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Bone Density in Adolescents Treated with a GnRH Agonist and Add-Back Therapy for Endometriosis

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Abstract

Study Objective—To evaluate the bone density of adolescents with endometriosis treated with a GnRH-agonist and “add-back” therapy with norethindrone acetate.

Design—Retrospective chart review.

Setting—Pediatric gynecology clinic at a tertiary care center.

Participants—36 adolescents, ages 13 to 21 years, with endometriosis.

Main Outcome Measures—Bone mineral density (BMD, g/cm²) by dual energy x-ray absorptiometry (DXA); BMD Z-scores of hip and spine.

Results—The mean BMD Z-score at the total hip was -0.24 ± 1.0 , with a range of -2.4 to 1.7 . At this site, 6 subjects had a BMD Z-score between -1.0 and -2.0 SD, while 2 had a Z-score ≤ -2.0 SD. The mean BMD Z-score at the lumbar spine was 0.55 ± 1.1 , with a range of -2.8 to 1.4 . At the spine, 11 subjects had a BMD Z-score between -1.0 and -2.0 SD, while 3 had a Z-score ≤ -2.0 SD. There was no correlation noted between duration of therapy with the GnRH-agonist plus add-back and BMD at the hip or spine.

Conclusion—BMD at the hip was normal in most adolescents with endometriosis who were receiving a GnRH-agonist plus add-back therapy with norethindrone acetate. Almost one third of subjects exhibited skeletal deficits at the spine. These data suggest that BMD should be carefully monitored in adolescents receiving treatment with GnRH agonists.

Keywords

Bone mineral density; GnRH-agonist; Add-back therapy; Norethindrone acetate; Endometriosis; Adolescence

Introduction

Endometriosis, while historically a disease that affects adult women, has become increasingly recognized as a chronic illness that may begin during adolescence and young

adulthood.¹ Endometriosis is highly prevalent within certain populations. It is estimated that between 25–38% of adolescents with chronic pelvic pain have endometriosis,¹ and approximately 70% of adolescents with a persistence of pelvic pain on combination oral contraceptive pills and non-steroidal anti-inflammatory agents have been found to have endometriosis.² Untreated endometriosis may lead not only to chronic pain, but also to infertility. As recognition of the need for prompt therapy increases, so does the length of time patients will be exposed to therapeutic modalities. As a result, there exists a pressing need to evaluate adjunctive measures that may limit the associated negative health consequences of treatment.

A gonadotropin-releasing hormone (GnRH) agonist is one medical therapeutic option commonly utilized for patients who have failed primary treatment regimens, such as nonsteroidal anti-inflammatory drugs and combination hormonal therapy. While GnRH agonists are efficacious in relieving symptoms, their long-term use is potentially problematic due to the deleterious effect on bone mineralization associated with their induced low-estrogen state.³ Adolescence is the critical time period for accrual of bone mineral density (BMD).⁴ Any agent that interferes with this process puts patients at risk for low bone mass, and thus fracture, in the future. Current literature suggests that GnRH agonist use is not only associated with increased bone turnover,^{5,6} but could also prevent acquisition of peak BMD in adolescents. It has been well-documented in studies of adult women that significant losses of BMD occur after only 3–6 months of GnRH agonist therapy.^{7–9} Additionally, BMD may not return to baseline levels following cessation of treatment.^{10,11}

Add-back therapy appears a promising adjunct to treatment with GnRH agonists for the prevention of this bone loss.^{7,8,12} Daily therapy with low-doses of a steroid hormone (such as estradiol, norethindrone, or medroxyprogesterone) preserves bone density in adult patients, without negatively impacting the primary therapeutic effect of the GnRH agonist.^{7,8,12} However, no data exist on the effect of GnRH agonist use with add-back therapy in the adolescent population. Given that this cohort of patients is at particular risk for deleterious effects from analog therapy, establishing efficacy of add-back therapy in this population is critically important.

The aim of the current study was to evaluate the bone density of adolescent and young adult women with endometriosis treated with a combined regimen of a GnRH-agonist and add-back therapy with norethindrone acetate.

Materials and Methods

Subjects

All patients who were referred to the Bone Health Program at Children's Hospital Boston by the Division of Gynecology between 1995 and 2005 were identified (n = 50). From this cohort, subjects were selected who met the following inclusion criteria: (1) a surgical diagnosis of endometriosis; (2) therapy with leuprolide acetate (Depo-Lupron®); and (3) adjunctive treatment with norethindrone acetate (Aygestin®). Subjects were excluded if they had other chronic medical conditions known to affect bone metabolism or were receiving other medications known to alter calcium or vitamin D metabolism.

All subjects received leuprolide acetate, 11.5 mg as an intramuscular injection every 3 months. Norethindrone acetate, 5 mg orally once daily, was started concurrently along with the GnRH agonist. All study procedures were reviewed and approved by the local institutional review board. Informed consent was obtained from all subjects or their parents. Minor subjects provided assent for participation.

Data Collection

A retrospective chart review was conducted to obtain information regarding demographic information and health history, including data regarding the date of diagnosis, length of medication use, and clinical course. At the time of the bone density measurement, anthropometric measurements were also obtained on all study subjects. Height (cm) was measured using a wall-mounted stadiometer. Weight (kg) was measured post-voiding, with subjects wearing a hospital gown. The same stadiometer and calibrated scale were used for all measurements. BMI (body mass index, kg/m^2) was calculated and BMI percentile was determined using standard percentile tables.¹³

Bone Density Evaluation

As part of routine clinical care, each patient treated with the GnRH-agonist had a bone density measurement at least 4 months after the initiation of leuprolide therapy. Areal bone density was evaluated by dual-energy x-ray absorptiometry (DXA) using a QDR-4500 with Delphi upgrade (Hologic, Inc., Waltham, MA, USA). Measurements of bone mineral density (BMD, g/cm^2) were obtained at the left total proximal hip and the lumbar spine (L1–L4). Hip, spine, and total body measurements were compared with age- and gender-matched controls, and BMD Z-scores were calculated.^{14,15} For participants aged less than 20 years, pediatric normative data were used to calculate Z-scores.¹⁶ The BMD Z-scores represent the standard deviations from the mean for age- and gender-matched controls. A Z-score of ≤ -2.0 SD was considered to be low, indicating a clinically significant low bone mass for age and gender. A Z-score between -1.0 and -2.0 SD is intermediate, and indicates that a patient may be at risk for low bone mass.

Data Analysis

One-sample *t*-tests were used to compare subjects' Z-scores to age- and gender-specific normative data. Pearson correlation analyses were performed to evaluate the relationships among BMD, duration of therapy, and anthropometric variables. Statistical analyses were performed with SAS (SAS Institute, Inc., Cary, NC). Level of significance was set at $P < 0.05$.

Results

We studied 36 adolescents and young women with endometriosis who were treated with a GnRH-agonist and add-back therapy with norethindrone acetate. Subject characteristics at the time of the bone density assessment are presented (Table 1).

Bone density as measured by DXA was normal at the hip in most subjects. The mean hip BMD by DXA was $0.91 \pm 0.13 \text{ g}/\text{cm}^2$. The mean BMD Z-score at the total hip was -0.24 ± 1.0 , with a range of -2.4 to 1.7 . At the total hip, 27 subjects had a normal BMD Z-score, 6 subjects had an intermediate BMD Z-score, and 2 subjects had a low BMD Z-score (Fig. 1).

A greater number of study subjects exhibited skeletal deficits at the lumbar spine. The mean lumbar spine BMD by DXA was $0.95 \pm 0.12 \text{ g}/\text{cm}^2$. The mean BMD Z-score at the lumbar spine was -0.55 ± 1.1 , with a range of -2.8 to 1.4 . At the lumbar spine, 21 subjects had a normal BMD Z-score, 11 subjects had an intermediate BMD Z-score, and 3 subjects had a low BMD Z-score (Fig. 1).

In this sample, there was no correlation noted between the duration of leuprolide/norethindrone acetate therapy and BMD at the hip (Fig. 2). Similarly, there was no correlation between these variables and the lumbar spine ($r = 0.17$; $P = 0.33$). The results did not change after adjustment for subjects' age. Hip BMD was positively associated with

BMI, even after adjusting for age (Fig. 3). This association was not found at the lumbar spine ($r = 0.27$; $P = 0.11$).

Discussion

We evaluated bone density at the lumbar spine and total hip from 36 adolescents and young women with endometriosis treated with a GnRH agonist and concurrent norethindrone acetate “add-back” therapy. In this patient sample, the mean BMD Z-score at both the hip and spine was significantly above a “clinically significant” threshold, defined as a BMD Z-score ≤ -1.0 SD (Fig. 4). In longitudinal studies of adult women with endometriosis treated with GnRH agonists alone, BMD losses of 2% to 6% have been reported after as few as 6 months of therapy.^{7-9,17} Given that the mean length of treatment at the time of DXA in our sample was greater than 11 months, it is encouraging that mean BMD was normal in these young patients.

While the majority of subjects had a normal BMD Z-score at the hip, approximately one third of subjects exhibited skeletal deficits (Z-score ≤ -1.0 SD) at the lumbar spine. This proportion is greater than would be expected in the general population. The deficits are likely due to the hypoestrogenic state induced by the GnRH agonist via down-regulation of the hypothalamic-pituitary axis. Since almost all of peak bone mass is achieved by age 18–20 years,¹⁸ even minimal interference with bone mineral accrual during adolescence could have critical long-term health implications.

Interestingly, duration of therapy with leuprolide and norethindrone acetate was not correlated with bone density at the hip or spine in this sample. In previous studies of adult women receiving GnRH agonist treatment without add-back, treatment duration has significantly impacted on BMD. Greater duration of therapy has been associated with more significant skeletal deficits.^{9,19} Our results indicate that concurrent add-back therapy may attenuate the anticipated loss of BMD. However, prospective studies of a larger sample size are needed to prove this hypothesis.

Our study has several limitations that must be considered. This sample of adolescents with endometriosis is a convenience sample taken from a tertiary care clinic, and may not be generalizable to all patients. The sample size was relatively small. To our knowledge, however, this study represents one of the first analyses of bone health in adolescent patients with endometriosis published to date. The cross-sectional nature of the data collection, the lack of baseline measures, and the lack of longitudinal data (follow-up measurements) are also important limitations that must be acknowledged.

In summary, the use of norethindrone acetate as add-back therapy in adolescents treated with a GnRH agonist for endometriosis appears promising for the preservation of skeletal health. BMD should be carefully monitored in adolescents receiving treatment with GnRH agonists, given that we found that almost one third of our participants exhibited some degree of skeletal deficit at the lumbar spine. While add-back therapy is an intriguing therapeutic option to preserve bone density, future prospective studies are needed to determine efficacy in this young patient population.

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References

1. ACOG Committee Opinion. Endometriosis in adolescents. *Obstet Gynecol.* 2005; 105:921. Number 310, April 2005. [PubMed: 15802438]
2. Laufer MR, Goitein L, Bush M, et al. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol.* 1997; 10:199. [PubMed: 9391902]
3. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? Add-Back Consensus Working Group. *Fertil Steril.* 1999; 71:420. [PubMed: 10065775]
4. Kanis, JA. Assessment of fracture risk: Who should be screened?. In: Favus, MJ., editor. *Primer on the metabolic bone diseases and disorders of mineral metabolism.* 5th ed.. Washington: American Society for Bone and Mineral Research; 2003. p. 316-323.
5. Amama EA, Taga M, Minaguchi H. The effect of gonadotropin-releasing hormone agonist on type I collagen C-telopeptide and N-telopeptide: the predictive value of biochemical markers of bone turnover. *J Clin Endocrinol Metab.* 1998; 83:333. [PubMed: 9467536]
6. Marshall LA, Cain DF, Dmowski WP, et al. Urinary N-telopeptides to monitor bone resorption while on GnRH agonist therapy. *Obstet Gynecol.* 1996; 87:350. [PubMed: 8598953]
7. Hornstein MD, Surrey ES, Weisberg GW, et al. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Lupron Add-Back Study Group. Obstet Gynecol.* 1998; 91:16. [PubMed: 9464714]
8. Surrey ES, Judd HL. Reduction of vasomotor symptoms and bone mineral density loss with combined norethindrone and long-acting gonadotropin-releasing hormone agonist therapy of symptomatic endometriosis: a prospective randomized trial. *J Clin Endocrinol Metab.* 1992; 75:558. [PubMed: 1386374]
9. Matsuo H. Prediction of the change in bone mineral density induced by gonadotropin-releasing hormone agonist treatment for endometriosis. *Fertil Steril.* 2004; 81:149. [PubMed: 14711558]
10. Revilla R, Revilla M, Hernandez ER, et al. Evidence that the loss of bone mass induced by GnRH agonists is not totally recovered. *Maturitas.* 1995; 22:145. [PubMed: 8538483]
11. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol.* 2002; 99:709. [PubMed: 11978277]
12. Kiesel L, Schweppe KW, Sillem M, et al. Should add-back therapy for endometriosis be deferred for optimal results? *Br J Obstet Gynaecol.* 1996; 103 Suppl. 14:15. [PubMed: 8916982]
13. [Accessed August 10, 2007] National Center for Health Statistics, in collaboration with Center for Disease Control. 2000 CDC Growth Charts: United States. 2000. Available: <http://www.cdc.gov/growthcharts>
14. Kelly TL. Bone mineral density reference databases for American men and women. *J Bone Miner Res.* 1990; 5:S249.
15. Looker AC, Wahner HW, Dunn WL, et al. Proximal femur bone mineral levels of US adults. *Osteoporos Int.* 1995; 5:389. [PubMed: 8800790]
16. Zemel BS, Leonard MB, Kalkwarf HJ, et al. Reference data for the whole body, lumbar spine, and proximal femur for American children relative to age, gender, and body size. *J Bone Miner Res.* 2004; 19 Suppl 1:S231.
17. Fernandez H, Lucas C, Hedon B, et al. One year comparison between two add-back therapies in patients treated with a GnRH agonist for symptomatic endometriosis: a randomized double-blind trial. *Hum Reprod.* 2004; 19:1465. [PubMed: 15105403]
18. Matkovic V, Jelic T, Wardlaw GM, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest.* 1994; 93:799. [PubMed: 8113412]
19. Hornstein MD, Yuzpe AA, Burry K, et al. Retreatment with nafarelin for recurrent endometriosis symptoms: efficacy, safety, and bone mineral density. *Fertil Steril.* 1997; 67:1013. [PubMed: 9176437]

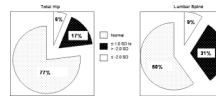


Fig. 1.

A. Distribution of BMD Z-scores at the total hip. 6 subjects had an intermediate BMD Z-score; 2 subjects had a low BMD Z-score; B. Distribution of BMD Z-scores at the lumbar spine. 11 subjects had an intermediate BMD Z-score; 3 subjects had a low BMD Z-score.

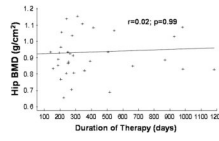


Fig. 2. Association between BMD at the total hip and duration of therapy with leuprolide/norethindrone acetate.

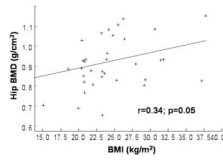


Fig. 3. Association between BMD at the total hip and BMI. BMI: Body mass index, kg/m².

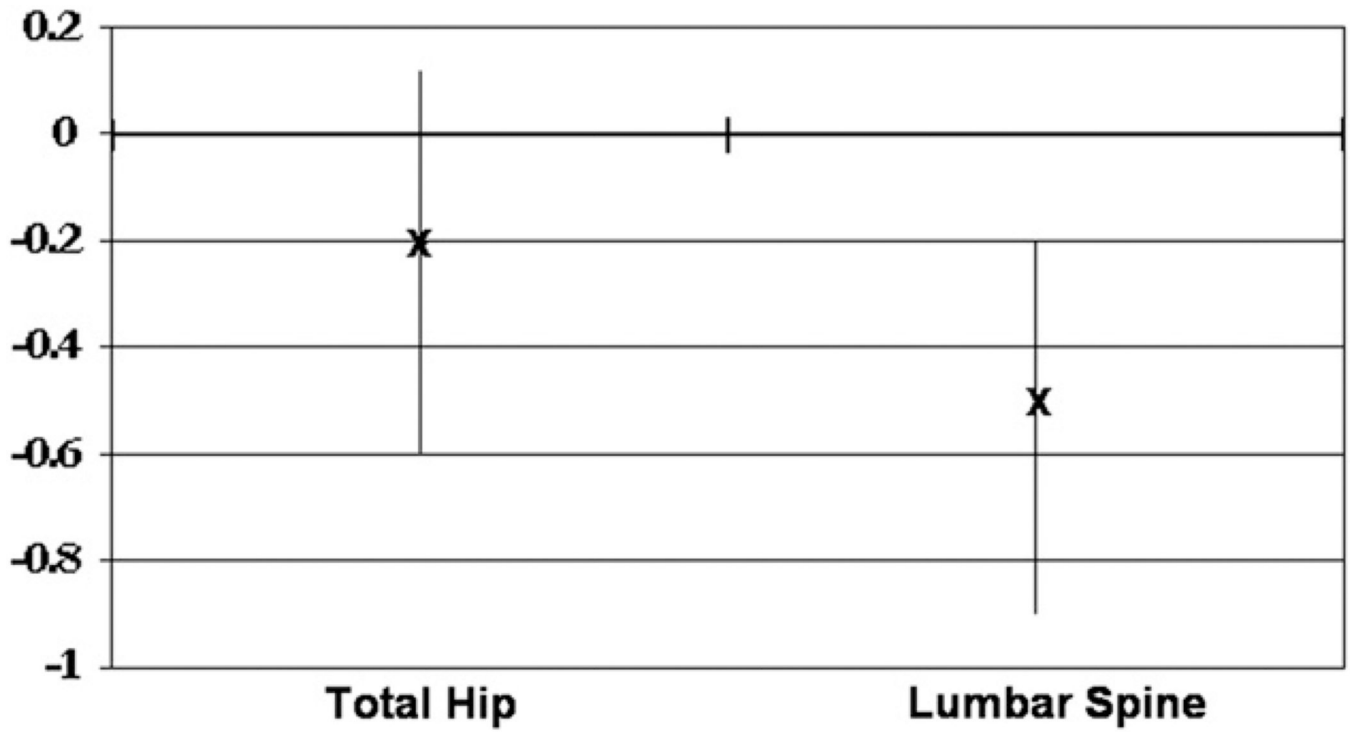


Fig. 4.
Mean BMD Z-score at the total hip and lumbar spine.

Table 1

Participant Characteristics at DXA (n = 36)

Characteristics	Mean \pm SD	Range
Age (years)	17.7 \pm 1.9	13.0–21.3
Height (cm)	160.5 \pm 12.9	143.4–177.8
Weight (kg)	62.9 \pm 12.9	38.9–95.2
BMI (kg/m ²)	24.5 \pm 4.9	15.0–37.7
Duration of treatment with leuprolide & norethindrone acetate (days)	392 \pm 276	140–1184