Treatments to Prevent Bone Loss in Functional Hypothalamic Amenorrhea: A Systematic Review and Meta-Analysis

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Objective: We conducted a systematic review and meta-analysis of studies that evaluated the effect of hormonal therapy [estrogen therapy including oral contraceptive pills (OCP)] and bisphosphonates in preventing bone loss in patients with functional hypothalamic amenorrhea (FHA).

Methods: We searched several electronic databases for controlled and noncontrolled studies that enrolled females of any age presenting with FHA (including athletic, weight loss, and stress-associated amenorrhea/oligomenorrhea) through 9 January 2017. The outcomes of interest were fractures and bone mineral density (BMD). Random effects meta-analysis was used to pool outcomes across studies expressed as weighted mean difference and 95% confidence interval (CI).

Results: Nine studies reporting on 280 patients that received different hormonal therapies were included. We did not identify studies that evaluated bisphosphonates. Meta-analysis demonstrated a statistically significant increase in BMD of the lumbar spine in patients receiving hormonal therapy after a median follow-up of 12 months (weighted mean difference, 0.032 g/cm^2; 95% CI, 0.017 to 0.047; percentage change in BMD, 3.30%; 95% CI, 1.74 to 4.86). There was no substantial effect of receiving hormonal therapy on BMD of the femoral neck, trochanteric region, Ward triangle, or total body BMD. The quality of evidence was low because of the high risk of bias, imprecision (small sample size), and indirectness (as BMD is a surrogate outcome). None of the studies reported the incidence of fractures.

Conclusion: The current evidence does not support using hormonal therapy for the sole purpose of improving bone health in patients with FHA. There are no data about bisphosphonates in this population.

Functional hypothalamic amenorrhea (FHA) is defined as the absence of menstruation because of an interruption of the hypothalamic -pituitary-ovarian axis with no apparent anatomic or organic disease [1]. Severe stressors such as excessive exercise, dieting, and psychological stress affect the hypothalamic -pituitary-ovarian axis, leading to FHA [2]. A

Abbreviations: AN, anorexia nervosa; BMD, bone mineral density; FHA, functional hypothalamic amenorrhea; OCP, oral contraceptive pill; RCT, randomized controlled trial; WMD, weighted mean difference.

previous systematic review by Gibbs *et al.* showed that the prevalence of primary and secondary amenorrhea from FHA in exercising women ranged from 0% to 56.0% and from 1.0% to 60%, respectively [3].

A study by Drinkwater *et al.* was conducted in 1984 and compared lumbar spine bone mineral density (BMD) between eumenorrheic athletes and amenorrheic athletes [4]. Vertebral mineral density was significantly lower in the amenorrheic group (mean, 1.12 g/cm^2) than in the eumenorrheic group (mean, 1.30 g/cm^2) [4]. Gibbs *et al.* reported that the prevalence of low BMD combined with menstrual disturbances, including FHA and oligomenorrhea, in exercising women ranged from 0% to 15.9% [3]. Davies *et al.* compared women age 16 to 40 years with past or current history of amenorrhea from various causes and of a median duration of 3 years with a control group of age-matched normal volunteers with no history of menstrual disorder. They found that the amenorrheic group had a mean reduction in BMD of 15% compared with controls [5]. Bone loss was related to the duration of amenorrhea and the severity of estrogen deficiency. Ten patients had a history of atraumatic fracture [5]. Another study of young ballet dancers showed that amenorrheic intervals were marked by prolonged hypoestrogenism and that a delay in menarche and prolonged intervals of amenorrhea were associated with scoliosis and stress fractures [6].

There are many suggested interventions to mitigate bone loss associated with FHA. These include, but not limited to, hormonal therapies [often in the form of oral contraceptive pills (OCPs)] and bisphosphonates [7]. In 2008, Vescovi *et al.* published a systematic review evaluating multiple treatment strategies, including hormonal therapy and bisphosphonates; however, meta-analysis was not performed because of the small number of available studies at that time [8].

To support the development of clinical practice guidelines by the Endocrine Society, we conducted a systematic review and meta-analysis to evaluate hormonal replacement therapy (estrogen therapy including OCPs) and bisphosphonates compared with placebo or no intervention in preventing bone loss in patients with FHA.

1. Methods

A protocol was developed in advance by the investigators to specify eligibility criteria, outcomes of interest, and analysis methods. The methodology and reporting of this systematic review comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [9].

A. Eligibility Criteria

We included randomized controlled trials (RCTs) and observational studies that enrolled female patients of any age presenting with FHA, including athletic, weight loss, and stress-associated amenorrhea/oligomenorrhea, as defined by studies' authors. We included controlled and uncontrolled cohort studies designed to evaluate hormonal replacement therapy (estrogen therapy including OCPs) and bisphosphonates. Included studies should evaluate the efficacy of the intervention measured as change in the number of fractures or change in BMD, reported as a *z* score or absolute BMD in grams per square centimeter.

We excluded studies that enrolled patients with amenorrhea resulting from anovulation (*e.g.,* polycystic ovarian syndrome), *bona fide* psychiatric disorders [*e.g.,* bulimia, anorexia nervosa (AN), depression], and organic forms of hypothalamic amenorrhea (*e.g.,* pituitary tumors, adenomas, Kallmann syndrome).

B. Search Methods

A comprehensive search of several databases from each database's earliest inception through 9 January 2017 without language restrictions was designed and conducted by an expert reference librarian (L.J.P.) with input from the investigators. Databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic

Reviews, and Scopus (Appendix). To identify additional candidate studies, we also searched previous systematic and narrative reviews for relevant studies [8, 10–15]. A Google search was also used to capture unpublished or gray literature.

C. Study Selection

Two reviewers (A.A.L. and B.G.C.L.) assessed the eligibility of candidate studies for inclusion in a blinded and independent manner by screening titles and abstracts followed by reviewing the retrieved full text publications of the included studies. Disagreements between the two reviewers were solved by meeting with a third reviewer (O.A.) and establishing consensus.

D. Data Collection Process

Data were abstracted from each study using a standardized, piloted, and Web-based data extraction form. Three independent reviewers (A.A.N., B.G.C.L., and O.A.) performed the abstraction in duplicate; disagreements were resolved by discussion among the three reviewers. The following data were abstracted: full description of enrolled patients (age, inclusion criteria, gynecological history, and lifestyle), detailed description of intervention received and control, follow-up monitoring, measures of outcomes, and source of funding.

E. Assessment of the Risk of Bias

Three independent reviewers (A.A.N., B.G.C.L., and O.A.) evaluated the methodological quality of included studies in duplicates. For RCTs, we used the Cochrane Risk of Bias tool in terms of adequacy of randomization, allocation concealment, blinding (patients, health care providers, data collectors, and outcome assessors), baseline imbalance, and extent of loss to follow-up [16]. For observational studies, we used the Newcastle-Ottawa quality assessment tool after adding a question to assess the method used to allocate patients. We evaluated allocation method, representativeness of the cohort, selection of the control cohort (if present), baseline imbalance, outcome assessment method, and adequacy of follow-up [17].

F. Statistical Analysis

For each of the included studies, we calculated the absolute and percentage change of the outcomes from the baseline to the end of the interventions for the intervention and the control group. We pooled the weighted mean difference (WMD) across studies using the DerSimonian and Laird random effects method [18]. A positive WMD implies improvement in BMD favoring the intervention.

We assessed heterogeneity across the studies using the Cochran's Q test and the I squared statistic, where P value < 0.10 or $I^2 > 50\%$ suggest substantial heterogeneity that is due to real differences in study populations, protocols, interventions, and/or outcomes. Although we planned to assess potential publication bias, we were not able to conduct formal tests because of the small number of studies included in the analysis [19]. All statistical analyses were conducted using STATA, version 12 (StataCorp, College Station, TX).

2. Results

A. Search Results

The search strategy identified 238 publications, of which nine were included (reported in 10 manuscripts) (Fig. 1). Three were RCTs [20–22], two were prospective comparative studies [23, 24], one was a retrospective comparative study [25], and three were prospective single-arm studies [26–29]. All of these studies evaluated hormonal therapy. The search did not identify any study that evaluated bisphosphonates in treating patients with FHA.
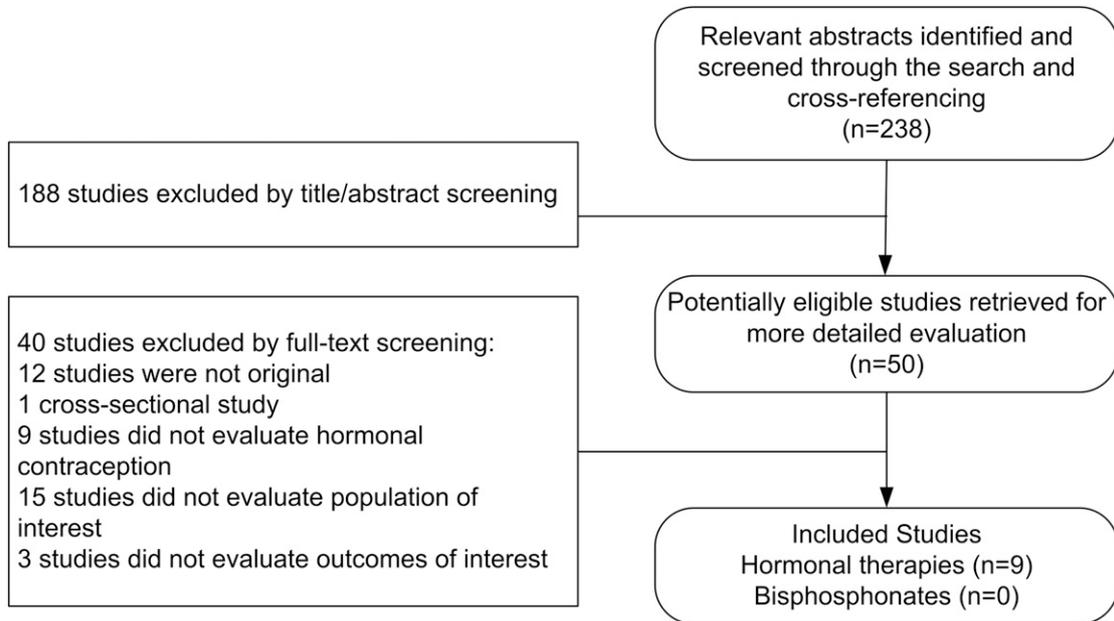
Figure 1. The process of study selection.

B. Evidence on Hormonal Therapies

The included studies evaluated 280 patients. The mean follow-up period ranged from 8 to 48 months, with a median of 12 months. The inclusion criteria, characteristics of the included patients, and the interventions they received are detailed in Table 1.

C. Types of Hormonal Therapy

The studies evaluated a variety of hormonal therapies: different combinations of oral contraceptive pills (ethinyl estradiol/desogestrel [20], ethinyl estradiol/cyproterone acetate [23], ethinyl estradiol/norethindrone [24], ethinyl estradiol/levonorgestrel [26], 17B-estradiol/dydrogesterone [27, 28], ethinyl estradiol/norgestimate [29]); transdermal patches of conjugated estrogen or estriol with oral medroxyprogesterone acetate [25]; oral conjugated estrogens and medroxyprogesterone [22]; and oral estriol, estradiol, and norethisterone acetate with calcium supplements [21]. The control groups received no treatment [20, 21, 23, 25], calcium supplements [21], placebo [24], or placebo with calcium supplements [22].

D. Etiology of FHA

Castelo-Branco and Sowińska-Przepiera included patients with amenorrhea/oligomenorrhea associated with stress (depression, anxiety, learning disabilities, and/or family problems). Cumming [25], Gibson et al. [21], De Cree et al. [23], Rickenlund et al. [26], and Warren et al. [22] included patients with amenorrhea/oligomenorrhea associated with exercise (athletic, endurance sportswomen and elite ballet dancers). Hergenroeder et al. [24] and Warren et al. [29] included patients with hypothalamic amenorrhea/oligomenorrhea with no specific risk factor.

D-1. Risk of bias (methodological quality)

For the three included RCTs, there was a high risk of bias. All of them reported that their studies were randomized but they did not provide details regarding the method of

Table 1. Characteristics of Included Studies

Study and F/U	Inclusion/Exclusion Criteria, Demographics, and Risk Factors	Interventions (No. of Patients)
Castelo-Branco, 2001 [20]	Inclusion criteria: amenorrhea (no menstruation for 6 mo) or oligomenorrhea (6 or fewer menstrual periods during the previous year). Depressed and anxiety prone. Exclusion: AN, current use of any drug that may affect bone mass, renal or GI disease, thyroid dysfunction, DM, moderate to severe osteopenia (T score ≤1.5) or osteoporosis (T score ≤2.5)	OCP (0.03 EE + desogestrel) [24]
Length of F/U: 12 mo	Demographics: age, 24.4 y ± 7.9; race, NR; BMI, 23.7 kg/cm²; length of amenorrhea, 16.7 ± 10.4 mo Risk factor: stress (patients were depressed and anxiety prone)	EE 0.030 mg and desogestrel 0.15 mg OCP (0.02 EE + desogestrel) [22] EE 0.020 mg and desogestrel 0.15 mg Control [18] No treatment
Cumming, 1996 [25]	Inclusion criteria: Confirmation of the pathophysiology of the amenorrhea and bone density measurement by DXA if amenorrheic for longer than 2 y. Bone density >1.0 SD below the mean value. Characteristic picture of exercise-associated amenorrhea (low/low-normal LH, FSH, estradiol, and prolactin)	HRT (CE/estradiol + MPA) [8]
Length of F/U: 24-30 months	Demographics: age, 23-34 y; race, NR; BMI, 17.1 kg/cm²; length of amenorrhea, 2-8 y	Conjugated estrogen 0.625 mg (n = 6), or estradiol transdermal patch 50 μg daily with cyclic medroxyprogesterone acetate 10 mg daily for 14 d monthly (n = 2) for at least 2 y
	Risk factor: exercise (run 35-75 miles/wk)	Control [5] No treatment
De Cree, 1998 [23]	Inclusion criteria: Sportswomen aged 18-29 y. Athletic amenorrhea with osteoporosis. Free for at least 3 months of any medical drugs known to interfere with calcium or sex hormone metabolism. Amenorrhea (no menstruation for at least 6 mo) or oligomenorrhea (decreased frequency of menstrual cycles in the previous year with only 1 menstrual period during last 3 mo)	OCP (EE + CPA) [7]
Length of F/U: 8 mo	Demographics: age, 21.9 ± 3.9 y; race, NR; BMI, NR; length of amenorrhea, NR (as defined previously) Risk factor: exercise (run 21.7 ± 9.3 miles/wk). Stress (27% had stressful life)	EE 0.05 mg and cyproterone acetate 2 mg Control [4] No treatment
Gibson, 1999 [21]	Inclusion criteria: subjects had to have trained for 3 y and currently training for a minimum of 3 h/wk and to run at least 40 km/wk. Exclusion: history of respiratory disease, DM, metabolic bone disorders, rheumatoid arthritis, thyroid or parathyroid disease, malignancy, cardiac, renal or inflammatory bowel disease. Patients taking oral or inhaled steroids	Hormone replacement (estriol, estradiol, and norethisterone) + calcium supplements [10]

Table 1. Continued

Study and F/U	Inclusion/Exclusion Criteria, Demographics, and Risk Factors	Interventions (No. of Patients)
Length of F/U: 9 mo (18 mo, but outcomes were reported for 9 mo of F/U)	Demographics: age, 27.5 ± 9.3 y; race, 100% white; BMI, 19.21 kg/cm^2; length of amenorrhea, 6.9 y	Daily oral treatment with Trisequens tablets (estriol 1 mg and estradiol 2 mg for 12 d; estriol 1 mg, estradiol 2 mg, and norethisterone acetate 1 mg for 10 d; estriol 0.5 mg and estradiol 1 mg for 6 d) + 1000 mg calcium carbonate
	Risk factor: exercise (run 53.1 ± 13.8 miles/wk)	Calcium supplements [14] 1000 mg calcium carbonate per day Control [10] No treatment
Hergenroeder, 1997 [24]	Inclusion criteria: hypothalamic amenorrhea (no menstrual bleeding in the past 6 mo) and oligomenorrhea (6 or fewer menstrual periods in the past 12 mo, with 1 or more menstrual periods in the past 6 mo) associated with a lifestyle that included exercise, weight loss, dieting, or stress. Exclusion: evidence of disease that would affect bone mineral, the use of medications that affect bone mineral, tobacco use, and obesity (>120% of estimated ideal weight)	OCP (EE + norethindrone) [5]
	Demographics: age, 20.1 ± 7.4 y; race, 100% white; BMI, 18 kg/cm^2; length of amenorrhea, NR (as defined previously)	EE 0.035 mg and norethindrone 0.5-1.0 mg/d on 21 d of each 28-d cycle
	Risk factor: exercise (80% of patients exercised as a part of a team or independently), dieting, stress	Medroxyprogesterone [5] Medroxyprogesterone 10 mg/d on the last 12 d of the calendar month Placebo [5] One placebo tablet daily for the last 12 d of the calendar month
Warren, 2003 [22]	Inclusion criteria: elite ballet dancers solicited from national and regional schools and dance companies, via advertisements in college publications, and by physician referrals for hormonal problems and interest in bone density measurements. Amenorrheics (no menstruation for at least 5 mo). Exclusion: patients taking hormones or oral contraceptives for 6 mo before the study	Hormone replacement (CE + MPA) [13]
Length of F/U: 24 months	Demographics: age 20.1 ± 4.6 y; race, 100% white; BMI, 18.87 kg/cm^2; length of amenorrhea, NR (as defined previously)	CE 0.635 mg on d 1-25 + medroxyprogesterone 10 mg on d 16-25, in a 30-d circle + calcium supplements
	Risk factor: exercise (dancing 24.0 ± 10.8 h/w)	Control [11] Placebo + calcium supplements
Rickenlund, 2004 [26]	Inclusion criteria: female athletes in endurance sports. 16-35 y, BMI 18-24, nulliparous, healthy, nonsmoking. Endurance training defined as a minimum of 6 h of aerobic weight-bearing training or a minimum of 70 km of running or 6 h of specific endurance training weekly. Amenorrhea (no menstruation for at least 3 mo) or oligomenorrhea (menstrual periods at intervals exceeding 6 wk)	OCP (EE + levonorgestrel) [13]
Length of F/U: 10 months	Demographics: age, 19.8 ± 4.6 y; race, NR; BMI, 19.4 kg/cm^2; length of amenorrhea, NR (as defined previously) Risk factor: exercise (train 8.1 ± 1.6 h/wk)	EE 0.03 mg + levonorgestrel 0.15 mg on d 1-21, followed by a hormone- and tablet-free interval on d 22-28

Table 1. Continued

Study and F/U	Inclusion/Exclusion Criteria, Demographics, and Risk Factors	Interventions (No. of Patients)
Sowińska-Przepiera, 2011/2011 [27, 28]	Inclusion criteria: girls 16-17 y with FHA. (1) At least 6 mo of amenorrhea preceded by at least 3 y of oligomenorrhea; (2) psychological problems (learning disabilities and/or family problems). Exclusion: PCOS, CAH, premature ovarian failure, low birth weight or preterm birth, confirmed episode of an eating disorder, poor dieting during childhood or puberty, episodes of impaired growth and body mass gain, extensive participation in sports, metabolic disorders associated with decreased bone mineralization, prolonged use of stimulants or drugs that may affect bone metabolism, familial history of osteoporosis, incomplete 4-y F/U	OCP (17B-estradiol + dydrogesterone)
Length of F/U: 24 mo	Demographics: age, 16.7 ± 1.2 y; race, NR; BMI, 18.7 ± 2.2 kg/cm^2; length of amenorrhea NR (as defined previously) Risk factor: stress (psychological problems, defined previously)	17-b estradiol (2 mg from the second to 25th day of the menstrual cycle) and dydrogesterone (10 mg from the 16th to the 25th day of the menstrual cycle)
Warren, 2005 [29]	Inclusion criteria: age, 18-40 y, with lumbar spine BMD ≥ 0.937 g/cm^2 (DXA scan) and BMI 16-24 kg/m^2. No menstrual periods during the last 3 months and 2 or fewer periods during the previous 12 mo or women with previously diagnosed FHA with no spontaneous menses during the previous 3 mo. Less than 6 months of hormonal therapy in the previous year. Women age 35-40 y required to be nonsmokers and those ages 18-34 y could not smoke more than 10 cigarettes per day. Exclusion: Pregnant, nursing, a contraindication for steroid hormonal therapy, evidence of cervical dysplasia, undiagnosed breast lesion, medical condition that could contribute to osteopenia, history of severe migraines, hypertension, hormonal therapy within 3-6 mo of screening, high prolactin, FSH, testosterone, LH/FSH ratio or LH >11, hirsutism, AN within 12 mo, or recent history of alcohol or other substance abuse. Medications that may interact with OCPs	OCP (EE + NGM) [27]
Length of F/U: 9 months	Demographics: age, 26.7 ± 6.64 y; race, 92.6% white and 7.4% other; BMI, 20.54 kg/cm^2; length of amenorrhea 18.5 mo Risk factor: NR	EE 0.035 mg and norgestimate 0.180-0.250 mg on 21 d of each 28-d cycle. 10-13 cycles

Abbreviations: BMI, bone mass index; CAH, congenital adrenal hypoplasia; CE, conjugated estrogen; CPA, cyproterone acetate; DM, diabetes mellitus; DXA, dual energy x-ray absorptiometry; EE, ethinyl estradiol; FSH, follicle-stimulating hormone; F/U, follow-up; HRT, hormone replacement therapy; GI, gastrointestinal; LH, luteinizing hormone; MPA, medroxyprogesterone acetate; NR, not reported; PCOS, polycystic ovarian syndrome; SD, standard deviation.

randomization or if the allocation was concealed. Gibson *et al.* [21] reported that they did not blind the OCP group, although they did blind the other control groups. Castelo-Branco *et al.* reported that 24% of their sample was lost to follow-up [20]. Although the included observational studies were well performed in terms of quality and reducing bias, their observational nature puts them at a high risk for bias [23–29]. Detailed description of the quality indicators of each study are presented in Tables 2 and 3.

Table 2. Randomized Controlled Trials

Study	Randomization	Allocation Concealment	Blinding	Baseline Imbalance	% Lost to F/U	Source of Funding
Castelo-Branco, 2001 [20]	Yes, method NR	NR	NR	NR	24	NR or unclear
Gibson, 1999 [21]	Yes, method NR	NR	OCP group had no blinding, the other 2 groups had double blinding	NR	NR	NR or unclear
Warren, 2003 [22]	Yes, method NR	NR	NR	NR	NR	NIH funded, but pharmaceutical company donated medications

D-2. Reported outcomes

None of the studies reported fractures or *z* score. Studies reported BMD measured in grams per square centimeter at different areas of the skeleton. All of the studies reported BMD of the lumbar spine [20–29]. Cumming [25], Gibson *et al.* [21], and Hergenroeder *et al.* [24] reported BMD of the femoral neck; only Gibson *et al.* reported BMD of the trochanteric region. Cumming [25] and Gibson *et al.* [21] reported BMD of Ward triangle. Hergenroeder *et al.* and Rickenlund *et al.* reported total body BMD [24, 26]; only Rickenlund *et al.* reported BMD of the legs. Only Warren *et al.* reported BMD of the wrist and foot [22]. Detailed results of individual studies are presented in Supplemental Table 1.

D-3. Change and percentage change in BMD measured in grams per square centimeter

Random-effects meta-analysis demonstrated a statistically significant change in BMD of the lumbar spine in patients receiving hormonal therapy (n = 213) compared with patients

Table 3. Nonrandomized Controlled/Single-Arm Trials

Study	Time and Design	Allocation	Representativeness of Population	Selection of Control	Baseline Imbalance	Assessment of Outcome	Adequacy of F/U	Source of Funding
Cumming, 1996 [25]	Retrospective (comparative)	Patient preference	Truly representative	Drawn from the same community of the exposed cohort	Study reported no substantial difference between groups in height, weight, BMI, serum estradiol levels, clinical record, or training level	Independent assessment	No LFU	NR or unclear
De Cree, 1998 [23]	Prospective (comparative)	Physicians allocated patients	Truly representative	Drawn from the same community of the exposed cohort	Study reported no substantial difference between groups in clinical record and training level	Independent assessment	No LFU	NR or unclear
Hergenroeder, 1997 [24]	Prospective (comparative)	Patients were alternately allocated in each group. Patients who did not want to receive hormones constituted the control group	Truly representative	Drawn from the same community of the exposed cohort	Study controlled for confounders: age, mean amenorrhea time, weight, and height	Independent assessment	6% LFU	Only not-for-profit source (*e.g.*, university, research center, NIH)
Rickenlund, 2004 [26]	Prospective (single arm)	According to inclusion/exclusion criteria	Truly representative	NA	NA	Independent assessment	No LFU	Only not-for-profit source
Sowińska-Przepiera, 2011/2012 [27, 28]	Prospective (single arm)	According to inclusion/exclusion criteria	Truly representative	NA	NA	Independent assessment	No LFU	NR or unclear
Warren, 2005 [29]	Prospective (single arm)	According to inclusion/exclusion criteria	Truly representative	NA	NA	Independent assessment	29% LFU	Includes for-profit source (pharmaceutical company)

Abbreviations: LFU, lost to follow up; NA, not available; NIH, National Institutes of Health.

receiving control (n = 67) with WMD = 0.032 g/cm^2 favoring hormonal therapy [95% confidence interval (CI), 0.017 to 0.047] and WMD of percentage change in BMD = 3.30% (95% CI, 1.74 to 4.86). The heterogeneity P value = 0.14.

Meta-analysis showed no statistically significant difference between patients receiving hormonal therapy (n = 23) and patients receiving control (n = 34) in BMD of the femoral neck (WMD = 0.002 g/cm^2, 95% CI, −0.048 to 0.052; WMD of percentage change = 0.20%, 95% CI, −5.93 to 6.33; heterogeneity P value = 0.96). No statistically significant difference was shown in BMD of trochanteric region (total n = 34; WMD = 0.019 g/cm^2 and WMD of percentage change = 2.8%; heterogeneity P value = 0.76), Ward triangle (total n = 47; WMD = 0.016 g/cm^2 and WMD of percentage change = 2.4%; heterogeneity P value = 0.80), or total body (total n = 23; WMD = 0.02 g/cm^2 and WMD of percentage change = 1.8%; heterogeneity P value = 0.61).

E. Evidence on Bisphosphonates

The search did not identify any study that evaluated bisphosphonates in treating patients with FHA. Nevertheless, we were able to identify four studies (Supplemental Table 2) that evaluated the effects of bisphosphonate on BMD in patients with AN and amenorrhea (a likely related population to FHA) by reviewing previous systematic reviews [30–32].

Golden *et al.* compared alendronate with placebo in a trial of 32 patients. After a year of follow-up, they found no statistically significant difference between the two groups in the percent increase in BMD of the lumbar spine or the femoral neck [31]. Nakahara *et al.* conducted a trial to compare etidronate, calcium supplements and vitamin D, and placebo. The trial included 41 patients and demonstrated that etidronate increased tibial BMD (measured by speed of sound technique) more than placebo, but they found no substantial difference between etidronate compared with calcium supplements and vitamin D [30]. Miller *et al.* compared 10 anorexic women receiving risedronate with published data of 14 anorexic women whom they studied prospectively in the past. At 9 months, they found that both lumbar spine BMD and total body BMD increased significantly in patients receiving risedronate compared with patients who received no treatment [32]. In another trial by Miller *et al.*, compared with placebo, risedronate significantly increased BMD in the spine and hip, but not in the radius after 1-year follow-up in patients with AN. The presence of menses was found not to be a predictor for response to bisphosphonates in this cohort [33]. In terms of the clinical importance of BMD change in response to bisphosphonate, the magnitude of BMD increase in the spine with 5 mg of risedronate was 4.1 ± 1.6% at 6 months and 4.9 ± 1.0% at 9 months [32].

3. Discussion

We conducted a systematic review and meta-analysis of studies evaluating the preventive effect of hormonal therapy and bisphosphonates on BMD in females with FHA. We found nine small studies evaluating hormonal therapy, none of which reported fractures. This body of evidence is very small (280 patients with a median follow-up of 12 months). Hormonal therapy increased BMD in the lumbar region only. The quality of this evidence according the Grades of Recommendation, Assessment, Development, and Evaluation approach was low [34, 35], rated down because of the high risk of bias, imprecision (very small sample size), and indirectness of BMD is a surrogate outcome. The changes in BMD of the femoral neck, trochanteric region, Ward triangle, and total body were not statistically significant. In terms of bisphosphonates, we found no studies evaluating its effectiveness in patients with FHA. Indirect evidence from populations with potentially related condition (AN and amenorrhea) was sparse and inconsistent with low quality.

In terms of the clinical implications of this meta-analysis, it seems that evidence of effectiveness of hormonal therapy (primarily oral contraceptives and estrogens, with a very small number of patients using transdermal patches) is very limited. This may be due to hypercortisolism, decreased thyroid function, or other reasons such as the persistent low body

weight of many of these individuals. Data on transdermal estrogen use in FHA are also very limited, and evidence may have to be extrapolated from patients with AN. A randomized trial in patients with AN compared 100 μg of 17β-estradiol (with cyclic progesterone) or placebo transdermally for 18 months. Spine and hip BMD z scores increased over time in those receiving physiologic transdermal estradiol replacement compared with the placebo group [36]. Therefore, a rationale for prescribing hormonal therapy to women with FHA for the sole purpose of bone protection is not supported by high-quality evidence.

Similarly, evidence supporting bisphosphonates is also very limited in patients with FHA. This means that the primary approach for the treatment of FHA depends on correcting the energy imbalance to improve hypothalamic-pituitary-gonadal axis function. This can be done by changing caloric consumption and exercise habits, and requires a multidisciplinary approach by physicians with expertise in this disorder, dieticians, psychotherapists, and other health professionals.

A. Limitations

This evidence synthesis has several limitations. The definition of amenorrhea and oligomenorrhea varied across studies. Hormonal therapy regimens and length of follow-up were also quite variable. The included studies had methodological limitations and were small. Some of the comparisons we conducted were across studies and subject to ecological bias. We were unable to assess publication bias because of the small number of included studies. Although we were interested in summarizing evidence on FHA excluding patients with *bona fide* psychiatric disorders such as AN, it is likely that some patients with AN may have been included in studies with populations labeled as having FHA.

B. Strengths

The strengths of this systematic review relate to measures undertaken by reviewers, such as screening studies and evaluating their quality in duplicate. The search strategy was comprehensive and included multiple databases and was supplemented by contacting experts and cross-referencing with existing documents. This systematic review is accompanied by a meta-analysis conducted to quantitatively evaluate the effectiveness of drug therapies for preventing bone loss in patients with FHA/oligomenorrhea.

4. Conclusion

The current evidence does not support using hormonal therapy for the sole purpose of improving bone health in patients with FHA. There are no data about bisphosphonates in this population.

Acknowledgments

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