Estrogen for the Treatment of Low Bone Mineral Density in Anorexia Nervosa

Subhanudh Thavaraputta,
Pouneh K. Fazeli*

Neuroendocrinology Unit, Division of Endocrinology and Metabolism, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Abstract

Anorexia nervosa is a disorder of chronic, self-induced negative energy balance which typically results in a low body weight. Functional hypothalamic amenorrhea is an adaptive response to states of negative energy balance and chronic undernutrition. A majority of women with anorexia nervosa are amenorrheic with resultant hypoestrogenemia, and longer durations of amenorrhea are associated with lower bone mineral density in this population. In this review, we highlight studies that have investigated the effects of estrogen replacement on bone mineral density in anorexia nervosa, including prospective and randomized studies that show no benefit to treatment with oral estrogen with respect to bone mineral density in either adolescent girls or women with anorexia nervosa. We also review data from a randomized, placebo-controlled study in adolescent girls and a prospective, open-label pilot study in women with anorexia nervosa suggesting that transdermal estrogen may have beneficial effects with respect to bone mineral density in this population.

Keywords

anorexia nervosa; bone mineral density; estrogen

FUNCTIONAL HYPOTHALAMIC AMENORRHEA IN ANOREXIA NERVOSA

One key hormonal response to states of undernutrition is the directing of energy away from the reproductive axis [1]. Although reproduction, an energetically costly process, is necessary for the survival of a species, it is not necessary for the survival of an individual, and therefore decreasing energy expenditure on reproduction is advantageous in states of undernutrition [1]. This directing of energy away from the reproductive axis during periods of decreased caloric intake is termed functional hypothalamic amenorrhea or hypogonadotrophic hypogonadism.

Anorexia nervosa is a psychiatric disorder characterized by a state of self-induced negative energy balance and typically results in a low body weight due to inappropriately low caloric intake [2]. A majority of women with anorexia nervosa have functional hypothalamic...
amenorrhea and amenorrhea was previously included in the diagnostic criteria for anorexia nervosa [3]. Functional hypothalamic amenorrhea, as well as the other adaptive responses to chronic undernutrition, which include growth hormone resistance and hypercortisolemia, likely contribute to the negative consequences of long-term undernutrition [1].

One of the most common negative consequences of chronic undernutrition is low bone mineral density [4]. Approximately 35% of women with anorexia nervosa have a bone mineral density value that is more than 2.5 standard deviations lower than the mean of women of similar age and an additional 50% of women have a bone mineral density value more than 1 standard deviation lower than the mean [4]; individuals with anorexia nervosa also have a higher risk of fracture [5-8]. In fact, a prospective study showed that women with anorexia nervosa were seven-times more likely to sustain a non-vertebral fracture compared to women of similar age [9]. Since bone mass accrual occurs during adolescence and peak bone mass is typically achieved before the age of 30 years old [10], a disorder such as anorexia nervosa, which most commonly develops during adolescence [11], can have lifelong effects due to the failure to achieve peak bone mass [12]. This coupled with the fact that anorexia nervosa is a chronic disorder with a long-term recovery rate of only approximately 50–60% [13,14] contribute to a long-term increased risk of fracture in this population [15].

Functional hypothalamic amenorrhea is a result of disruption in hypothalamic secretion of gonadotropin releasing hormone [16-20]. Functional hypothalamic amenorrhea is characterized by low estrogen levels and low estrogen levels increase bone resorption resulting in a loss of bone mass [21-24]. In anorexia nervosa, the length of time with amenorrhea is directly associated with decreased bone mineral density, such that women with longer durations of amenorrhea have lower bone mineral density [12,25].

**ESTROGEN REPLACEMENT IN ANOREXIA NERVOSA**

Given the fact that low estrogen levels are common in anorexia nervosa, due to functional hypothalamic amenorrhea, and hypoestrogenemia is associated with higher rates of bone resorption, it is not surprising that estrogen has been investigated as a possible treatment for the low bone mass in anorexia nervosa (Table 1). Three cross-sectional studies investigating the effects of prior oral estrogen use on bone mineral density in anorexia nervosa showed that women with a history of prior oral estrogen use had higher bone mineral density at the lumbar spine compared to women without a prior history of use [12,26,27]. Yet prospective, randomized studies of oral estrogen have not shown the same benefit [28-30]. Multiple prospective studies in both adult and adolescent populations, ranging in length from 9 months to two years, demonstrate that oral estrogen does not result in improvements in bone mineral density in girls or women with anorexia nervosa (Table 1).

**WHAT IS THE POSSIBLE REASON FOR THIS LACK OF BENEFIT OF ORAL ESTROGEN?**

Estrogen suppresses IGF-1 production in the liver [36,37]. IGF-1 is a nutritionally-dependent hormone with bone anabolic effects and levels of IGF-1 are decreased in states
of starvation due to growth hormone resistance—an energy-preserving adaptation in states of undernutrition [38]. IGF-1 is suppressed by estrogen in a route-dependent manner such that oral estrogen suppresses IGF-1 to a greater degree than transdermal estrogen [36]. Therefore, further suppression of IGF-1—a bone anabolic hormone—in anorexia nervosa by oral estrogen may result in the lack of benefit with respect to bone mineral density observed in prospective studies of oral estrogen treatment.

In contrast to oral estrogen, transdermal estrogen leads to an increase in bone mineral density in adolescents with anorexia nervosa [34]. An 18-month randomized placebo-controlled study in adolescent girls with anorexia nervosa demonstrated that girls (ages 12–18 years) who were treated predominantly with transdermal physiologic estrogen had a significantly greater increase (2.6%) in lumbar spine bone mineral density after 18 months as compared to adolescent girls treated with placebo, who had a 0.3% increase in lumbar spine bone mineral density after 18 months [34]. The doses of estrogen that were used in this study were also more physiologic than the more potent formulations used in oral contraceptive pills and importantly IGF-1 suppression is not only dependent on the route of administration, but IGF-1 is also suppressed in a dose-dependent manner, such that lower doses of estradiol are less suppressive than higher doses [37]. Therefore, this randomized, placebo-controlled study demonstrated that physiologic estradiol treatment has a beneficial effect on bone mineral density in adolescent girls with anorexia nervosa.

**CAN WE EXTRAPOLATE THESE DATA TO ADULTS?**

Healthy adolescent girls are in a state of bone acquisition whereas by the age of approximately 20–30 years, the majority of bone mass has been accrued and peak bone mass has essentially been achieved [10]. Therefore, bone modeling and remodeling differ in adolescents as compared to adults. When compared to healthy adolescent girls, adolescents with anorexia have a lower bone formation rate but similar bone resorption rate [39-41]. In contrast, compared to normal-weight adult women, women with anorexia nervosa have a lower bone formation rate and a greater degree of bone resorption [42-45]. These differences in bone modeling and remodeling in adults versus adolescents likely contributes to the differences that have been observed in response to treatments for low bone mineral density in adolescents with anorexia nervosa as compared to adults [1]. For example, bisphosphonate treatment has been shown to have a beneficial effect with respect to bone mineral density in adult women with anorexia nervosa [46] but not in adolescents with anorexia nervosa [47]. Similarly, treatment with recombinant human IGF-1 has beneficial effects on bone mineral density in adult women with anorexia nervosa [29] but not adolescent girls [48]. Therefore, although physiologic transdermal estrogen therapy improves bone mineral density in adolescents with anorexia nervosa, it also needs to be studied separately in adult women with anorexia nervosa. We conducted an open-label six-month study in women (n = 11) with anorexia nervosa who were a mean (SEM) of 37.2 ± 2.3 years of age [35]. Study participants had anorexia nervosa for a median (interquartile range) of 16 (10, 23) years and were amenorrheic for a median of 157 (36, 180) months [35]. Six months of treatment with a transdermal estradiol patch (45 mcg/24 h) resulted in a mean 2% increase in lumbar spine bone mineral density [35]. A significant change in total hip or femoral neck bone mineral density was not observed after six-months of treatment.
As all individuals with an intact uterus must be treated with progesterone in addition to estrogen to prevent endometrial hyperplasia, the patch administered in the study (Climara Pro; Bayer Pharmaceuticals, Whippany, NJ, USA) also included levonorgestrel (0.015 mg/day) [35]. Importantly, administration of continuous estrogen/progesterone typically does not result in cyclic bleeding resembling a menstrual period, which is in contrast to oral estrogen in the form of an oral contraceptive pill. Therefore, oral contraceptives may have the added negative effect of masking amenorrhea, as women with anorexia nervosa may have regular, monthly withdrawal bleeds while using oral contraceptives. In turn, this may hinder recovery, as women using oral contraceptives will not know if they are persistently amenorrheic. Given these promising pilot data suggesting benefit with respect to bone mineral density in adult women with anorexia nervosa, we are now studying the effects of this dose of transdermal estradiol in an 18-month randomized, placebo-controlled study.

CONCLUSIONS

Although amenorrhea is no longer a part of the DSM criteria for anorexia nervosa, a majority of women with anorexia nervosa have functional hypothalamic amenorrhea and resultant hypoestrogenemia [2,3]. Although duration of amenorrhea is associated with bone mineral density, such that the longer the duration of amenorrhea the lower the bone mineral density in women with anorexia nervosa [12,25], prospective studies investigating the effects of oral estrogen use, predominantly in the form of an oral contraceptive pill, on bone mineral density have not demonstrated benefit. In contrast, physiologic, transdermal estrogen use has been shown to be beneficial with respect to bone mineral density in adolescent girls with anorexia nervosa. As data from adolescent studies cannot be extrapolated to adults due to differences in bone modeling and remodeling in the two populations, the effects of physiologic, transdermal estrogen must also be studied in adults [1]. Preliminary, open-label data in women with anorexia nervosa suggest that transdermal estrogen may also be beneficial in this population [35] and a randomized, placebo-controlled study is currently underway investigating its effects on bone mineral density in women with anorexia nervosa.

FUNDING

This work was supported in part by the following grant from the National Institutes of Health: R01 HD099139. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICTS OF INTEREST

PKF has funding support from the National Institutes of Health (R01 HD099139) and is a consultant for Regeneron Pharmaceuticals and Xeris Pharmaceuticals. ST declares no conflicts of interest.

REFERENCES

1. Fazeli PK. Low bone mineral density in anorexia nervosa: Treatments and challenges. Clin Rev Bone Miner Metab. 2019;17(2):65–76. [PubMed: 31938025]
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Washington (DC, US): American Psychiatric Association; 2013.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed. Washington (DC, US): American Psychiatric Association; 1994.

J Psychiatr Brain Sci. Author manuscript; available in PMC 2022 July 21.
4. Miller KK, Grinspoon SK, Ciampa J, Hier J, Herzog D, Klibanski A. Medical findings in outpatients with anorexia nervosa. Arch Intern Med. 2005;165(5):561–6. [PubMed: 15767533]

5. Vestergaard P, Emborg C, Stoving RK, Hagen C, Mosekilde L, Briëxen K. Fractures in patients with anorexia nervosa, bulimia nervosa, and other eating disorders: a register study. Int J Eat Disord. 2002;32(3):301–8. [PubMed: 12210644]

6. Faje AT, Fazeli PK, Miller KK, Katzman DK, Ebrahimi S, Lee H, et al. Fracture risk and areal bone mineral density in adolescent females with anorexia nervosa. Int J Eat Disord. 2014;47(5):458–66. [PubMed: 24430890]

7. Nagata JM, Golden NH, Leonard MB, Copelovitch L, Denburg MR. Assessment of Sex Differences in Fracture Risk Among Patients With Anorexia Nervosa: A Population-Based Cohort Study Using The Health Improvement Network. J Bone Miner Res. 2017;32(5):1082–9. [PubMed: 28019700]

8. Frølich J, Winkler LA, Abrahamsen B, Bilenberg N, Hermann AP, Støving RK. Fractures in women with eating disorders—Incidence, predictive factors, and the impact of disease remission: Cohort study with background population controls. Int J Eat Disord. 2020;53(7):1080–7. [PubMed: 31922277]

9. Rigotti NA, Neer RM, Skates SJ, Herzog DB, Nussbaum SR. The clinical course of osteoporosis in anorexia nervosa. A longitudinal study of cortical bone mass. JAMA. 1991;265(9):1133–8. [PubMed: 19959999]

10. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Matkovic V, et al. Peak bone mass. Osteoporos Int. 2000;11(12):985–1009. [PubMed: 11256898]

11. Hudson JJ, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61(3):348–58. [PubMed: 16815322]

12. Seeman E, Szmkul GI, Formica C, Tsalamandris C, Mestrovic R. Osteoporosis in anorexia nervosa: the influence of peak bone density, bone loss, oral contraceptive use, and exercise. J Bone Miner Res. 1992;7(12):1467–74. [PubMed: 1481732]

13. Lowe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. J Clin Psychol. 2001;57(5):881–90. [PubMed: 11459385]

14. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery From Anorexia Nervosa and Bulimia Nervosa at 22-Year Follow-Up. J Clin Psychiatry. 2017;78(2):184–9. [PubMed: 28002660]

15. Lucas AR, Melton LJ III, Crowson CS, O’Fallon WM. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clin Proc. 1999;74(10):972–7. [PubMed: 10918862]

16. Wiegelmurt W, Solbach HG. Effects of LH-RH on plasma levels of LH and FSH in anorexia nervosa. Horm Metab Res. 1972;4(5):404. [PubMed: 4566864]

17. Mecklenburg RS, Loriaux DL, Thompson RH, Andersen AE, Lipsett MB. Hypothalamic dysfunction in patients with anorexia nervosa. Medicine. 1974;53(2):147–59. [PubMed: 4593749]

18. Travaglini P, Beck-Peccoz P, Ferrari C, Ambrosi B, Paracchi A, Severgnini A, et al. Some aspects of hypothalamic-pituitary function in patients with anorexia nervosa. Acta Endocrinol. 1976;81(2):252–62.

19. Nilhus SJ, Fries H, Wide L. Successful induction of follicular maturation and ovulation by prolonged treatment with LH-releasing hormone in women with anorexia nervosa. Am J Obstet Gynecol. 1975;122(8):892–8. [PubMed: 1098466]

20. Boyar RM, Katz J, Finkelstein JW, Kapen S, Weiner H, Weitzman ED, et al. Anorexia nervosa. Immaturity of the 24-hour luteinizing hormone secretory pattern. N Engl J Med. 1974;291(17):826–5. [PubMed: 4412035]

21. Riis BJ, Rodbro P, Christiansen C. The role of serum concentrations of sex steroids and bone turnover in the development and occurrence of postmenopausal osteoporosis. Calcif Tissue Int. 1986;38(6):318–22. [PubMed: 3089552]

22. Seeman E. Estrogen, androgen, and the pathogenesis of bone fragility in women and men. Curr Osteoporos Rep. 2004;2(3):90–6. [PubMed: 16036088]
23. Falahati-Nini A, Riggs BL, Atkinson EJ, O’Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest. 2000;106(12):1553–60. [PubMed: 11120762]

24. Finkelstein JS, Lee H, Leder BZ, Burnett-Bowie SA, Goldstein DW, Hahn CW, et al. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. J Clin Invest. 2016;126(3):1114–25. [PubMed: 26901812]

25. Biller BM, Saxe V, Herzog DB, Rosenthal DL, Holzman S, Klibanski A. Mechanisms of osteoporosis in adult and adolescent women with anorexia nervosa. J Clin Endocrinol Metab. 1989;68(3):548–54. [PubMed: 2493036]

26. Karlsson MK, Weigall SJ, Duan Y, Seeman E. Bone size and volumetric density in women with anorexia nervosa receiving estrogen replacement therapy and in women recovered from anorexia nervosa. J Clin Endocrinol Metab. 2000;85(9):3177–82. [PubMed: 10999805]

27. Maimoun L, Renard E, Lefebvre P, Bertet H, Philibert P, Seneque M, et al. Oral contraceptives partially protect from bone loss in young women with anorexia nervosa. Fertil Steril. 2019;111(5):1020–9.e2. [PubMed: 30922647]

28. Klibanski A, Biller BM, Schoenfeld DA, Herzog DB, Saxe VC. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab. 1995;80(3):898–904. [PubMed: 8720956]

29. Grinspoon S, Thomas L, Miller K, Herzog D, Klibanski A. Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. J Clin Endocrinol Metab. 2002;87(6):2883–91. [PubMed: 12050268]

30. Strokosch GR, Friedman AJ, Wu SC, Kamin M. Effects of an oral contraceptive (norgestimate/ethinyl estradiol) on bone mineral density in adolescent females with anorexia nervosa: a double-blind, placebo-controlled study. J Adolesc Health. 2006;39(6):819–27. [PubMed: 17116511]

31. Golden NH, Lanzkowsky L, Schebendach J, Palestro CJ, Jacobson MS, Shenker IR. The effect of estrogen-progestin treatment on bone mineral density in anorexia nervosa. J Pediatr Adolesc Gynecol. 2002;15(3):135–43. [PubMed: 12106749]

32. Munoz MT, Morande G, Garcia-Centenera JA, Hervas F, Pozo J, Argente J. The effects of estrogen administration on bone mineral density in adolescents with anorexia nervosa. Eur J Pediatr. 2002;161(4):45–50. [PubMed: 11751066]

33. Legroux-Gerot I, Vignau J, Collier F, Cortet B. Factors influencing changes in bone mineral density in patients with anorexia nervosa-related osteoporosis: the effect of hormone replacement therapy. Calcif Tissue Int. 2008;83(5):315–23. [PubMed: 18836675]

34. Misra M, Katzman D, Miller KK, Mendes N, Snelgrove D, Russell M, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res. 2011;26(10):2430–8. [PubMed: 21698665]

35. Resulaj M, Polineni S, Meenaghan E, Eddy K, Lee H, Fazeli PK. Transdermal Estrogen in Women With Anorexia Nervosa: An Exploratory Pilot Study. JBMR Plus. 2020;4(1):e10251. [PubMed: 31956852]

36. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. J Clin Endocrinol Metab. 1991;72(2):374–81. [PubMed: 1991807]

37. Kam GY, Leung KC, Baxter RC, Ho KK. Estrogens exert route- and dose-dependent effects on insulin-like growth factor (IGF)-binding protein-3 and the acid-labile subunit of the IGF ternary complex. J Clin Endocrinol Metab. 2000;85(5):1918–22. [PubMed: 10843175]

38. Fazeli PK, Klibanski A. Determinants of GH resistance in malnutrition. J Endocrinol. 2014;220(3):R37–65. [PubMed: 24363451]

39. Soyka LA, Grinspoon S, Levitsky LL, Herzog DB, Klibanski A. The effects of anorexia nervosa on bone metabolism in female adolescents. J Clin Endocrinol Metab. 1999;84(12):4489–96. [PubMed: 10599707]

40. Saggese G, Bertelloni S, Baroncelli GI, Di Nero G. Serum levels of carboxyterminal propeptide of type I procollagen in healthy children from 1st year of life to adulthood and in metabolic bone diseases. Eur J Pediatr. 1992;151(10):764–8. [PubMed: 1425800]
41. Heer M, Mika C, Grzella I, Heussen N, Herpertz-Dahlmann B. Bone turnover during inpatient nutritional therapy and outpatient follow-up in patients with anorexia nervosa compared with that in healthy control subjects. Am J Clin Nutr. 2004;80(3):774–81. [PubMed: 15321821]

42. Hotta M, Fukuda I, Sato K, Hizuka N, Shibasaki T, Takano K. The relationship between bone turnover and body weight, serum insulin-like growth factor (IGF) I, and serum IGF-binding protein levels in patients with anorexia nervosa. J Clin Endocrinol Metab. 2000;85(1):200–6. [PubMed: 10634387]

43. Weinbrenner T, Zittermann A, Gouni-Berthold I, Stehle P, Berthold HK. Body mass index and disease duration are predictors of disturbed bone turnover in anorexia nervosa. A case-control study. Eur J Clin Nutr. 2003;57(10):1262–7. [PubMed: 14506487]

44. Bolton JG, Patel S, Lacey JH, White S. A prospective study of changes in bone turnover and bone density associated with regaining weight in women with anorexia nervosa. Osteoporos Int. 2005;16(12):1955–62. [PubMed: 16027954]

45. Viapiana O, Gatti D, Dalle Grave R, Todesco T, Rossini M, Braga V, et al. Marked increases in bone mineral density and biochemical markers of bone turnover in patients with anorexia nervosa gaining weight. Bone. 2007;40(4):1073–7. [PubMed: 17240212]

46. Miller KK, Meenaghan E, Lawson EA, Misra M, Gleysteen S, Schoenfeld D, et al. Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2011;96(7):2081–8. [PubMed: 21525157]

47. Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebendach J, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2005;90(6):3179–85. [PubMed: 15784715]

48. Singhal V, Bose A, Slattery M, Haines MS, Goldstein MA, Gupta N, et al. Effect of Transdermal Estradiol and Insulin-like Growth Factor-1 on Bone Endpoints of Young Women With Anorexia Nervosa. J Clin Endocrinol Metab. 2021;106(7):2021–35. [PubMed: 33693703]
Table 1. Studies investigating the effects of estrogen on bone mineral density in anorexia nervosa.

OCP: oral contraceptive pill; SD: standard deviation; SEM: standard error of the mean; rhIGF-1: recombinant human IGF-1; N/A: not applicable; BMD: bone mineral density.

| Study                        | Study design       | Anorexia nervosa study population characteristics                                                                 | Estrogen type     | Follow-up time | Findings                                                                                                                                 |
|------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Seeman et al., 1992 [12]     | Cross-sectional    | 65 women with anorexia nervosa (16 women with history of OCP use) Mean age of women with history of OCP use: 27.6 ± 1.9 years | OCP               | N/A            | Mean BMD at lumbar spine greater in women with history of OCP use as compared to those without history of OCP use                         |
| Klibanski et al., 1995 [28]  | Randomized         | 48 study participants with anorexia nervosa (22 randomized to oral estrogen) Age range: 16.3–42.5 years with mean age: 24.9 ± 6.9 years (SD) | Oral estrogen     | Mean: 1.5 years | No difference in change in spine BMD in oral estrogen versus placebo overall. In women with baseline ideal body weight of <70%, there was a significant treatment effect: 4% ± 8.9% increase in spine BMD in estrogen group versus 20.1% ± 16.2% decrease in control group (posthoc analysis) |
| Karlsson et al., 2000 [26]   | Cross-sectional    | 135 women with active anorexia nervosa (58 women with history of estrogen use for a mean of 4.3 years) Mean age of women with history of estrogen use: 25.9 ± 0.8 years | Oral estrogen     | N/A            | Areal and volumetric BMD of the L3 vertebra significantly greater in women with history of estrogen use as compared to those without     |
| Grinspoon et al., 2002 [29]  | Randomized study of OCP and rhIGF-1 | 60 women with anorexia nervosa (15 randomized to placebo, 15 randomized to OCP alone, 16 randomized to rhIGF-1 alone, and 14 randomized to OCP+rhIGF-1) Mean age: 25.2 ± 0.7 years | OCP               | 9 months       | No difference in change in lumbar spine BMD when comparing women randomized to OCP to women randomized to no OCP treatment          |
| Golden et al., 2002 [31]     | Prospective, open-label | 50 girls/women (13–21 years of age) with anorexia nervosa (22 received estrogen) Mean age: 16.8 ± 2.3 years (SD)       | OCP               | Mean: 23.1 months | No difference in change in lumbar spine or femoral neck BMD in estrogen group compared to group not prescribed estrogen after 1 year of follow-up. |
| Munoz et al., 2002 [32]      | Prospective, open-label | 38 girls/women with anorexia nervosa (mean age: 17.3 years)                                                         | Oral estrogen     | 1 year         | No significant change in lumbar spine BMD after 1 year of treatment                                                                     |
| Strokosch et al., 2006 [30]  | Randomized, placebo-controlled | 43 girls with anorexia nervosa were included in a study of 112 adolescent girls (age: 11–17 years) with either anorexia nervosa or an eating disorder not otherwise specified (EDNOS); 18 with anorexia nervosa randomized to estrogen | OCP               | 1 year         | No difference in change in lumbar spine BMD after 1 year in subset of patients with anorexia nervosa                                     |
| Legroux-Gerot et al., 2008 [33] | Prospective, observational | 45 girls/women with anorexia nervosa [age range: 15–41 years with mean (SD) age: 25.3 ± 6.7 years]. Those with a T-score <−2.5 (n = 12) were treated with estrogen | Estradiol gel     | 2 years        | No difference in change in lumbar spine or femoral neck BMD in estrogen-treated patients                                               |
| Misra et al., 2011 [34]      | Randomized, placebo-controlled | 110 adolescents with anorexia nervosa (ages: 12–18 years with mean age: 16.5 years); 55 randomized to estrogen     | Predominantly transdermal estradiol (100 mcg/day); 96 participants randomized to transdermal estradiol | 18 months       | Significant 2.6% increase in lumbar spine BMD after 18 months of treatment in estrogen treated group compared to 0.3% in the group not treated with estrogen |
| Study                      | Study design          | Anorexia nervosa study population characteristics | Estrogen type                                    | Follow-up time | Findings                                                                 |
|----------------------------|-----------------------|-------------------------------------------------|-------------------------------------------------|----------------|--------------------------------------------------------------------------|
| Revulaj et al., 2020 [35] | Prospective, open-label | 11 women with anorexia nervosa Mean age: 37.2 ± 2.3 years (SEM) | Transdermal estradiol (45 mcg/day) | 6 months       | 2% increase in lumbar spine BMD                                          |
| Maimoun et al., 2019 [27] | Cross-sectional       | 305 adolescent and adult women with anorexia nervosa (age range: 14.5–34.9 years with mean age of 22.4 ± 4.6 years (SD) | OCP (84 participants using estrogen-containing OCP and 15 progestin only) | N/A            | Areal BMD at lumbar spine and femoral neck greater in women with history of OCP use as compared to those without history of OCP use |