Prevention of Bone Loss with Alendronate in Amenorrheic Female Athletes

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A. Rationale:

While not a particularly common occurrence, athletic amenorrhea has serious implications for the girls and women who suffer from it. Of particular concern is that amenorrheic athletes may prematurely lose bone mass and be susceptible to the fractures of osteoporosis. The prevalence of secondary amenorrhea among female athletes has been reported to range from 3.4 to 43% and among highly trained endurance athletes from 25 to 45%.[1] Amenorrheic athletes are at increased risk of stress fractures when compared with eumenorrheic athletes. The majority of such fractures occur in the lower extremities where overload is most likely to occur in weight-bearing activities. Extended periods of amenorrhea result in low bone density at multiple skeletal sites in addition to those subject to impact loading during exercise.[2] A 1994 study by Rencken et al demonstrated that 72% of the amenorrheic women studied, aged 17 to 39 years, recruited from the community, having exercised a minimum of 45 minutes 4 days per week, met the diagnostic criteria for osteopenia or osteoporosis at the spine and/or hip; in comparison to 15% of the eumenorrheic women who met the diagnostic criterion for osteopenia and none of the eumenorrheic women who met the criterion for osteoporosis.[2] Given that every standard deviation decrease in BMD approximately doubles fracture risk[3], there is cause for concern about future osteoporotic fractures in this particular group of women.

Bone mass deficiency may result from either failure to reach peak bone mass or loss of bone in chronically hypo-estrogenic athletes. Although the exact mechanism of estrogen's action on bone is unclear, the etiology of athletic amenorrhea results from loss of the normal pulsatility of LH and FSH leading to suppression of menstrual cycles and low estrogen levels. There is evidence to suggest that a critical metabolic or "energy" balance is tied to the regulation of GnRH pulsatility, and neuroendocrine adaptation to marginal energy intake is the root of the problem in athletes. [4] There is also evidence to support that the optimal treatment for athletic amenorrhea consists of proper nutrition, decreased exercise, and increased weight to restore a more appropriate physiologic condition. Lindberg et al found that female runners who reduced their mileage by 43% increased their body weight by 5%, resumed their menses, increased their estrogen levels, and increased their BMD.[5] Unfortunately, women who are highly competitive athletes may be resistant to keeping weight near normal or to lowering activity levels. Similarly, such women may be resistant to a hormonal therapy such as an oral contraceptive given the unfavorable side effect profile of weight gain, bloating, menstrual bleeding, breast tenderness, etc. Alternatively, a non-hormonal therapy that may be of benefit is the bisphosphonate, alendronate.

There is a substantial body of evidence for the use of alendronate in managing osteoporosis. The safety and tolerability of alendronate have been evaluated in among >17,000 women and men in clinical trials of up to 7 years duration. Most compelling, the FIT Trial demonstrated the efficacy of alendronate in osteoporosis treatment. More than 6000 women with osteopenia at the hip +/- prior vertebral fractures were randomized to either 5mg/ day alendronate, which was increased to 10mg/day after 2 years with the release of new safety/ efficacy data, or placebo. Women with osteoporosis or low BMD who were randomized to alendronate experienced substantial increases in BMD of approximately 7-9% at the spine and 5-8% at the hip relative to placebo. Alendronate reduced the incidence of new vertebral fractures by 47% and new hip fractures by 63%. Reductions in fracture risk were found to occur soon after starting placebo and within 1-2 years of discontinuing alendronate, there was either no change in BMD or a slow resumption in bone loss. Also significant is the EPIC Trial which demonstrated the efficacy of alendronate in osteoporosis prevention. More than 900 women were randomized to either 5mg alendronate per day or placebo. At one year the treatment group gained 2.7 +/- 0.1% SE in bone mineral

density in the lumbar spine (P<.001) compared with the placebo group who lost bone density. [6,7] Whether anti-resorptive therapy can prevent osteoporosis in amenorrheic athletes is unknown. The purpose of this study is to determine whether alendronate prevents bone loss in amenorrheic female athletes with osteopenia.

B. Question:

Does alendronate prevent bone loss in amenorrheic female athletes with osteopenia?

C. Study Subjects:

Subjects will be recruited from metropolitan area NCAA Division 1 Cross Country teams: Columbia University, Manhattan College, Fordham University, SUNY Stony Brook, St. John's University, Hofstra University, Iona College, Wagner College, St. Francis College, and Long Island University through a brief (5-10 minute) informational session followed by distribution of flyers at the start of a routine in-season work out. Signed informed consent approved by the Columbia University Human Subjects Review Committee will be obtained.

Inclusion Criteria:

- Female
- Have experienced menarche
- 18-22 years old
- Amenorrheic. Defined as <3 menstrual periods in the last year or 0 menstrual periods in the last 6 months confirmed by estradiol and progesterone measurements. Estradiol < 20pg/ml and progesterone <2ng/ml.

Exclusion Criteria:

- Pregnancy, Serum Beta HCG > 3mIU/ml
- Hyperprolactinemia, Serum Prl > 15ng/ml
- Hypertestosteronemia, Serum testosterone > 1ng/ml
- Thyroid Dysfunction, TSH < 0.4 or > 5microU/ml
- Abnormal renal function, Cr >1.5 mg/dl
- Peptic ulcer or esophageal disease requiring prescription medication within the last five years
- Regular therapy with a phosphate binding antacid
- Oral contraceptive use within the past 6 months
- Normal BMD by DEXA Scan, BMD z-score > -1
- Osteoporosis by DEXA Scan, BMD z-score < -2.5
- Vitamin D deficiency, Serum 1,25-dihydroxy vit D <25 –pg/ml, 25-hydroxy vit D < 14 ng/ml
- Hypocalcemia, Serum ionized calcium <4.5 mg/dl
- Malignancy
- Steriod medication, other than topical
- Anorexia nervosa
- Smoker

D. Study Design:

Randomized, placebo-controlled, double blind trial.

E. Protocol:

All subjects will have blood samples taken in the ICCR at CPMC. Blood samples will be analyzed at Quest Laboratories in Teaneck, New Jersey according to laboratory standards. All subjects will report the the laboratory at 8am after an overnight fast. A 30ml sample of venous blood will be drawn after a 20 minute sitting period. The samples will be allowed to clot, centrifuged, and serum stored at –20 degrees until assay for estradiol, progesterone, Beta HCG, prolactin, testosterone, TSH, creatinine, vitamin D levels within 48 hours per established protocol.[1] Each subject will complete a brief questionairre concerning her menstrual history, athletic activities, past medical history, medication use, and smoking status. A registered dietician will meet with each of the subjects to explain the procedure for maintaining a 3-day diet history. Diaries are returned directly to the nutritionist in a pre-payed envelope. The dietician will then confer individually with each subject by telephone to verify the information contained. The registered dietician will screen for anorexia nervosa at the initial visit by administering a brief, previously validated questionairre. The subjects will be weighed and BMI calculated.

The subjects will be scheduled for bone mineral density measurement within the same month.

F. Treatment:

Subjects will be stratified according to spine BMD: Spine BMD z-score –1.5-2, and –2-2.5. The subjects will be randomized to alendronate 35 mg orally once per week or placebo. The pills will be identical in size, taste, texture, and odor. The pills will be dispensed at the CPMC ICCR in 3- month supplies. The subjects will be instructed to take the study medication per established recommendations for alendronate: once weekly in the morning on an empty stomach, with a full 8 ounces of water, remain sitting or standing upright for 30 minutes after taking the study medication. All patients will be advised to maintain adequate intake of dietary calcium (at least 1200 mg/d, including supplements if necessary) and vitamin D (400 IU per day) per National Osteoporosis Foundation Guidelines.

G. Measurement of Bone Mineral Density:

The bone mineral density of the lumbar spine (L1-L4) and hip will be measured by dual-energy x-ray absorptiometry (model 2000, Hologic, Waltham MA) at baseline, 6 months, and 12 months. The measurements will be taken by a single trained technician at the CPMC Osteoporosis Center. Position of the subjects during absorptiometry and data analysis will be standardized, as will be calibration of the machine. Hologic Medical Data Management Services will be responsible for handling all aspects of the quality assurance for BMD measurements including calibration of the machines, training of the technician, assessment of the machine performance, adequacy of scans obtained, analysis performed, and data management without knowledge of treatment assignment. The reliability coefficient as previously determined is 0.99 for the lumbar spine and hip.

H. Primary End Point:

The percent change from baseline in the anteroposterior lumbar spine (L1-L4).

I. Statistical Analysis:

Differences between groups will be analyzed by a t-test.

J. Sample Size Calculation:

$N= 1 + 16 (2.7/2.1)^2 = 11$

K. Additional Information:

1) The following biochemical markers of bone turnover will be measured at 0, 6 and 12 months: serum bone specific alkaline phoshatase, and osteocalcin and urinary excretion of collagen cross-linked N-telopeptide
2) Radiation exposure during DEXA is minimal, <10mrem, which is about 1/10 th radiation exposure of a chest x-ray or the equivalent o radiation exposure received during a flight from LA to New York
3) Potential risks include unknown risk to the fetus during future pregnancy in women treated with alendronate. Benefits include potential reduction in osteoporotic fractures and associated morbidity.
4) Alternative Therapies: None proven effective. Oral contraceptives, hormone replacement, selective estrogen receptor modulators.
5) Minors: None enrolled.
6) Alendronate has been designated as pregnancy category C, uncertain safety, no human or animal studies show an adverse effect.

L. References

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