

HORMONES AND SPORT

The effects of intense exercise on the female reproductive system

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Abstract

Women have become increasingly physically active in recent decades. While exercise provides substantial health benefits, intensive exercise is also associated with a unique set of risks for the female athlete. Hypothalamic dysfunction associated with strenuous exercise, and the resulting disturbance of GnRH pulsatility, can result in delayed menarche and disruption of menstrual cyclicality.

Specific mechanisms triggering reproductive dysfunction may vary across athletic disciplines. An energy drain incurred by women whose energy expenditure exceeds dietary energy intake appears to be the primary factor effecting GnRH suppression in athletes engaged in sports emphasizing leanness; nutritional restriction may be an important causal factor in the hypoestrogenism observed in these athletes. A distinct hormonal profile characterized by hyperandrogenism rather than hypoestrogenism is associated with athletes engaged in sports emphasizing strength over leanness. Complications associated with suppression

of GnRH include infertility and compromised bone density. Failure to attain peak bone mass and bone loss predispose hypoestrogenic athletes to osteopenia and osteoporosis.

Metabolic aberrations associated with nutritional insult may be the primary factors effecting low bone density in hypoestrogenic athletes, thus diagnosis should include careful screening for abnormal eating behavior. Increasing caloric intake to offset high energy demand may be sufficient to reverse menstrual dysfunction and stimulate bone accretion. Treatment with exogenous estrogen may help to curb further bone loss in the hypoestrogenic amenorrheic athlete, but may not be sufficient to stimulate bone growth. Treatment aimed at correcting metabolic abnormalities may in fact prove more effective than that aimed at correcting estrogen deficiencies.

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Introduction

Women have become increasingly physically active over the past several decades. Research confirming the benefits of exercise, physician endorsement, legislation creating new opportunities for women in sports, societal changes and media attention have all been instrumental in encouraging women to participate in athletics. While exercise provides substantial health benefits, rigorous physical activity is also associated with a unique set of risks for the female athlete.

The female reproductive system is highly sensitive to physiological stress, and reproductive abnormalities including delayed menarche, primary and secondary amenorrhea and oligomenorrhea occur in 6–79% of women engaged in athletic activity. The prevalence of observed irregularities varies with athletic discipline and level of competition (Table 1) (Pettersen *et al.* 1973, Feicht *et al.* 1978, Singh 1981, Abraham *et al.* 1982, Shangold & Levine 1982,

Brooks-Gunn *et al.* 1987, Glass *et al.* 1987, Sanborn *et al.* 1987).

The reproductive abnormalities observed in female athletes generally originate in hypothalamic dysfunction and disturbance of the gonadotropin-releasing hormone (GnRH) pulse generator, although specific mechanisms triggering reproductive dysfunction may vary across athletic disciplines. The clinical consequences associated with suppression of GnRH include infertility and compromised bone density, which appears to be irreversible.

This article reviews the pathophysiology, clinical consequences and treatment strategies for exercise-associated reproductive dysfunction.

Pathophysiology

Although specific hormonal profiles of athletes with reproductive irregularities may vary across athletic

Table 1 The prevalence of menstrual irregularities (oligomenorrhea and amenorrhea) in different athletic disciplines

	Study	Number of subjects	Percentage with irregularities
General population	Petterson <i>et al.</i> (1973)	1862	1.8
	Singh (1981)	900	5.0
Weight-bearing sports			
Ballet	Abraham <i>et al.</i> (1982)	29	79.0
	Brooks-Gunn <i>et al.</i> (1987)	53	59.0
	Feicht <i>et al.</i> (1978)	128	6–43
	Glass <i>et al.</i> (1987)	67	34.0
	Shangold & Levine (1982)	394	24.0
Running	Sanborn <i>et al.</i> (1987)	237	26.0
Non-weight-bearing sports			
Cycling	Sanborn <i>et al.</i> (1987)	33	12.0
Swimming	Sanborn <i>et al.</i> (1987)	197	12.0

From Constantini & Warren MP (1994) with permission.

disciplines, exercise-associated reproductive abnormalities generally stem from dysfunction at the hypothalamic level. The hormonal profile of women engaged in sports which emphasize low weight, such as ballet, long-distance running, gymnastics and figure skating, is characterized by hypoenestrogenism resulting from disruption of the hypothalamic–pituitary–ovarian axis. Specifically, suppression of hypothalamic pulsatile release of GnRH, which normally occurs every 60–90 min, limits pituitary secretion of luteinizing hormone (LH) and, to a lesser extent, follicle-stimulating hormone (FSH), which, in turn, limits ovarian stimulation and estradiol production. A prolonged follicular phase, or the absence of a critical LH or estradiol surge mid-cycle, results in the mild or intermittent suppression of menstrual cycles observed in these athletes. Very low LH levels result in delayed menarche or primary or secondary amenorrhea (Warren 1980, Baker *et al.* 1981, Loucks *et al.* 1989).

Original hypotheses for reproductive dysfunction in these athletes emphasized body composition and effects of ‘exercise stress’; however, mounting evidence suggests that an energy drain incurred by women whose energy expenditure exceeds dietary energy intake is the primary factor affecting GnRH pulsatility. The body composition hypothesis suggests that menarche occurs in girls when body fat rises to 17% of body weight, and menstrual function is lost when body fat decreases to less than 22% of body weight (Frisch & McArthur 1974). Although widely accepted in the lay and clinical communities, the body composition hypothesis is based entirely on correlation rather than experimental evidence (Schneider & Wade 1997). In fact, body composition does not vary significantly between eumenorrheic and amenorrheic athletes (Loucks & Horvath 1984).

Proponents of the exercise stress hypothesis theorize that intensive athletic training activates the hypothalamic–pituitary–adrenal axis, which disrupts GnRH pulsatility and hence menstrual function. However, experiments attempting to induce menstrual dysfunction in women have shown that exercise coupled with caloric restriction effects LH suppression, whereas exercise alone has no effect on LH pulsatility (Loucks 2000).

The suppression of reproductive function in women engaged in sports emphasizing leanness may be a neuro-endocrine adaptation to caloric deficit (Warren 1980, Winterer *et al.* 1984). Recent research suggests that the hormone leptin, a protein product of the obesity (ob) gene which is secreted by the adipocyte and which appears to be an independent regulator of metabolic rate (Zhang *et al.* 1994), may be a significant mediator of reproductive function. Leptin levels fluctuate in response to fat stores and energy availability: leptin levels positively correlate with body mass index (BMI) in humans (Macut *et al.* 1998) and are disproportionately lowered in the presence of fasting (Maffei *et al.* 1995). Additionally, the diurnal rhythm of leptin concentration is suppressed in response to low energy intake.

Multiple studies have demonstrated that rodents without an active form of leptin tend to be amenorrheic and infertile (Legradi *et al.* 1997, 1998), and other studies suggest there may be a chronic low leptin level in women below which menstruation does not occur (Kopp *et al.* 1997, Ballauff *et al.* 1999). In fact, low leptin levels have been reported in amenorrheic women when controlling for body fat, and the typical diurnal pattern of leptin concentration in these women is absent (Laughlin & Yen 1997, Weigle *et al.* 1997). Furthermore, leptin receptors have been found on hypothalamic neurons involved in

control of the GnRH pulse generator (Cheung *et al.* 1997); thus leptin may be a critical factor involved in signaling low energy availability to the reproductive axis. Mammals partition energy among five major metabolic activities: cellular maintenance, thermoregulation, locomotion, growth and reproduction (Wade & Schneider 1992), therefore suppression of reproductive function may be a mechanism which allows the body to adapt to a chronic energy deficit.

Pathological eating behavior and negative energy balance are common among women in sports which require the maintenance of very low body weight for enhanced performance or aesthetic appearance (Warren 1983, Rosen *et al.* 1986, Warren & Brooks-Gunn 1989, Brooks-Gunn *et al.* 1988). Both the reproductive and metabolic hormonal profiles of amenorrheic women engaged in these sports closely parallel those of amenorrheic women with eating disorders such as anorexia nervosa (Warren 1983, Schweiger 1991). Nutritional restriction and the associated metabolic adaptations may thus be important causal factors in the menstrual dysfunction of these athletes.

The energy drain theory is inadequate to explain the reproductive dysfunction of women in all athletic disciplines, however. Sports which emphasize strength over leanness, such as swimming and rowing, are not associated with low weight and restrictive eating patterns (Rosen *et al.* 1986, Brooks-Gunn *et al.* 1988, Barr 1991), yet athletes engaged in these sports are vulnerable to menstrual irregularities as well. The endocrine profile of athletes engaged in these sports is characterized by mildly elevated LH levels, elevated LH/FSH ratios and mild hyperandrogenism rather than the hypoestrogenism observed in athletes engaged in sports requiring thinness (Bonen *et al.* 1981, Carli *et al.* 1983, Frisch 1984, Cumming *et al.* 1987, Baker & Demers 1988, Buchanan *et al.* 1988, Constantini & Warren 1995).

Activation of the hypothalamic–pituitary–adrenal axis may occur in this syndrome, resulting in increased levels of androgens, in particular dehydroepiandrosterone sulfate (DHEA-S). Chronically high concentrations of DHEA-S, or the repeated acute elevations of DHEA-S which have been shown to occur in swimmers (Frisch *et al.* 1984, Dulac *et al.* 1986, Rosen *et al.* 1986), may impair follicular development and result in the anovulation or amenorrhea observed in these women. Alternatively, because high levels of androgens positively affect muscle mass and may therefore be advantageous in sports in which power is a major determinant of performance, naturally elevated levels of androgens may be self-selected in these sports (Constantini & Warren 1995). The syndrome observed in these athletes is less common and has been less extensively studied than that observed in athletes engaged in sports which emphasize thinness, and future research is necessary to ascertain whether the hormonal profile of these women is genetically determined or secondary to activation of the adrenal axis.

Clinical consequences

Delayed menarche and altered pubertal progression

Delayed menarche among athletes has been well documented (Zacharias *et al.* 1976, Marker 1979, Frisch *et al.* 1981, Warren *et al.* 1986), particularly among athletes engaged in sports emphasizing low weight (Fig. 1) (Warren *et al.* 1986). Low gonadotropin (LH and FSH) secretion and minimal thelarche (breast development), as defined by Tanner (1962), of premenarchial ballet dancers suggest ballet training during adolescence may prolong the prepubertal state. Progression of pubertal development and onset of menarche in adolescent dancers appear to be related to activity level, with marked pubertal progression and initiation of menses occurring during periods of relative inactivity (Warren 1980). The delay in pubertal progression and menarche may be related to the energy drain typically incurred by these adolescent athletes.

Low leptin levels associated with nutritional insult may play a critical role in the initiation of puberty and onset of menarche. Studies in rats suggest that leptin may regulate the initiation of puberty by suppressing the pro-thyrotropin (TSH) gene at the hypothalamic–pituitary–thyroid axis (Legradi *et al.* 1997, 1998). Evidence of leptin mutations in humans who exhibit TSH suppression and lack of pubertal development (Clement *et al.* 1998) provides further support for a role for leptin in regulating reproductive function.

The prolonged hypogonadism associated with delayed menarche may favor long-bone growth, resulting in the decreased upper to lower body ratio and increased arm span which has been observed in ballet dancers, in particular (Warren 1980). Alternatively, the physical characteristics associated with late maturation may be more suitable for successful athletic performance, and the prevalence of delayed menarche and associated eunuchoidal proportions among female athletes may simply reflect genetic differences (Malina 1983).

Amenorrhea

The gonadotropin pattern in athletes who develop amenorrhea appears to revert to a premenarchial pattern, although LH is more selectively suppressed than FSH. The reversion of secondary amenorrhea observed among ballet dancers during periods of rest (Warren 1980) suggests a relationship between the discontinuation of menses and activity level and provides further support for the energy-drain hypothesis.

Infertility

The incidence of inadequate luteal phase, anovulation and oligomenorrhea is considerably greater in athletes than non-athletes (Pettersen *et al.* 1973, Vollman 1977, Frisch

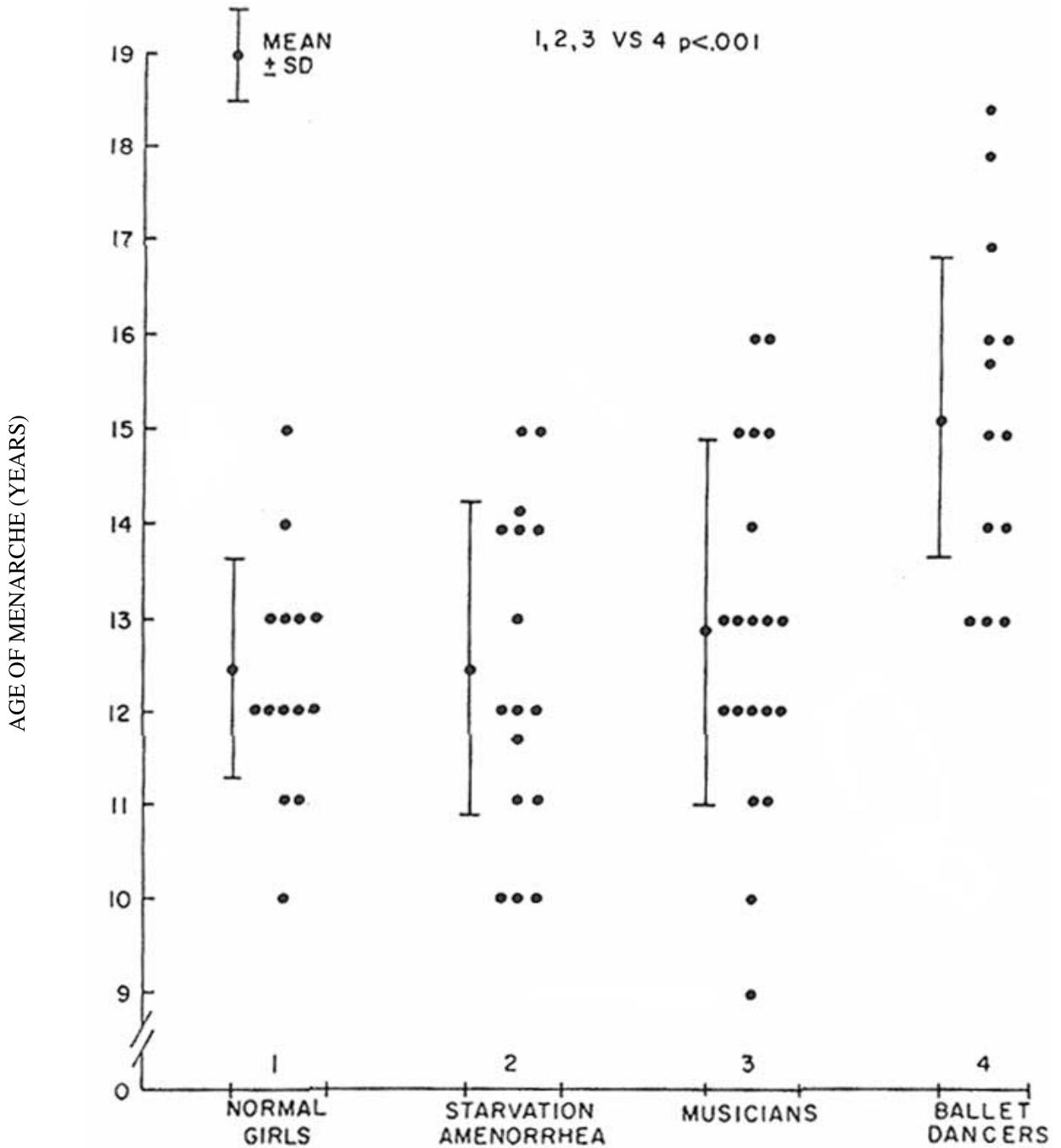


Figure 1 Age of menarche in ballet dancers compared with those in three other groups. From Warren (1980).

et al. 1981, Singh 1981, Hight 1989). The exact incidence of these abnormalities is unknown, however, as many 'eumenorrhic' athletes are actually suffering from hidden menstrual irregularities such as inadequate luteal phase or anovulatory cycles (Shangold *et al.* 1979, Bonen

et al. 1981, Prior *et al.* 1982, Loucks *et al.* 1989). Dale *et al.* (1979) found that only 50% of runners ovulated during a test month compared with 83% of controls. The incidence of infertility associated with these problems may also be greater than suspected.

Table 2 Markers of bone turnover

	Study (n)	Bone		
		Formation	Resorption	Turnover
Model				
Post-menopausal estrogen deficiency	Manolagas & Jilka (1995) (review)	↑	↑	↑
Exercise-induced amenorrhea (runners)	Okano <i>et al.</i> (1995) (8)	↓ (osteocalcin)	NA	?
Exercise-induced amenorrhea (runners)	Zanker & Swaine (1998) (9)	↓ (osteocalcin BAP*)	↓ (deoxypyridinoline)	↓

*Bone-specific alkaline phosphate.

Skeletal problems

Reproductive dysfunction resulting from the GnRH suppression observed in athletes engaged in sports emphasizing leanness has its most profound negative impact on the skeleton. Failure to attain peak bone mass, bone loss and failure of weight-bearing bone to mineralize with stress predispose hypoestrogenic athletes to osteopenia and osteoporosis, and increase their risk of scoliosis and bone fracture. Decreased bone density constitutes the final element of the 'female athlete triad', i.e. eating disorders, amenorrhea and osteoporosis.

Forty-eight percent of skeletal mass is attained during adolescence and accumulation continues into the thirties (Benson *et al.* 1985). Bone mass accretion is compromised in late-maturing girls (Dhuper *et al.* 1990, Frusztajer *et al.* 1990, Warren *et al.* 1991), and low bone mineral density has been consistently reported in athletes with hypoestrogenic amenorrhea (Drinkwater *et al.* 1984, Marcus *et al.* 1985, Frusztajer *et al.* 1990). These athletes generally do not attain peak bone mass and may enter menopause with significantly lower bone density than normal women (Highet 1989).

Injuries commonly result from overuse of bone weakened by osteopenia (Myburgh *et al.* 1990, Warren 1992). Numerous studies have shown a correlation between menstrual irregularities and incidence of scoliosis and stress fractures among athletes (Cann *et al.* 1984, Drinkwater *et al.* 1984, Lindberg *et al.* 1984, Marcus *et al.* 1985, Warren *et al.* 1986, Lloyd *et al.* 1987, Barrow & Saha 1988). In one study, scoliosis was reported in 24% of ballet dancers, much higher than that in the general population; 83% of dancers with scoliosis had delayed menarche, whereas only 54% of dancers without scoliosis reported delayed menarche (Warren *et al.* 1986). The prevalence of stress fractures among dancers has been positively correlated with duration of amenorrhea (Warren *et al.* 1986). Similarly, the prevalence of stress fractures and multiple

stress fractures has been associated with incidence of menstrual irregularities in runners (Barrow & Saha 1988).

Original theories attempting to explain the well-documented association between hypoestrogenic amenorrhea and bone loss focused on the role of estrogen as a mediator of bone resorption (Cann *et al.* 1984, Drinkwater *et al.* 1984, Marcus *et al.* 1985). However, accumulating evidence suggests that metabolic factors associated with nutritional deprivation may be more important in regulating bone activity. Studies of bone turnover in amenorrheic distance runners have shown a pattern of bone remodeling characterized by reduced bone turnover and reduced bone formation (Okano *et al.* 1995, Zanker & Swaine 1998) rather than the increased bone turnover and increased bone resorption typical of hypoestrogenism (Table 2) (Hergenroeder 1995, Manolagas & Jilka 1995). Acute or chronic energy deficit is known to elicit metabolic aberrations including depressed levels of nutritional markers 3,5,3'-tri-iodothyronine (T_3) and insulin-like growth factor (IGF-I) (Grinspoon *et al.* 1996a, Laughlin & Yen 1997). Both T_3 and IGF-I are bone trophic hormones, and their suppression can lead to inadequate bone formation. In fact, estimated energy balance, BMI and serum levels of T_3 and IGF-I correlated positively with serum levels of bone formation markers in the amenorrheic distance runners (Zanker & Swaine 1998). Furthermore, leptin receptors have been found in bone (Bradley *et al.* 1997, Dyson *et al.* 1997), thus depression of leptin levels and suppression of the diurnal leptin rhythm associated with low energy intake may mediate not only reproductive function but also bone accretion. The osteopenia observed in amenorrheic athletes involved in sports emphasizing leanness may therefore be another adaptive response to chronic low energy intake.

Nutritional deprivation in amenorrheic anorexics has been shown to negatively affect attainment of normal skeletal mass (Ward *et al.* 1997). Additionally, restrictive eating habits have been positively correlated with the

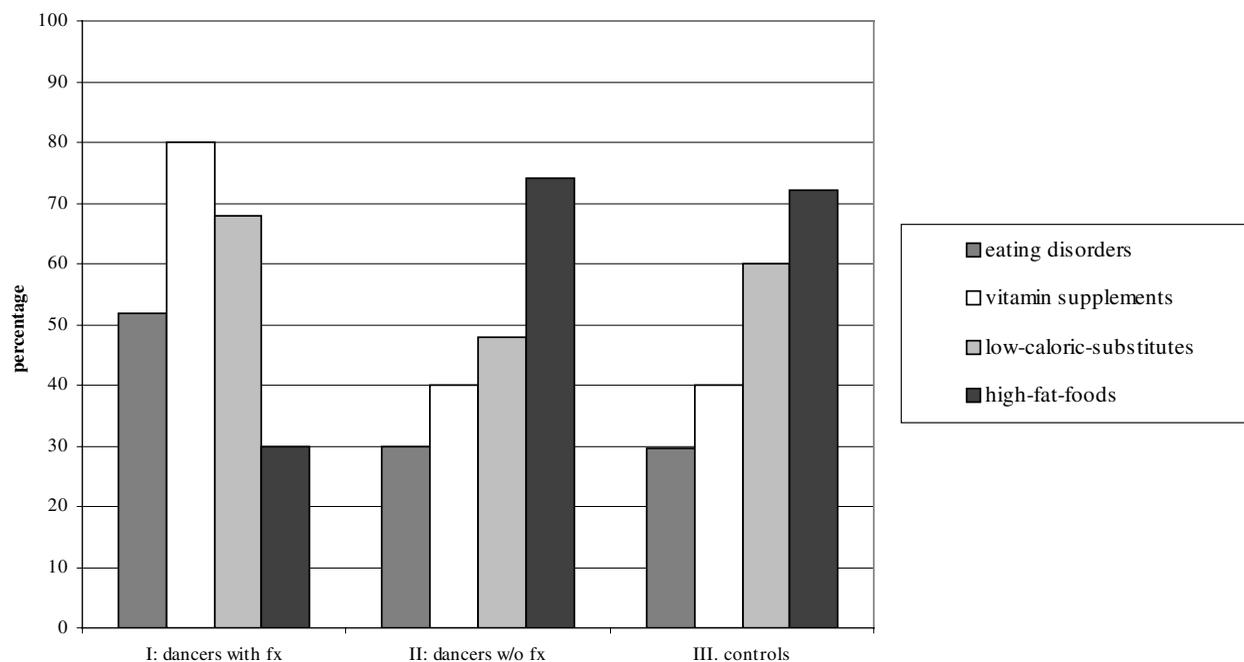


Figure 2 Eating habits of amenorrheic women with and without stress fractures. From Warren *et al.* (1986).

incidence of stress fractures among dancers. In a carefully matched sample of dancers with and without stress fractures, dancers with fractures showed a significantly greater tendency to restrict food intake, manifested by a greater percentage eating less than 85% of the recommended dietary allowance, lower fat intake, higher intake of low-calorie foods and sugar substitutes, and greater incidence of eating disorders (Fig. 2). These patterns emerged irrespective of menstrual abnormalities, which were the same in both groups (Frutzajer *et al.* 1990). Furthermore, it has been suggested that nutritional deprivation and the resulting delay in sexual maturation results in delayed epiphyseal closure of long-bones, which may in turn predispose athletes to scoliosis (Warren 1980).

Weight-bearing exercise has been shown to have a positive impact on bone density of hypoestrogenic postmenopausal women (Notelovitz *et al.* 1991, Karlsson *et al.* 1993, Henderson *et al.* 1995). However, while exercise during a critical adolescent period has been shown to somewhat modulate the negative effects on bone accretion associated with hypoestrogenic amenorrhea, exercise does not sufficiently protect the amenorrheic athlete from bone loss (Kahn *et al.* 1999). The expected increase in bone density of mechanically stressed bone does not occur in amenorrheic dancers and runners (Warren *et al.* 1991, Warren & Holderness 1992).

Diagnosis and treatment

Diagnosis of exercise-associated amenorrhea remains a diagnosis of exclusion. End-organ failure and prolactin-

secreting pituitary tumors should be ruled out. Differentiation between hypoestrogenism and hyperandrogenism can be made via patient history and hormonal evaluation.

Often a weight gain of 1–2 kg or a 10% decrease in exercise load (in either duration or intensity) is sufficient to reverse reproductive dysfunction (Prior & Vigna 1985, Drinkwater *et al.* 1986). Many patients will resist this route, however, fearing weight gain or decreased performance. Nutritional counseling may be advised.

Alternatively, ovulation can be induced with clomiphene or GnRH if pregnancy is desired. Oral contraceptives can be administered to regulate menses of oligomenorrheic athletes.

In cases of hypoestrogenic amenorrhea, diagnosis should include careful screening for nutritional insult. Treatment of the possible underlying nutritional deprivation may both restore menses and stimulate bone accretion. Alternatively, hormonal replacement therapy (HRT) may be prescribed to prevent further bone loss, although dosages given to postmenopausal women (0.625 mg for 25 days with 10 mg medroxyprogesterone on days 16–25, followed by 7 days without therapy) appear to be insufficient to curb bone loss (Emans *et al.* 1990, Hergenroeder 1995, Klibanski *et al.* 1995, Warren 1996). Although results have been inconsistent, recent research indicates that higher dose oral contraceptives may effectively prevent further bone loss, but will not replace bone lost prior to intervention. A summary of treatment of hypothalamic amenorrhea is shown in Table 3. In younger amenorrheic athletes, HRT should be administered only after bone growth is complete.

Table 3 Treatment of amenorrhea

Model	Study	Therapy (n)	BMD		
			Spine	Hip	Total
Hypothalamic amenorrhea (including eating disorders)	Hergenroeder (1995)	Oral contraceptive (5) randomized, 12 months 0.035 mg ethinyl estradiol 0.5–1.0 mg norethindrone	↑	NS	↑
Exercise-induced amenorrhea	Cumming <i>et al.</i> (1987)	HRT (8) observed 24–30 months	↑	↑	—
Exercise-induced amenorrhea	Warren <i>et al.</i> (1986)	HRT (13) randomized, 24 months	NS	NS	NS
Anorexia nervosa	Klibanski <i>et al.</i> (1995)	HRT (22) randomized	NS*	—	—

*Patients with the lowest BMD showed some increase.

Due to the apparent role of metabolic factors in bone accretion, treatment aimed at stimulating osteoblast activity may prove more effective than that aimed at retarding osteoclast activity. Administration of IGF-I to anorexic women has been shown to stimulate a dose-related increase in serum concentrations of bone formation markers (Grinspoon *et al.* 1996b). Further research is necessary to determine the most effective treatment strategy for nutritionally linked bone remodeling imbalance.

As bone preservation depends on both calcium intake and bioavailability (Drinkwater *et al.* 1984, Heaney 1987, Dalsky 1990), promotion of a diet rich in calcium and vitamin D is important. Alternatively, calcium (1500 mg) and vitamin D (400 mg) may be given as daily supplements.

Loss of bone mineral density is directly related to duration of amenorrhea (Gulekli *et al.* 1994, Ward *et al.* 1997, Buchanan *et al.* 1988) and appears to be irreplaceable (Drinkwater *et al.* 1990, Bachrach *et al.* 1991, Jonnavithula *et al.* 1993, Guleki *et al.* 1994). It is therefore crucial to restore menses of amenorrheic athletes as soon as possible so as to minimize bone loss and bone complications resulting from osteopenia and osteoporosis.

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