one cycle with a short luteal phase (mean, 4.4±2.3 such cycles per year) and the 13 women with one or more anovulatory cycles had significant decreases in spinal bone density (4.3±4.2 mg per cubic centimeter per year [P<0.001] and 6.4±3.8 mg per cubic centimeter per year [P<0.001], respectively). The change in bone density in the women who had entirely normal cycles did not differ from that in the women who had only one short luteal phase (1.5±3.9 vs. −0.74±3.3 mg per cubic centimeter per year, P = 0.14) (Fig. 2). When the women with normal cycles and those with only one short luteal phase per year were considered as a group, however, the change in bone density differed significantly from the changes in either the women with more than one short luteal phase or the women who had one or more anovulatory cycles (0.42 vs. −5.0 mg per cubic centimeter per year, P<0.0001).

We also examined the relation between the menstrual-cycle experience over the year and serum levels of gonadal steroids. The mean estimated serum progesterone levels during the luteal phase were lower in the women who had more than one short luteal phase and the women with one or more anovulatory cycles than in the women with normal cycles or one short luteal phase per year (12.0±4.8 vs. 18.7±9.8 nmol per liter, P = 0.0006). The serum estradiol levels in the women with abnormal ovulatory function did not differ, however, from those in the women with normal ovulatory function (271±116 vs. 281±103 pmol per liter, P = 0.75). The luteal-phase index correlated with the estimated serum progesterone level in the luteal phase (r = 0.322, P = 0.01) but correlated less well with the serum estradiol level (r = 0.225, P = 0.07).

To explore further a relation between the change in bone density and hormonal levels, the women were grouped according to whether they had an increase or a decrease in spinal bone density. The 19 women who had an increase had a higher mean estimated serum progesterone level in the luteal phase than the 47 women who had a decrease (18.2±10.8 vs. 12.9±5.4 nmol per liter, P = 0.01). The mean serum estradiol levels did not differ, however, in these two groups (274±121 vs. 277±81 pmol per liter).

The mean serum concentrations of luteinizing hormone, follicle-stimulating hormone, prolactin, cortisol, triiodothyronine, and testosterone were normal (data not shown), did not differ between groups, and did not relate to the annual change in bone density.

Discussion

Women are at higher risk than men for early osteoporosis. Bone loss related to menopause is considered to be the most important reason for this difference. This study documents that short luteal phases and especially lack of ovulation in menstrual cycles of normal length may be other potential risk factors for excess bone loss in women.

Our initial hypothesis — that women in training for a marathon would have more bone loss than less active women — proved incorrect. We found that marathon training also did not cause amenorrhea in ovulating women. The marathon runners probably did not have menstrual-cycle changes or bone loss (in contrast to data from cross-sectional studies), because we initially excluded women who had causes other than exercise for disruption in their menstrual cycles,[36] and

Table 4. Determinants of the One-Year Change in Spinal Bone Mineral Density, According to Multiple Regression Analysis.*

Characteristic	F	R^2	Regression Coefficient ±SE	P Value
Luteal-phase index	4.53	0.235	32.82±7.24	0.001
Mean caloric intake/day	2.13	0.0520	0.0032±0.0015	0.052

*Age, length of menstrual cycle, body-mass index, measurements of skin-fold thickness, dietary calcium intake, kilometers run per cycle, kilometers run per day, kilometers per run, TRIMPs (see Methods), and all hormone levels were tested and found not to be explanatory variables. The multiple correlation of the determinants shown was 0.568; when family history of osteoporosis was included, it was 0.606.

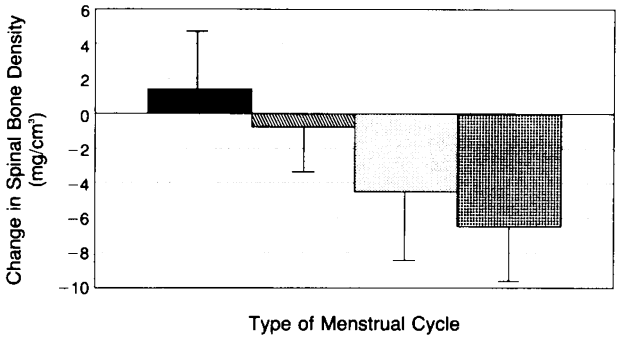

Figure 2. Mean (±SD) Change in Spinal Bone Density, as Measured by QCT, in Relation to the Menstrual-Cycle Experience of 66 Normal Premenopausal Women Studied for One Year.

The 13 women with luteal phases of consistently normal length (10 to 16 days) during the year (solid bar) and the 12 women with a short luteal phase during only one cycle (hatched bar) had bone-density values that were significantly different from those of the 28 women who had more than one cycle with a short luteal phase (stippled bar) or of the 13 women who had anovulatory cycles (dotted bar) ($T = 5.37$, $P<0.0001$).

we included only women who had had two consecutive ovulatory cycles of normal length, were of normal weight for height, and were not exercising compulsively.

Our chief finding, that spinal bone density decreased in association with disturbances, especially anovulatory cycles, was possible because we prospectively determined luteal function in a prescreened population of ovulating women who had minimal changes in the interval of the menstrual cycle. We expected that women who were normally active or were consistent runners would have regular ovulatory cycles. Disturbances in the menstrual cycle were as common in these two groups, however, as in the marathon runners. These characteristics of the data allowed us to associate bone loss with ovulatory disturbances, especially anovulatory cycles (Fig. 2).

We explored a number of explanations for the change in spinal bone density in these women. Disturbances in the menstrual cycle, caloric intake, and family history of osteoporosis proved to be significant. Other factors, including age, serum estradiol level, cycle length, total calcium intake, body weight, and exercise, were less important (Table 4).

Fourteen women over 40 years old and described as perimenopausal had a decrease in spinal bone density of approximately 3 percent per year as measured by QCT.[22] Even so, we were surprised to find that healthy young adult women (averaging 34 years of age) who had regular menstrual cycles had a 2 percent decrease in spinal bone density over a one-year period. If the normal menstrual-cycle intervals in these women indicate normal estrogen production, then the bone loss is even more perplexing.

Estrogen treatment prevents bone loss in postmenopausal women. Why then does the apparently normal endogenous production of estradiol not prevent spinal bone loss in younger women with ovulatory disturbances? Perhaps a partial answer is that progesterone increases bone turnover in addition to facilitating the formation of bone.[17] Even if bone formation is enhanced, increased remodeling would decrease bone mineral density, at least in the short term. Other explanations for the bone loss documented in this study, such as amenorrhea, excess cortisol production, or inadequate calcium intake, are not supported by the data.

Ovulatory disturbances are common during exercise training[9-11,13-15] as well as in response to stress,[37,38] but they have not been reported previously with such frequency in a population of mature, ovulating women.[37] The women we studied appear to be representative of an urban, active population with respect to demographic and socioeconomic factors. If the results of this study are confirmed, normal ovulation cannot be assumed to be present in menstrual cycles of normal length. Even among the group of 23 sedentary women taken alone, the changes in bone density and the luteal-phase index remained strongly correlated ($r = 0.583$, $P = 0.003$).

We have shown that inadequate production of progesterone (in cycles with short luteal phases and anovulatory cycles) is associated with accelerated bone loss, despite normal production of estradiol and the preservation of normal cycle intervals. These results suggest that the maintenance of peak bone density throughout adulthood requires normal ovarian production of both estrogen and progesterone. It is possible that a substantial percentage of premenopausal women who have apparently normal menstrual cycles may instead have asymptomatic ovulatory disturbances — specifically, short luteal phases or anovulatory cycles. If these disturbances, which we have shown to be associated with a rate of spinal bone loss of 4 percent per year, continue to cause this accelerated rate of bone loss for several years, sufficient bone density could be lost before menopause to create an increased risk of osteoporosis.

To confirm the prevalence of disturbances in the luteal phase and the association of ovulatory dysfunction and spinal bone loss, longer studies using other methods to document the luteal phase and conducted in population-based random samples are needed. In addition, randomized, controlled trials in which anovulatory but menstruating women are treated for 10 days per cycle with doses of progesterone equivalent to those produced in the luteal phase are necessary to prove that ovulatory disturbances that result in decreased progesterone production are a factor in the pathogenesis of osteoporosis.

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