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Editorial

Irreversible Bone Loss in Former Amenorrheic Athletes

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Abstract. Small gains in bone mineral density (BMD) have been reported in the first year following resumption of menses in amenorrheic athletes but there have been no long-term outcome studies. The purpose of this study was to determine whether the BMD of former oligomenorrheic or amenorrheic athletes normalizes following several years of normal menses or use of oral contraceptives. Twenty-nine athletes first studied in this laboratory 8.1 years (range 6–10 years) ago were available for follow-up. At recruitment (time 1) 29 athletes, mean age of 30.6 years, were non-smokers, exercised 4 or more days/week for at least 45 min, had not used oral contraceptives, and had no medical conditions affecting bone metabolism. At time 1, 9 women (R/R) had always menstruated regularly, 9 (R/O/A) had experienced intermittent oligo/amenorrhea as well as regular menses, and 11 (O/A) had never menstruated regularly. At follow-up (time 2) mean age of the women was 38.2 years and there were no significant changes in height, weight or activity patterns. BMD (g/cm^2) was measured at the lumbar vertebrae (L1–4 and femoral neck by dual-energy X-ray absorptiometry and expressed as a percentage of R/R values. Vertebral BMD was significantly lower in the O/A group compared with the R/R group at both time 1 and time 2 ($p < 0.05$). The R/O/A group had intermediate values and did not differ significantly from R/R or O/A at either time. Differences in technique between machines for determining femoral neck BMD made it difficult to detect the longitudinal effect of menstrual status at that site. Despite several years of normal menses or use of oral contraceptives, the mean vertebral BMD of former oligo-amenorrheic athletes remained low, being 84.4% of the R/R value compared to 84.8% at time 1. Those experiencing menstrual regularity with intermittent oligo/amenorrhea remained at an intermediate position of 94.7% of the R/R mean. Our results suggest early intervention is necessary to prevent irreversible vertebral bone loss in oligo/amenorrheic athletes.

Keywords: Amenorrhea; Athletes; Bone density; Oligomenorrhea; Osteoporosis

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Introduction

During the last 10 years many studies have reported a significantly lower vertebral bone mineral density in amenorrheic athletes when compared with eumenorrheic athletes and non athlete controls [1–5]. Two studies [6,7] have also reported osteopenia at other skeletal sites. It is thought that the deficit of endogenous estrogen production associated with athletic amenorrhea is responsible for the deleterious effect on bone.

The present concern is that many women athletes whose rigorous training schedules and restrictive dietary practices have led to extended periods of amenorrhea may have also suffered irreversible bone loss. If so, the implications are alarming. Osteopenia has been associated with an increased risk of stress fractures and even non-traumatic fracture in athletes and may put the athlete at risk for premature osteoporotic fractures in the future [8–10].

Currently, however, the long-term consequences of oligomenorrhea and amenorrhea remain unknown. There are no long term follow-up studies of former amenorrheic athletes which enable us to determine whether normal bone mineral densities can be attained following

several years of normal menses or the use of oral contraceptives. Two early studies examining this question did observe gains of approximately 6% in vertebral bone mineral density over 14 months in former amenorrheic runners who resumed menses following a reduction in training and a small gain in weight [11,12]. However, further data on those runners studied in this laboratory indicate that this gain subsequently ceased so that at 4 years after resumption of menses their vertebral bone mineral density remained well below average for their age group [13]. The aim of this study was to investigate whether normal menses or use of oral contraceptives over a longer time period would have sufficient osteogenic influence to normalize bone mineral density in former oligo/amenorrheic athletes.

Subjects and Methods

Forty-five female athletes who participated in studies in this laboratory 6–10 years ago (time 1) were contacted for this study. Seven of these women did not wish to participate in the current study, 5 had moved away long-distance and were unable to attend for bone mineral density (BMD) measurement, and 2 were pregnant and therefore could not be included in this study. Thirty-one women gave their informed consent to participate in this follow-up investigation (time 2). Two of these had to be excluded: one was severely obese preventing accurate BMD measurement and one was excluded because at the time of the first study she had been anovulatory but not hypoestrogenic.

The 29 remaining women were divided into three groups based on their menstrual classification at time 1 [13]. Menstrual status was originally determined by questionnaire and estrogen and progesterone levels measured at weekly intervals for 1 month. Menstrual status at time 1 and menstrual history prior to that date were combined to form three categories: (1) Regular/Regular (R/R) – women who had always had regular cycles and had normal estrogen and progesterone values at time 1, $n = 9$; (2) Regular/Oligomenorrheic/Amenorrheic (R/O/A) – women who had had periods of regular cycles interspersed with episodes of oligomenorrhea and/or amenorrhea, $n = 9$; and (3) Oligomenorrheic/Amenorrheic (O/A) – women who were amenorrheic of oligomenorreic at time 1 and who had never had regular cycles, $n = 11$. Regular menses was defined as between 10 and 13 cycles per year, oligomenorrhea as three to six cycles per year and amenorrhea as fewer than two cycles per year or no cycles in the past 6 months.

Each woman attended the laboratory on one occasion for approximately 1 h. At this visit the individual had BMD measurements of the lumbar spine and hip, height and weight measurements, and a structured interview with A.K. During the structured interview each woman provided information about her exercise levels, exercise-related injuries, weight changes, calcium intake, menstrual pattern, pregnancies and breastfeeding, medical conditions and medications taken including oral contraceptives during the intervening 6–10 years.

Dual energy X-ray absorptiometry (DXA) (Norland XR-26, Norland, Fort Atkinson, WI) was used to measure current BMD (g/cm^2) at two sites: the lumbar vertebrae (L1–4) and right proximal femur. The coefficient of variation for this technique using the Norland and Hologic phantoms is less than 1%. In vivo reproducibility in this laboratory was evaluated in 14 women using duplicate scans obtained on the same day with repositioning between scans. The correlation coefficients between the first and second scans were $r = 0.99$ for the lumbar spine and $r = 0.98$ for the femoral neck. Mean absolute differences between scans were 0.015 g/cm^2 and 0.016 g/cm^2 for the lumbar spine and femoral neck respectively.

Twenty of our subjects had BMD measurements of their lumbar vertebrae and right femoral neck at time 1 using dual photon absorptiometry (DPA) (Series 84, Ohio Nuclear, Cleveland, OH). A test–retest of 13 normal young women over 6 months in this laboratory using this technique produced a reliability correlation coefficient of $r = 0.98$ for the lumbar vertebrae and $r = 0.88$ for the femoral neck. The other 9 women had time 1 BMD of their lumbar spine and right femoral neck measured using DXA (Hologic QDR 1000, Hologic, Waltham, MA). This densitometer has been shown to be a reliable system capable of achieving an in vitro precision error of less than 1% in this laboratory and in a multicenter cross-calibration study [14]. The in vivo reproducibility in this laboratory was evaluated in a control group of 15 eumenorrheic young athletes. The correlation coefficient between two scans 6 months apart was $r = 0.99$ for the lumbar spine and $r = 0.98$ for the femoral neck. Measurements for both sites on all machines were performed with strict adherence to the procedures and instructions as specified in the operator's manuals.

As BMD was obtained on three different machines, it was necessary to adjust the data to correct for differences in measurement techniques. The Hologic spine phantom was measured 10 times on both the Hologic QDR 1000 and the Norland XR-26. Since the mean absolute difference was only 0.0074 g/cm^2, no corrections were deemed necessary for these data. The BMD values obtained by the DPA at the University of Washington Osteoporosis Center had been converted to Hologic DXA values for a clinical study using a linear regression model (SEE = 0.07). This correction was applied to the R/R data to determine whether there had been any marked change in BMD over time. The BMD of the other women was expressed as a percentage of the actual R/R mean for either the DPA or Hologic R/R group. It was not possible to use the standard z or T scores as the normative data bases were different for each machine.

BMD measurements obtained using DPA are not comparable to those obtained using DXA techniques; consequently we could not make direct comparisons of actual values from time 1 to time 2 in this study. We

therefore analyzed the BMD data by calculating each individual's value for both the lumbar vertebrae and right femoral neck as a percentage of the mean of the R/R group at time 1 and time 2. This method assigns a value of 100% to the R/R group mean, the R/O/A and O/A means being calculated as the average of the individual percentages.

Data were analyzed with a two-factor ANOVA with repeated measures on factor B (Time). Post-hoc comparisons examined differences between groups where main effects of factor A (Group) or factor B (Time) were significant. There were no significant interactions requiring analysis of simple main effects. Pearson product–moment correlations were used to assess relationships between age, height, weight and BMD. A chi-square test was used to examine differences in incidence of stress fractures between groups. A significance level at or below $p<0.05$ was selected for all analyses.

Results

The physical characteristics, activity levels and relative BMD values of the R/R, R/O/A and O/A groups are shown in Table 1. Other than being 3–4 years older at time 1 than the groups from which they were drawn, they were similar in physical characteristics. No significant differences were found between the three groups in age, height or weight at either time 1 or time 2. At time 1 there was a significant difference ($p<0.05$) between the R/R and O/A groups in hours of activity per week (Table 1); this difference disappeared at time 2. There was no significant change in height, weight or activity from time 1 to time 2. At time 1 all women had been participating in some form of weight-bearing activity such as running, race walking or aerobics, and had continued to do so in the intervening years. All were premenopausal, had remained non-smokers and none had any medical condition or took any medications (other than oral contraceptives) that were related to bone metabolism.

Table 1. Physical characteristics, activity levels, and bone mineral density (%R/R mean) of R/R, R/O/A and O/A athletes at time 1 and time 2 (mean ± SE)

	R/R (n=9)	R/O/A (n=9)	O/A (n=11)
Time 1			
Age (years)	31.0 ± 1.1	31.4 ± 1.7	30.3 ± 1.8
Height (cm)	168.3 ± 1.6	165.6 ± 1.2	166.1 ± 2.3
Weight (kg)	57.2 ± 2.1	55.8 ± 2.2	52.7 ± 2.2
BMI (kg/m^2)	20.1 ± 0.4	20.3 ± 0.6	19.1 ± 0.5
Activity (h/weeks)	6.9 ± 1.2	9.8 ± 1.4	12.4 ± 2.1[c]
BMD (%R/R Mean) L1–4	100.0 ± 3.5	95.7 ± 5.3	84.8 ± 4.0[a]
Femoral neck	100.0 ± 2.8	114.4 ± 7.0	95.2 ± 4.4[b]
Time 2			
Age (years)	38.3 ± 1.6	40.8 ± 1.6	38.0 ± 1.6
Height (cm)	168.3 ± 1.6	165.6 ± 1.2	166.1 ± 2.3
Weight (kg)	61.8 ± 3.2	56.3 ± 2.7	53.8 ± 2.6
BMI (kg/m^2)	21.8 ± 1.0	20.5 ± 0.8	19.4 ± 0.6
Activity (h/weeks)	8.3 ± 1.8	9.0 ± 1.9	9.2 ± 1.1
BMD (%R/R Mean) L1–4	100.0 ± 3.3	94.7 ± 5.7	84.4 ± 4.5[a]
Femoral neck	100.0 ± 4.1	111.6 ± 8.6	91.0 ± 3.8[b]

R/R, had always menstruated regulary; R/O/R, had experienced intermittent aligo/amenorrhea as well as regular menses; O/A, had never menstruated regulary.
[a]$p<0.05$ O/A < R/R; [b]$p<0.01$ O/A < R/O/A; [c]$p<0.05$ O/A > R/R.

All 9 of the R/R group had continued to have regular menses since time 1; one had also used oral contraceptives during the last 2 years. Three women in this group had experienced at least one full-term pregnancy. Of the 9 women in the R/O/A group, 6 were having regular cycles at time 1 and have continued to do so. One woman elected to use oral contraceptives soon after time 1 and has continued to use them to the present. The remaining 2 athletes were amenorrheic at time 1. One has used oral contraceptives consistently since that time and the other resumed normal cycles after a further year of amenorrhea and has used oral contraceptives for the last 3 years. Four of this group have had one or more full-term pregnancies since time 1.

Eight of the O/A group had resumed normal menses within a year of the previous study; 2 of these have also used oral contraceptives. Two women continued to be amenorrheic, 1 for an additional year and 1 for 7 more years before electing to use oral contraceptives. One of the O/A athletes remained amenorrheic from time 1 to time 2. One woman in this group has experienced two full-term pregnancies.

A significant group effect was found for the lumbar BMD ($p<0.05$). Post-hoc comparisons revealed that L1–4 BMD was significantly lower ($p<0.05$) in the O/A group than in R/R at both time 1 and time 2 (Table 1). R/O/A did not differ significantly from either the R/R or O/A groups. There was no significant change over time nor significant interaction between time and group factors, indicating that both R/O/A and O/A had retained their positions relative to R/R. Initial spinal BMD for the R/R group at time 1 was estimated at 1.083 g/m^2 (actual plus predicted Hologic values) and at time 2, 1.075 g/m^2 (Norland values). At the femoral neck the R/O/A group had significantly higher BMD than the O/A group at time 1 and time 2 ($p<0.05$). There was, however, no significant difference between the R/R and O/A groups at this site at either time 1 or time 2.

Age was not related to either lumbar or femoral neck BMD for any group. However, height was significantly ($p<0.05$) correlated with the femoral neck BMD in the R/R group and with BMD at both sites in the R/O/A group. For O/A height was related only to lumbar BMD ($p<0.05$). Weight had no relationship with any BMD values in the R/R group but was significantly correlated with both lumbar and femoral neck BMD in the R/O/A and O/A groups ($p<0.05$).

Exercise-related stress fractures were reported more frequently in the O/A group than the R/O/A and R/R groups; 4 versus 2 and 0 respectively. However, statistical significance was not achieved due to the small sample size.

Discussion

The results suggest that in spite of several years of normal menses and/or use of oral contraceptives former oligo/amenorrheic athletes continued to have a significantly lower BMD at the lumbar spine in comparison with athletes who had always had regular cycles. Their vertebral BMD was approximately 85% of that of the R/R athletes at both time 1 and time 2.

While the apparent lack of change (<0.1%) in lumbar BMD for R/R supports the conclusion that there has been no marked improvement in lumbar BMD in former amenorrheic athletes who have resumed menses or used oral contraceptives for a number of years, there is always the possibility of error when comparing values obtained from DPA with DXA, or between one DXA machine and another. However, when the absolute L1–4 values at time 2 are compared with the value for L1–4 peak bone mass, R/R (1.078 g/cm^2) = 103%, R/O/A (1.038 g/cm^2) = 99% and O/A (0.910 g/cm^2) = 87%, confirming the lower BMD for former O/A athletes.

Data for the femoral neck are less clear. In addition to the differences between measurement devices there are differences in how the respective software determines the area to be evaluated and how the value for soft tissue is obtained. When absolute femoral neck values at time 2 are compared with peak bone mass, R/R = 93%, R/O/A = 96% and O/A = 82%.

The 1 athlete who has remained amenorrheic since time 1 has continued to lose bone relative to the R/R group over 6 years. Her vertebral BMD was 72.0% of the R/R mean at time 1 and is currently 69.3% of the present R/R mean. Her femoral neck BMD also declined relative to the R/R group from 77.9% of the time 1 R/R mean to 69.0% of the current R/R mean.

The early optimism created by two studies [11,12] finding a small gain in vertebral BMD over 14 months following resumption of menses in former amenorrheic runners of similar age is now tempered. Our current data suggest that even after 6–10 years of normal menses or oral contraceptives oligo/amenorrheic athletes do not show significantly improved vertebral BMD values when compared with eumenorrheic athletes over the same period. A recent study of premenopausal ultramarathon runners aged 29–39 years also reported that prior periods of oligo/amenorrhea resulted in lower lumbar BMD in women who had regained normal menses [5]. Although this was a cross-sectional study, the data support our results suggesting irreversible bone loss in women who have not had extended periods of normal menses.

Our current data and those of a previous study also suggest that months of regular menses between episodes of amenorrhea or oligomenorrhea exert some protective effect on bone [13]. The possibility that the total months of endogenous estrogen sufficiency is the critical determinant of spinal density in these women is supported by Micklesfield et al. [5] who reported that the number of estimated menstrual periods since age 13 years was positively correlated with current lumbar BMD. At this time it is impossible to state with certainty the number of menses per years that may prevent bone loss in oligomenorrheic women, but the fact that our R/O/A group had a minimal loss of lumbar BMD and no apparent loss of femoral neck BMD suggests that oligomenorrheic and amenorrheic women should not be grouped in studies examining the effect of a hypoestrogenic state on the BMD of premenopausal women.

It is possible that our result is specific to the age group of the athletes we studied. The mean age of our subjects at time 1 was 30.9 years, and although age of peak vertebral BMD is not certain, studies suggest it reaches a maximum somewhere between late adolescence and 29 years [15]. Increments in vertebral BMD after this age may not be possible. Studies of younger amenorrheic women, dancers, and recovering anorexia nervosa (AN) patients [16–19] have observed some vertebral BMD incremented over relatively short time periods, although complete normalization of bone mass was not reported in any of these studies. Interestingly, however, in one study greater gains were observed in the adolescent AN patients (less than 18 years old) than in the adult patients (18+ years old) [18]. This study also reported that weight gain prior to resumption of menses was sufficient to bring about gains in BMD, suggesting that body mass was an independent determinant of vertebral BMD in low-weight women. Although the women in our current study were within the normal range of body mass, weight was significantly related to BMD at both sites in the R/O/A and O/A groups.

In summary our current follow-up study of premenopausal athletes suggests that complete normalization of the low vertebral BMD in former amenorrheic athletes is unlikely. Even after several years of normal menses and/or use of oral contraceptives the lumbar BMD of the athletes who at time 1 had never had regular menstrual cycles remained at 85% that of those athletes who had always been eumenorheic. However, periods of regularity seemed to attenuate the deleterious effect of estrogen depletion in the R/O/A group. Our data suggest that the effect of intermittent decreases in endogenous estrogen levels was most marked at the spine, an area more sensitive to the influence of estrogen deficits because of its higher trabecular component. The smaller deficit at the femoral neck in comparison did not reach significance, possibly due to the small sample size and greater variability in this measurement.

In conclusion, physicians should consider early intervention in young athletes presenting with amenorrhea in order to minimize the threat of irreversible vertebral bone loss and the long-term risks for osteoporosis. Ideally, a sensible training load and adequate calories to retain normal menstrual functioning will enable the young female athlete to optimize her peak bone mass. Failing this, the use of hormonal therapies may help to avoid the negative effects of the 'Female Athlete Triad' of disordered eating, amenorrhea and osteoporosis [20]. However, the effectiveness of hormone therapies in this population of premenopausal women has yet to be established.

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