Exercise-Induced Amenorrhea and Bone Health in the Adolescent Athlete

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Female participation in high school athletics has increased 800% in the last 30 years. The problem of exercise-induced amenorrhea was initially thought to be analogous to hypoestrogenism, but recent studies suggest that nutritional issues underlie most of the pathophysiology and that the mechanism is different from that seen in the primary hypogonadal state. Exercise-induced amenorrhea can be an indicator of an energy drain, and the presence of the other components of the female athlete triad—bone density loss and eating disorders—must be determined as well. Addressing skeletal problems related to nutritional and hormonal deficiencies in this population is of very high priority.

Key words: **amenorrhea; hypothalamic amenorrhea; bone density; bone turnover marker; eating disorder; female athlete triad**

Introduction

In 1972, Title IX of the Education Amendments Act was passed in the United States, allowing for equal sports opportunities for school-age male and female athletes. Female participation in high-school athletics has increased 800% in the last 30 years.[1] In 1992, an association was defined among disordered eating, amenorrhea, and osteoporosis as the female athlete triad. There is evidence that the childhood and adolescent years provide the best opportunity to maximize bone mass and strength.[2,3] Weight-bearing exercise during the growth years can enhance both short-term bone mineralization and can lead to higher peak bone mass in adulthood.[4,5] Conversely, the female athlete triad can pose long-term health consequences for both bone mineral density and fertility. In this chapter, we examine the literature related to the components of the triad and adolescents, provide an overview of treatment, and note areas in need of further inquiry.

Epidemiology

Amenorrhea has been defined as the absence or cessation of normal menses.[6] Secondary amenorrhea, amenorrhea occurring after menarche, typically requires the absence of menses for 3 months or more. Oligomenorrhea has been defined as irregular period cycles lasting more than 40 days. The American Society for Reproductive Medicine has defined primary amenorrhea as failure to menstruate by age 15 in the presence of normal secondary sexual development.[7]

The prevalence of secondary amenorrhea and oligomenorrhea in the general population has been described as anywhere between 2 and 5%.[8,9] In studies involving women engaged in sports that emphasize leanness, such as ballet or running, the prevalence of amenorrhea has been found to be as high as 69% (among ballet dancers)[10] and 65% (among runners).[11] Younger athletes are especially at risk for menstrual cycle disturbances. In runners younger than 15 years of gynecologic age (i.e., age at menarche subtracted from chronological age), the prevalence of secondary amenorrhea has been found to be much higher than among older women (67% versus 9%).[12] Primary amenorrhea, relatively rare in the general population, with a prevalence of approximately 1%,[13] has been found in one study to be more than 22% among gymnasts, cheerleaders, and divers.[14] Eating disorders are part of the syndrome seen in exercise-associated amenorrhea, particularly in adolescents.

In the only two large well-controlled studies related to eating disorders and elite athletes, the prevalence of eating disorders in female athletes has been found to be between 25 and 31%, as opposed to between 5.5–9% in the general population.[15,16]

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The Female Athlete Triad

The link between energy availability and menstrual status was further elaborated in 1992, when the association of disordered eating, amenorrhea, and osteoporosis was formally defined as the female athlete triad.[17,18] A position stand was published in 1997 by the American College of Sports Medicine,[19] and an updated position stand was issued in 2007, providing a review of the research and recommendations for screening, diagnosis, treatment, and prevention of the triad.[20] The female athlete triad specifically refers to the clinical syndrome of amenorrhea, eating disorders, and osteoporosis.

Prior to the 1997 position stand, much work had previously been done associating exercise-induced amenorrhea with osteoporosis[21–25] and anorexia with osteoporosis.[26–30] Loss of bone mineral density has also been documented in young women suffering from stress- or weight loss–induced hypothalamic amenorrhea[31] and ovulatory dysfunction.[32] A direct relationship between amenorrhea and fractures and stress fractures in young, exercising women has been demonstrated.[33]

Mechanism of Relationship between Energy Drain and Amenorrhea

In 1980, the first study linking menstrual disorders in dancers and energy drain was published.[34] Since then multiple studies have documented this relationship between energy drain in athletes and menstrual disorders.[18–20,24,35–39] Amenorrhea is caused by disruptions in the normal signaling processes between the hypothalamus and the pituitary gland. Normal functioning of the reproductive system requires pulsatile release of GnRH from neurons of the hypothalamus and pulsatile release of LH from the pituitary. Irregular and infrequent LH pulsatility can suppress normal ovarian function, including follicular development, ovulation, and luteal function.

In a study of 29 regularly menstruating, inactive young women of normal body weight, investigators measured LH pulsatility after manipulating energy availability, defined as the difference between caloric intake and output.[35] Study subjects were randomized to restricted energy availability treatments (10, 20, and 30 kcal/kg lean body mass [LBM] per day) and underwent repeated trials in which diet and exercise were controlled for 5 days in the early follicular phase of the menstrual cycle. The study found that energy availability of 30 kcal/kg LBM per day had no affect on LH pulsatility, but below this benchmark LH pulse frequency decreased, while LH pulse amplitude increased. Study subjects with shorter luteal phases were most sensitive to the decrease in energy availability as shown by the disruption of their respective LH pulses. This study demonstrated the dependent relationship of LH pulsatility to energy availability.

In recent years, the hormone leptin has been credited as an important mediator between nutritional status and reproduction. Leptin is a hormone secreted by the adipose tissue, and physiological levels of leptin are known to be proportional to fat mass and to respond to changes in caloric intake. It has been previously shown that when energy availability is limited, physiological mechanisms reduce the energy used for many processes, including reproduction, in order to compensate.[40] Some researchers have posited that body fat levels must reach a certain critical level, and be maintained at that level in order for normal reproductive function to occur. The signals that integrate nutritional status, including body fat, energy availability, and leptin, have been increasingly studied.

Leptin levels have been shown to decrease during periods of short-term fasting, even before marked decreases of fat mass could occur.[41,42] One study showed a suppression of leptin levels disproportionate to the change in fat mass after only a 72-hour fasting period, and the rebound of leptin levels after r-metHULeptin administration.[43] It has been proposed that this demonstrated decrease in serum leptin levels may serve as a mechanism to promote survival over reproduction during periods of starvation, and that there is some threshold level of energy availability required for normal reproductive function.[40]

The importance of leptin as a reproductive mediator has been further supported by a pilot study of patients with amenorrhea. These study patients were diagnosed with hypothalamic amenorrhea due to low nutritional intake and/or high levels of exercise. The administration of leptin caused an increase in the mean and pulsatile LH levels of these patients, along with enlargement of the ovaries, an increase in the number and size of dominant follicles, and a rise in estradiol concentration. Most importantly a return of menses in 3 of 8 subjects was demonstrated. These increases occurred even though patients maintained their usual nutritional intake, exercise, and lifestyles.[44]

While the exact signaling process linking homeostasis and reproduction remains elusive, these recent studies have provided evidence that leptin plays an important role. One recent paper[45] reported a 24-hour study of leptin, LH, and metabolic rate in a group of normal, menstruating women. The study found that leptin has a diurnal rhythm in ovulating women and that

the nightly leptin peak (roughly between 12 AM and 4 AM) correlates with a decrease in LH pulse frequency and an increase in LH pulse amplitude. A decrease in metabolic rate corresponds to these changes in LH pulse character. This suggests that in normal, ovulating women, the baseline levels of leptin correspond to fat stores; however, 24-hour, minute-to-minute leptin secretion may actually depend on the availability of oxidative fuels. The decrease in leptin levels seen in this cohort at night most likely corresponds also with low availability of oxidative fuels. In women with hypothalamic amenorrhea, these leptin patterns may be altered as a result of a lower amount of fat-store availability and may correspond with the leptin levels in fasting subjects.

Other studies suggest that the diurnal rhythm in leptin levels seen in normal, ovulating women is absent in amenorrheic athletes.[46] Hypoleptinemia has been consistently observed in anorexia nervosa.[47] These findings support the importance of the link between energy drain and menstrual disturbance. Other neuropeptides may be involved. One study in exercising women of normal weight showed that ghrelin was a better discriminator in hypothalamic amenorrhea.[48]

Mechanism of Bone Loss and the Female Athlete Triad

Knowledge of the mechanisms of bone loss is best understood by a review of the work on eating disorders. Bone turnover markers are an indirect measure of bone formation and bone breakdown. These markers can be measured in blood serum and in urine. Recent studies have shown that the pathophysiology underlying osteoporosis in hypothalamic amenorrhea is directly related to nutritional issues.[49–51]

Reduced bone formation has been found to be linked to both low BMI and estrogen deficiency.[51] In a group of amenorrheic distance runners with negative energy balance, reduced bone turnover was demonstrated, highlighting the potential link between body mass index, energy deficit, and hypothalamic dysfunction.[51]

Similar changes in bone turnover have been reproduced in normal women under dietary restriction. In healthy women with restricted energy availability, a direct relationship between energy availability and bone turnover has been seen.[52] Recovery from anorexia is associated with increases in markers of bone formation, but elevated bone resorption does not decline until menses return. These findings indicate there may be a both a nutritional component affecting formation and an estrogen-related component affecting resorption.[53] These data suggest that estrogen deficiency alone cannot be the only cause of dysfunction in bone formation.

Uncoupling of markers of bone turnover also has been found in normal women undergoing nutritional restriction in an experimental situation. Depression in the concentrations of the markers of bone turnover osteocalcin and PICP (procollagen type I) concentrations occurred in a group of healthy exercising women who had restricted energy availability diets (all $P < 0.05$).[52] Levels of PICP decreased linearly only with severe restriction (10, 20, and 30 kcal/kg LBM per day) ($P < 10^{-6}$), while osteocalcin levels decreased most significantly between 20 and 30 kcal/kg LBM per day ($P < 0.05$). However, the indices of bone resorption showed an increase only at treatment levels below 10 kcal/kg LBM per day. These findings further elaborate the complexity of the relationship between energy availability and bone turnover and the uncoupling of bone formation and resorption.

Women with eating disorders often suffer from chronic energy deficit, and this group has been shown to have an increased risk of fracture compared to the general population. One study[54] found that for women with anorexia nervosa, the risk for all types of fractures compared with that of the general population was 2.6, for women with bulimia nervosa (BN) it was 1.4, and for women with eating disorders not otherwise specified (EDNOS) it was 1.8. Those with anorexia nervosa had a 5.3 increased risk of hip fracture compared to the general population. The authors concluded that suspicion of anorexia nervosa should be raised in a severely underweight young woman or girl without accompanying medical conditions who presents with a fracture sustained from a low-energy trauma, especially in sites such as the femoral neck, which is normally resistant to fracture.

Even many years after diagnosis of an eating disorder, women are at an increased risk of fracture. For women previously suffering from anorexia nervosa, a prolonged increase in fracture risk has been demonstrated as many as 10 years after diagnosis (incidence rate ratio: 1.98, 95% CI: 1.60–2.44).[55] A statistically significant increase in fracture risk was found before diagnosis in women suffering from bulimia nervosa (1.31, 95% CI: 1.04–1.64). EDNOS patients have been shown to have a significant increase in fracture risk before (1.39, 95% CI: 1.06–1.81) and after diagnosis (1.77, 95% CI: 1.25–2.51). These findings show the importance of long-term monitoring of the bone density of patients previously diagnosed with eating disorders.

TABLE 1. Effect of hormonal treatment of anorexia nervosa on bone mineral density (randomized control trials)[a]

Model	Study	Rx (N)	Bone mineral density		
			Spine	Hip	Total
Anorexia nervosa	Klibanski *et al.* (1995)[70]	0.625 mg Premarin/5 mg Provera ($N = 16$), 35 mcg EE ($N = 6$) 18 months	NS	–	–
Anorexia nervosa	Gordon *et al.* (2002)[71]	20 mcg EE + 0.1 mg levonogestrel 50 mg ($N = 30$)	NS	–	–
		Dehydroepiandrosterone ($N = 31$)	NS	–	–
Anorexia nervosa	Grinspoon *et al.* (2002)[72]	35 mcg EE + 0.4 mg norethindrone ($N = 15$), 30 mcg/kg rhIGF-1 ($N = 14$), 30 mcg/kg rfIGF-1 + 30 mcg EE + 0.4 mg norethindrone ($N = 16$)	NS	NS	NS
Anorexia nervosa/EDNOS	Strokosch *et al.* (2006)[77]	180–250 mcg norgestimate + 35 mcg EE ($N = 53$) 13–28 day cycles	NS	NS	

[a]Adapted from Liu and Lebrun.[78]

TABLE 2. Hormone/oral contraceptive treatment of hypothalamic amenorrhea (randomized control trials)[a]

Model	Study	Rx (N)	Bone mineral density		
			Spine	Hip	Total
Hypothalamic amenorrhea and osteopenia	Warren *et al.* (2005)[66]	Norgestimate 180–250 μg/ethinyl estradiol 35 μg ($N = 15$); oral contraceptive double-blind placebo controlled	1.5% increase	NS	
Hypothalamic amenorrhea	Hergenroeder *et al.* (1997)[67]	35 μg EE + 0.5–1 mg norethindrone ($N = 5$); oral contraceptive 12 months	5.4% increase	–	1.1% decrease
Hypothalamic amenorrhea	Castelo-Branco *et al.* (2001)[68]	30 μg EE+ 0.15 mg desogestrel ($N = 24$)	2.4% increase	–	–
		20 μg EE+ 0.15 mg desogestrel ($N = 22$); oral contraceptive	2.5% increase	–	–
Exercise-induced amenorrhea	Gibson *et al.* (1999)[79]	Estrogen-treated (1 mg estriol +2 mg estradiol (days 1–12, 1 mg estriol + 2 mg estradiol +1 mg norethisterone acetate (days 13–22), 0.5 mg estriol + 1 mg estradiol (days 23–28)	NS	–	–

[a]Adapted from Liu and Lebrun.[78]

Treatment

Several clinical guidelines have been published for the diagnosis and treatment of the triad disorders including eating disorders,[56–59] amenorrhea,[7,60] and premenopausal osteoporosis.[61–63] Practical guidelines also exist specifically for the management of amenorrhea in adolescent girls[64] and adolescent athletes.[65] Hormone replacement therapy is often used as treatment for hypothalamic amenorrhea; however, the clinical findings of the effect of both hormone replacement and oral contraceptives on bone mineral density (BMD) have been mixed. (TABLES 1 and 2). The best treatment is weight restoration and a decrease in exercise compatible with energy intake or an associated increase in caloric intake.[53] Very significant (6–20%) increases in BMD occur with return of menses, increases that are much more significant than those achieved by treatment with pharmacologic agents (TABLE 3).

Lumbar spine BMD was found to increase in levels ranging from 1.5–5.4% in several randomized control studies of patients with hypothalamic amenorrhea treated with hormone replacement therapy/oral contraceptives (HRT/OCs) (TABLE 2).[66–68] Cohort studies have been mixed (TABLE 4).[69]

However, no trials on patients with anorexia nervosa have shown benefit to date.

For young women with anorexia nervosa and low BMD, no statistically significant increases in BMD

TABLE 3. Hypothalamic amenorrhea and return of menses

Study	Age (yr)	Duration of study (BMI)	% BMD increase	Normalized (*N*)	Fx
Drinkwater (1986)[21]	26.7–27.9	14.4 months (1.9 kg of wt gain)	6.3%	No (9)	Yes; injuries
[a]Lindberg (1987)[80]	28–30	15 months (3% increase in body weight)	Spine: 6.6%	(7)	Yes; stress fx
Keen (1997)[81]	31.4–40.8	6–10 years (BMI 20.3->20.5)	No change reported as % of normal	No (9)	Yes; stress fx
[a]Warren (2002)[82]	22.4–24.4	2 years (BMI 18.51->18.94)	Spine: 17%	No (7)	Yes; stress fx of foot
[a]Warren (2003)[76]	22–24	2 years (BMI 18.8->19.2)	Spine: 11%	No (5)	Yes; stress fx foot
Zanker (2004)[83]	24.8–36.9	12 years (BMI 16.4->17.6, 8.1% kg wt gain)	16.9%	No (1)	Stress fx tibia; rib fx' on OCPs pubic rami fx
Fredericson (2005)[84]	22.9–30.8	8 years (BMI 15.8->21.3)	Spine: 25%		
			Hip: 19%	Yes (1)	Yes; stress fx of femoral head
Miller *et al.* (2006)[85]	18–40	6–69 months (BMI 16.1–18.2)	Spine: 3.6%		
			Hip: 2.1%	No	Not stated

[a]Performed on same machine.

TABLE 4. Oral contraceptive treatment of hypothalamic amenorrhea: effect on BMD[a]

Study type	No effect of OCs	Positive effect of OCs (*N*)	Negative effect of OCs
Cohort	Gremion *et al.* (2001) ($n=9$)[86]	DeCree *et al.* (1988)[87] ($N=7$); increase 9.5% in lumbar spine BMD Gulekli *et al.* (1994)[69] ($N=85$); 2.1% increase in BMD Haenggi *et al.* (1994)[88] ($N=15$); 0.2–2.9% increase in lumbar spine and Ward's triangle BMD Cumming *et al.* (1996)[89] ($N=8$); 8.0% increase in vertebral BMD; 2.1% increase in femoral BMD Rickenlund *et al.* (2004)[90] ($N=13$); 1.8% increase in total BMD	
Case report			Zanker *et al.* (2004)[83] ($n=1$); 9.8% decrease in lumbar spine; 12.1% decrease in proximal femur

[a]Adapted from Liu and Lebrun.[78]

were shown in three randomized control trials examining the effect of hormone therapy on BMD of anorexic women.[70–72] These findings support the idea that patients with anorexia and hypothalamic amenorrhea will not have improvement in bone mineral density with oral contraceptive therapy alone. The findings related to the effects of recombinant human insulin growth factor-1 (rhIGF-1) therapy in combination with oral contraceptive pills (OCPs) only show a small benefit, whereas IGF-1 alone did not.[72]

Two studies[73,74] have investigated the effects of the use of bisphosphonates on anorectics with osteopenia. One study[74] found that daily treatment with 5 mg risedronate for 9 months resulted in an increase in AP spinal bone density of $4.1 \pm 1.6\%$ at 6 months and $4.9 \pm 1.0\%$ at 9 months of treatment. This same study found that bone resorption in these patients, as measured by a marker of bone turnover N-telopeptide (NTX), decreased 23.8% at one month and 29.6% at three months, from the high-normal to mid-normal range of young women. The differences in bone formation and bone resorption in this study were seen even after controlling for weight gain in the patients. Another study used alendronate, 10 mg daily for one year, in a similar patient population and found that while assignment to treatment group was important, increased BMI was the most important predictor for BMD increase.[73] Of the subjects who completed the study ($n=29$), 51.7% were weight-restored ($n=15$). The weight-restored patients demonstrated significant increases in both spine and hip BMD. At 1-year follow-up, BMD was significantly higher in subjects who experienced weight gain in comparison with those who remained at low weight ($P=0.002$, femoral neck;

$P = 0.04$, lumbar spine). However use of these drugs is not approved for premenopausal women, and their long half-life in bone (up to 10 years) raises issues on possible effects on the developing fetus in women who may later become pregnant. Recommendations await the findings in women who have had this exposure, although no registry has been implemented at present. The onset and return of menses are powerful predictors of an increase in spine BMD (TABLE 3).[75]

It must be stressed that the osteopenia and osteoporosis experienced by young women with hypothalamic amenorrhea differ from the osteoporosis seen in post-menopausal women. In these young women with nutritionally restrictive diets and or energy drain, the normal response of bone to chronic weight-bearing stress is absent. In addition postmenopausal women who present with osteoporosis and osteopenia, estrogen replacement therapy can be appropriately used to reduce the risk of fracture and further bone demineralization. In young women with osteoporosis and osteopenia associated with hypothalamic amenorrhea, treatment of the estrogen deficiency is important only after nutritional rehabilitation of these patients has been established.[53] A stress fracture in a female adolescent athlete should be taken as a sign of an eating disorder.

Delayed menarche in young female athletes can also serve as a powerful fracture predictor.[76] Poor reproductive and nutritional health among these young women compromise bone mass accretion during a crucial period of development. Treatment of the underlying nutritional deficiencies in this group should be a priority, as the resolution of energy deficits can support the resumption of normal bone formation and the return of menses.

Areas for Future Research

The physiology of the reproductive dysfunction and the bone loss in exercise-associated amenorrhea is incompletely understood, but overwhelming evidence suggests that energy homeostasis is linked by a central mechanism to reproduction and that an important integration of neuropeptide function is involved. Leptin and ghrelin most likely play an important role, but further research will elucidate their role, as well as the role of other neuropeptides and lead to more appropriate interventions than those presently available. Data also suggests that the exercise *per se* is not the offending factor in the development and persistence of the amenorrhea, but rather the chronic energy deficit induced by exercise in individuals with poor reserve, that is, low weight and or poor nutritional status. The mechanism of an energy drain on reproduction and bone loss needs further research. The bone loss represents an irreversible problem with significant morbidity and high fracture risk. The physiology of the bone loss is unique, and further work is necessary to understand its mechanism. Interventions which suppress bone turnover and provide estrogen replacement may not be appropriate and the condition may progress despite these therapies. Nutritional rehabilitation represents the best therapy, but little is known of the mechanism involved. The use of oral contraceptives to treat this syndrome is of questionable benefit for both the reproductive dysfunction and the bone loss, and the effects of this therapy in the long term need to be examined. Lastly, there is a great need for a registry for women with this syndrome and other forms of hypothalamic amenorrhea to determine whether biphosphonates, which are used despite a lack of indication in young women with this problem, leads to risk to the fetus in future pregnancies.

Conclusion

Adolescent girls engaged in athletic activities should be closely monitored for menstrual disturbance. Exercise-induced amenorrhea can be an indicator of an energy drain, and the presence of the other components of the female athlete triad, bone density loss, and eating disorders, must be determined. Loss of bone mineral density related to nutritional and hormonal deficiencies in this population are a high-priority concern. Bone density loss in this population is different from that associated with pure hypoestrogenism. The uncoupling of bone turnover markers suggests that treatment with anti-resorptives, including oral contraceptives, is not advised until bone formation is restored. In adolescent girls with exercise-induced amenorrhea, response of bone to weight-bearing stress may be deficient, putting patients at risk for fracture. Weight gain and an increase in energy availability in these young women are clinical priorities to facilitate resumption of menses.

Conflicts of Interest

The authors declare no conflicts of interest.

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