STRESS INJURY TO BONE IN THE FEMALE ATHLETE

Aurelia Nattiv, MD, and Thomas D. Armsey, Jr, MD

In the last decade, much research has centered around the unique medical concerns of the female athlete. Research in the area of bone health in the athletic woman has reached a heightened level of knowledge. Although the mechanisms underlying the complex interactions of mechanical, hormonal and nutritional factors on bone health have not been fully elucidated, most scientists agree that an evaluation of bone health and stress injury to bone encompasses an interactive model, including mechanical, hormonal, and nutritional environmental factors, as well as genetic predisposition (Fig. 1). In this model, stress injury to bone lies on a continuum, with the normal dynamic processes of bone modeling and remodeling occurring on one end of the continuum, progressing on to bone fatigue and frank fracture. Fracture occurs when the external demands on the specific skeletal site exceeds the micro- and macroarchitectural structural intrinsic properties of bone at that site.

DEFINITION OF STRESS INJURY

The diagnosis of a clinical stress fracture was first introduced by a Prussian surgeon named Breithraupt in 1855,[9] and used to describe the painful, swollen feet of young military recruits subjected to repetitive, submaximal stress. Approximately 42 years later, the advent of roentgenography allowed these classic metatarsal stress fractures to be visual-

From the Division of Family Medicine (AN, TDA), the Department of Orthopaedic Surgery, and the Osteoporosis Center (AN), University of California at Los Angeles, Los Angeles, California

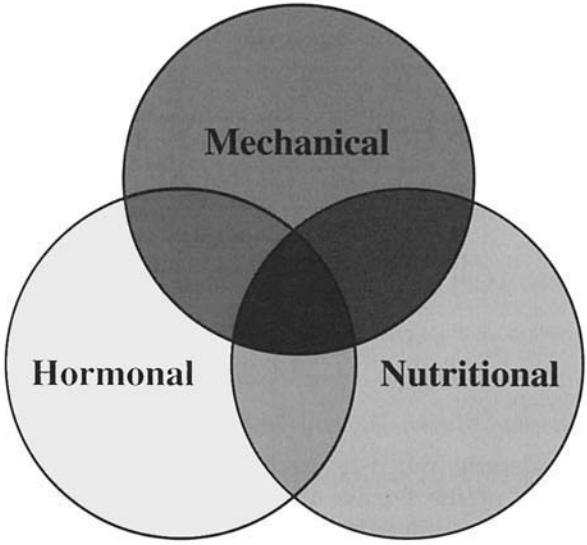

Figure 1. Stress Injury to Bone. The etiology, management, and treatment of stress injury to bone in the female athlete involves an understanding of the predisposing mechanical factors, as well as the hormonal and nutritional milieu of the individual.

ized.[116] Further advances in the understanding and imaging of these overuse injuries has led to the belief that stress injury to bone occurs on a continuum, ranging from normal bone remodeling/repair to frank cortical fractures. Currently, terms such as *bone strain*[79] and *stress reaction*[57] are used to reflect this progression of bone injury toward a frank cortical stress fracture, which is defined as a partial or complete fracture of a bone resulting from its inability to withstand nonviolent stress that is applied in a rhythmic, repeated, subthreshold manner.[80]

OSTEOPOROSIS IN THE FEMALE ATHLETE

A discussion of bone health and injury would not be complete without a discussion of osteoporosis. Osteoporosis is defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.[22] The magnitude of the problem of osteoporosis in the United States and worldwide is great[22, 106] and beyond the scope of this article. Although osteoporosis is known to be a disease often seen in the postmenopausal female, more recent studies have elucidated its presence in young female athletes.[13, 25–27, 76, 88, 89]

The prevalence of osteopenia and osteoporosis in this premenopausal population of female athletes is not known, but the potential

effects and morbidity on future bone health are alarming.[26, 27, 76, 90, 130] Of concern is that there are no treatments to date in the premenopausal female athlete with osteopenia or osteoporosis that have demonstrated a significant increase in bone density. The low bone density that is detected in these young athletic women, therefore, most likely represents irreversible bone loss. Physicians and healthcare providers caring for young female athletes should have a heightened awareness of the risk of premature osteopenia and osteoporosis, especially in the female athlete who presents with stress injury to bone, as well as in those with a history of disordered eating or menstrual dysfunction. An important goal in the evaluation and treatment of an individual with stress injury to bone is to prevent the morbidity of future fractures by appropriate screening and risk factor assessment.

BONE BIOLOGY OVERVIEW

Bone is a specialized dynamic tissue that is continuously renewed by the process of bone remodeling. Remodeling is comprised of cycles of bone resorption (osteoclastic activity) and bone formation (osteoblastic activity) that occurs throughout skeletal life. During growth and adolescence, bone formation is greater than bone resorption, which leads to increases in bone mass until somewhere in the second decade. Although there is some controversy about the age of peak bone mass accrual, most agree that this occurs around ages 25 to 30.[54, 103] After this period, there is an increase in bone resorption compared to bone formation, so that overall bone mass decreases. In women, this decrease is accentuated during the postmenopausal period, secondary to estrogen withdrawal, which markedly increases osteoclastic bone resorption and may lead to osteoporosis. Theoretically, the hypoestrogenic female athlete may be subjected to the same process of accelerated bone loss, which may contribute to premature osteoporosis. In addition, bone formation may be significantly effected in the young athlete due to hormonal and nutritional environmental factors; however, the underlying mechanisms resulting in bone loss in this population are still unclear.

Complex regulation of the cellular events involved in bone remodeling occur intrinsically through local and systemic factors, as well as extrinsically by mechanical forces. During bone formation, mature osteoblasts synthesize the major proteins of the bone matrix, type I collagen and osteocalcin, via the production of growth hormones (transforming growth factor [TGF]-β, bone morphogenetic protein, insulin-derived growth factor [IGF] I and II, platelet-derived growth factor [PDGF], heparin-binding fibroblast growth factor).[45] Systemic hormones, namely 1,25 dihydroxyvitamin D, control the mineralization of this matrix into

new bone. Bone resorption occurs through osteoclastic proton production and release, which demineralizes bone, followed by proteolytic enzymes (β-glucuronidase, β-galactosidase, cathepsin D)[121] that degrade the remaining matrix. This resorption is controlled by a number of systemic hormones (parathyroid hormone, calcitonin, 1,25 dihydroxyvitamin D),[81, 87, 97] as well as local factors (IL-1, TNF, lymphotoxin, thyroid hormones, systemic sex hormones).[86] Of note, it takes 7 to 10 days to complete the osteoclastic resorptive phase whereas new bone formation takes approximately 3 months, creating a window of vulnerability during which bone is most susceptible to injury.[57, 74]

The mechanical forces that regulate bone remodeling exist mainly in two forms: compressive and tensile. The compressive forces are resisted by the mineral component of bone whereas the tensile forces are resisted by the collagen component. This complex interaction of transmitted forces upon the organic/mineral matrix of bone and the resultant adaptive remodeling is expressed in Wolff's law. The bony adaptation is a function of the number of loading cycles, cycle frequency, amount of strain, strain rate, and strain duration per cycle. Bone responds to excess strain by osteonal remodeling (i.e., resorption of circumferential lamellar bone and replacement by dense osteonal bone). Whether adaptation results in strengthening or weakening of the tissue is dependent on a multitude of factors: metabolic state, present level of fitness, biochemical changes, menstrual patterns, age, sex, and ethnicity.[117] Carter and Caler[17] suggest that bone remodeling occurs as a result of the piezoelectric phenomena. This suggests that tension forces create an electropositivity that results in bone resorption by initiating osteoclastic activity. Weakened bone is therefore created, and is susceptible to injury or fracture. Alternatively, compression forces develop an electronegative field that induces bone deposition by osteoblastic activity and strengthens bone. Carter has shown that most cortical stressors are tension in nature and tend to result in microfractures. Cyclic overuse leads to cortical thinning, osteoporosis, and development of a stress fracture if the force is continued.

Subsequently, Frost[32] proposed a new theory of bone biology to help understand the skeletal adaptations that occur with mechanical usage. This paradigm is based on a "mechanostat theory" to explain the structural and density changes of bone that ensue when bone is repeatedly stressed by its mechanical environment (Fig. 2).[32, 43] The mechanostat theory is based on two main premises. First, there exists a minimum strain threshold for modeling (MESm) and another minimum strain threshold for remodeling (MESr). These two thresholds are viewed as "setpoints," between which most normal activity occurs (within the physiologic loading zone depicted in Figure 2). Second is that a "controller" of bone biology (the mechanostat) senses bone strain induced by mechanical usage and compares it to the MESm and MESr

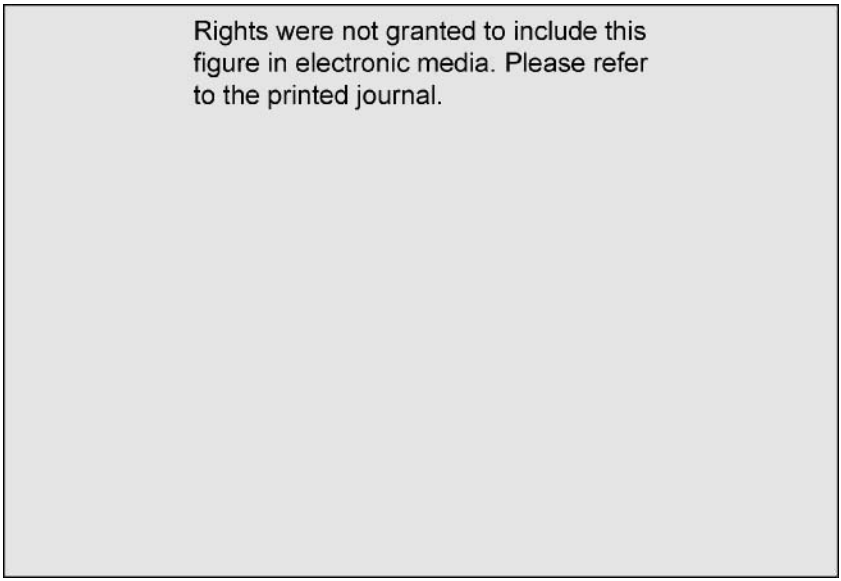

Figure 2. The mechanostat theory, proposed by Frost,[32] helps explain bone adaptations and mass to mechanical and environmental factors. The mechanostat senses bone strains and activates an appropriate adaptive biologic response. Shifts in the minimum effective strain thresholds (or setpoints) for modeling and remodeling (MESm and MESr) may result from changes in hormonal, nutritional, and mechanical, environmental stimuli. (*Adapted from* Martin RB, Burr DB: Structure, Function and Adaptation of Compact Bone. New York, Raven Press, 1989, pp 143–185; with permission.)

thresholds and activates an adaptive cellular response. The mechanostat theory, therefore, helps to bridge the gap between bone adaptations to mechanical stress (exercise) and environmental factors. It allows for multiple risk factors, such as hormonal and nutritional disorders, to reset the MESm and MESr to different levels, therefore constantly changing "normal mechanical usage."[43]

RISK FACTORS FOR STRESS INJURY

The concept that risk factors for stress fractures exist has been extensively researched in the past decade. The outcomes of these studies seem to suggest that stress fractures may be similar to other disease entities, such as cardiovascular disease, in that there are both intrinsic and extrinsic risk factors that predispose individuals to this injury.[83]

Although stress fractures are one of the most common overuse injuries suffered by athletes and other physically active individuals, only a few risk factors have been clearly identified by either experimental or epidemiologic studies. The difficulty in performing such studies lies in the fact that although millions of people worldwide participate in regu-

lar exercise programs, these individuals do not fall under any form of central control, leading to various confounding factors. Many studies have investigated overuse injuries in the military basic training, which provides a unique situation in which large numbers of healthy subjects of similar age perform activities under similar circumstances. These studies have been most helpful in determining prevalence rates (Table 1) because of the known denominator, whereas this has been more difficult in the general population of exercising and athletic individuals. Nevertheless, a number of risk factors for stress injury have been postulated in the athletes. These risk factors, which include female gender, are most likely interrelated and complex. It is likely that genetic, hormonal and nutritional factors, as well as other environmental factors, play a much larger role in the development of stress injury to bone than previously thought.

Table 1. STRESS FRACTURE RATES IN FEMALE AND MALE ATHLETES AND MILITARY TRAINEES

Study (year)	Population	Design	Observation Period	Stress Fracture Rates* (Female/Male)
Bennell (1996)	Track and field athletes	Prospective	12 months	21.7%/20.4%
Bennell (1995)	Track and field athletes	Retrospective	Previous history	41.5%/—
Goldberg (1994)	Collegiate athletes	Retrospective	3 years	2.7%/1.4%
Johnson (1994)	Collegiate athletes	Prospective	2 years	6.9%/2.0%
Jones (1993)	Army trainees	Prospective	8 weeks	12.3%/2.4%
Kadel (1992)	Professional ballet dancers	Retrospective	Previous history	31.5%/—
Ha (1991)	Professional and recreational athletes	Prospective	6 years	48.1%/51.9%
Brunet (1990)	Recreational runners	Retrospective	Previous history	13.2%/8.3%
Cameron (1990)	Competitive runners	Retrospective	Previous history	26.6%/28.0%
Barrow (1988)	Collegiate distance runners	Retrospective	Previous history	37%/—
Brudvig (1983)	Army trainees	Retrospective	8 weeks	3.4%/0.9%
Reinker (1979)	Army trainees	Retrospective	8 weeks	12.0%/2.0%
Protzman (1977)	West Point cadets	Retrospective	8 weeks	10.0%/1.0%

*Because study design and methodology varied, stress fracture rates are reported as percentage of females or males that sustained a stress fracture (based on the total number of athletes or military trainees studied) during the observation period noted.

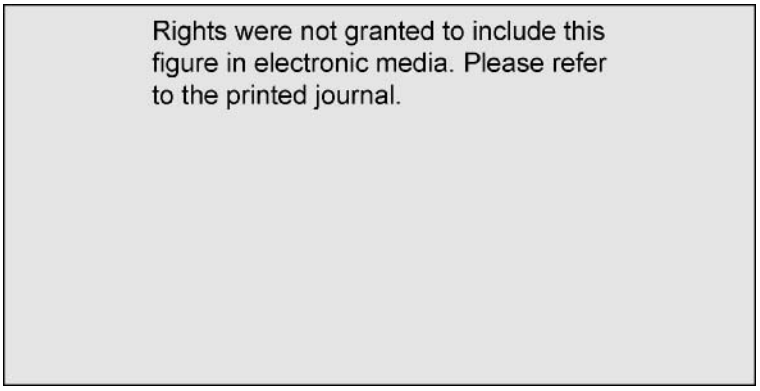

Figure 3. Attainment of a high-peak bone mass is an important preventive strategy for minimizing risk for future fractures. Even with bone loss in later years, the individual with a high-peak bone mass is more likely to avoid a future fracture when compared to the individual with low-peak bone mass. (*Adapted from* Snow-Harter CM: Bone health and prevention of osteoporosis in active and athletic women. Clin Sports Med 13:389–404, 1994.)

Pediatric Bone Health: Low-Peak Bone Mass

Low-peak bone mass has been a postulated risk factor for future fracture. The individual who does not reach her or his optimal peak bone mass, whether it be due to nutritional, hormonal, or other factors, is at increased risk for falling below the presumed fracture threshold later in life (Fig. 3).

Maximizing peak bone mass has been an important preventive strategy for minimizing future risk for significant osteopenia and osteoporotic fractures.[54] Studies of bone growth and development have therefore focused on factors that may be important for optimal skeletal bone maturation.[43, 114, 117] Although the precise age of attainment of peak bone mass is controversial,[54, 103] most bone acquisition occurs during the adolescent growth spurt, with approximately 90% of peak skeletal mass present by age 18.[43, 114, 118] This rate of bone acquisition during skeletal growth is equivalent to an increase in bone density of about 6% to 8% per year,[8] which is approximately two to three times greater than the rates of bone loss in health or disease.

Genetic factors are hypothesized to account for 60% to 80% of peak skeletal mass,[113] with the remainder influenced by environmental factors, specifically calcium nutrition, hormonal status, and weightbearing exercise. Increases in height and weight are also strongly correlated with skeletal mineralization during puberty.[113] Thus, it appears that through optimal lifestyle patterns and preventive health measures, children have the potential to reach a higher peak bone mass and reduce their risk for future fracture.

Gender

Gender differences in bone mineral density (BMD) are apparent at the time of puberty. Peak bone acquisition appears to occur earlier in females (ages 11–14) than in males (ages 13–17) in both lumbar spine and femoral neck, with bone growth declining in females 2 years after menarche.[118] The influence of puberty on skeletal mineralization depends on skeletal site. Trabecular bone (lumbar spine, greater trochanter) appears to be more sensitive to changing hormonal concentrations than cortical bone.[114]

Studies on stress fracture risk, which assess gender differences, fall into two separate categories: those in the military population and those in the athletic population. In the United States military training populations, most studies demonstrate that women sustain disproportionately higher numbers of stress fractures. While undergoing similar training programs as their male counterparts, female recruits have had an increased risk of stress fractures ranging from 1.2 to 10 times that of male recruits.[11, 35, 60, 101, 105, 111]

Whether female athletes are also at increased risk of stress fracture is not entirely certain, although most studies suggest this to be the case. A review of clinical records of patients seen at sports medicine centers have shown that stress fractures in female athletes compared with male athletes make up more of the total injuries.[21, 73] An increase in risk of stress fracture in female athletes ranging from 1.5 to 3.5 times has been reported.[12, 41, 54, 96, 131] Recently, studies by Bennell[5] and Cameron[14] suggest that the discrepancy in results of athletes may be due to only sex-related factors, such as diet, menstrual history, and bone density, and not to gender inherently. There is a need for more prospective studies that carefully assesses risk factors for stress injury in male and female athletes. An overview of reported stress fracture rates in females versus males in selected military and athletic populations is illustrated in Table 1.

The site distribution of stress fractures appears to differ between male and female athletes. Although the tibia is the most common site for stress fractures in both men and women, studies suggest that women develop significantly more femoral,[5] metatarsal,[5, 51, 94] and pelvic[5, 51] stress fractures and fewer fibular stress fractures[5, 51] than men. This site distribution difference is most likely due to multiple factors and not to gender alone, but controlled studies are presently lacking.

Ethnicity

There is a lack of information that assesses stress fracture prevalence in women and men of different ethnicity. The prevalence of osteoporosis

and the incidence of vertebral fractures are significantly lower in African-American than in white adult women and men, but there are limited data on the ethnic differences in bone mass acquisition during adolescence. Although both black and white adolescents achieve increases in BMD in adolescence, Gilsanz and colleagues[40] demonstrated a significant increase in the magnitude of BMD increases during puberty in black adolescents compared with white adolescents, although no difference was noted before puberty. These ethnic changes in bone acquisition were especially noted during a brief period late in pubertal development. These data suggest that hormonal factors and other metabolic variables may be important determinants of racial differences in bone mass in women.[40] More research is needed that examines genetic effects of ethnicity on bone health and susceptibility to injury in the female and male athlete.

Age

Two studies in the military population[11, 35] suggest that increasing age is associated with an increased risk of stress fracture; only one of these studies[11] included women. In this study, the risk of stress fracture increased from 1.27% for 17- to 22-year-old army recruits, to 2.32% of 23 to 28 year olds, and up to 5.01% for 29 to 34 year olds; this trend was seen for both male and female recruits. A recent prospective study[81] in male Israeli military recruits, however, found the risk of stress fracture to be inversely proportional to age, which contradicts the previous studies. There have been no controlled studies to date in male and female athletes participating in similar exercise regimes that have assessed the incidence of stress fractures in individuals of various age groups.

Mechanical Factors

Extrinsic Mechanical Factors

Training Regimen. One of the major extrinsic risk factors for stress fractures includes an acute change in training routine (duration, intensity, frequency). This has been well documented in multiple military studies where a progressively more intense training regimen occurs as basic training continues. The peak incidence in stress fractures during these studies ranges anywhere from the first week to the ninth week in both male and female trainees.[6, 7, 36, 42, 62, 65, 101] This clearly demonstrates that the peak occurrence of stress fractures from one population to another is highly variable and likely to be dependent on the training

regimen used as well as the initial fitness level of the recruits. Another consideration to explain the variability of these results is to recognize the different modalities used to diagnose stress fractures (radiograph versus bone scan versus computed tomography and MR imaging). Symptoms of stress fractures were also documented in a number of these studies and found to vary from 4.5 weeks to 8 to 9 weeks.[41, 47] Although the influence of a change in training as a risk factor may be questioned with the discrepancy of these results, it should be noted that by modifying activities in the third week of basic training to decrease the frequency, intensity, and duration of loading cycles on the lower extremities of military trainees, the risk of stress fractures sustained decreased to 1.6% whereas the unmodified controls' stress fracture rate remained 4.8%.[111] Similar studies in athletes have revealed that modification of the training regimen to include rest periods intermittently with periods of strenuous activity also significantly decreased the stress fracture rates. Therefore, it seems that an acute increase in training activity is highly correlated to the occurrence of stress fractures.

Footwear. Another possible extrinsic risk factor contributing to the occurrence of stress fractures includes footwear. Numerous military studies examined the effect of adjuncting the shock-absorbing capabilities of combat boots with insoles. No difference in stress fracture incidence was found between the adjuncted group and controls.[35] More apropos to the athletic population, a military study examined the effect of wearing different running shoes on the likelihood of sustaining a stress fracture, using price as the measure of shoe quality (>$40, high quality; <$25, low quality). Wearing the high-quality versus low-quality shoe revealed no significant difference in incidence of stress fracture.[35] One factor did appear significant in this study: shoe age. Those wearing new shoes were less likely to suffer a stress fracture than those wearing old shoes.

Fitness Level. Fitness level at the commencement of a training program has also been examined as a potential extrinsic risk factor for stress fractures. This presumption that the less fit individual has a higher likelihood of sustaining a stress fracture during training correlated well with Markey's fatigue theory. Markey[77] suggested that muscle mass may disperse forces that are transmitted to bone and that early fatigue of the muscles (as in unfit individuals) may cause more forces to be transmitted to bone, causing eventual stress fractures. Several military and athletic studies support this suspicion that the most sedentary and least-fit individuals entering a training program are the most likely to suffer stress fractures.[3, 15, 39, 52, 56, 102]

Running Surface/Terrain. Running on hard surfaces may be associated with an increased risk of stress fractures because of the increased mechanical shock introduced to the bone. Alternatively, running on soft

surfaces may hasten muscle fatigue, therefore predisposing athletes to stress fractures according to Markey's theory. Aside from one report by Macera[72] indicating a high risk for women who run primarily on concrete, an effect of running surfaces on stress injury has not been proven. Also, uneven running terrain (up or down hills) has empirically been thought to produce injury to bone; however, after controlling for weekly distance, no difference in stress fracture rates were reported because of the different types of running terrain.[72, 78, 122]

Intrinsic Mechanical Factors

Tibial Bone Width and Area Moments of Inertia. Military and athletic trainees develop forces several times their body weight at the interface between the foot and the ground during running.[75] These forces are transmitted proximally through the kinetic chain. Lanyon et al[64] have shown by strain gauge studies that large compression and tension forces are created in the tibia with walking and running. Therefore, the possibility exists that tibial stress fractures occur when these external forces exceed the tibia's intrinsic resistance strength. Frankel and Burstein,[31] using engineering principles, showed that the compression and bending strength of the tibia are related to the cross-sectional area moment of inertia (proportional to the square of the radius and the fourth power of the radius of the tibia, respectively). Therefore, the wider tibias in the mediolateral plane should have significantly greater resistance to these transmitted forces, and narrower cross-sectional areas should exhibit less resistance. In other words, the larger cross-sectional area allows the forces to be transmitted over a greater unit area. In a study of 295 male military recruits, Giladi[37] found that the 31% of recruits who sustained femoral, tibial, or foot stress fractures possessed narrower mediolateral tibial widths than those recruits without stress fractures during identical training. Because bone size throughout the skeleton is proportional, narrow tibial width may provide an indicator of biomechanically weaker skeletal structures that are more likely to sustain a stress injury to bone. The statistical correlation between tibial bone width (area moment of inertia) and the incidence of stress fractures is the first physical parameter of the bone to be identified as a risk factor.

Although Giladi studied only males, a previous study by Miller and Purkey[84] found that women have relatively narrower bones than men. This may help explain why the incidence of stress fractures is higher in women than men when exposed to identical training regimens.

Research in the University of California, Los Angeles lab has shown that area moments of inertia of the tibia, measured at the most narrow tibial diameter by dual-energy x-ray absorptiometry (DEXA), was correlated highly to digitized, cross-sectional measurements from the correspond-

ing region.[91] This information may be of significant clinical relevance in determination of female athletes at risk for stress injury to bone.

External Rotation of the Hip. Another intrinsic risk factor for the development of stress fractures may be the degree of external rotation at the hip joint. Giladi[38] found that male recruits with greater passive external rotation of the hip (>60 degrees) had a higher incidence of tibial stress fractures than those with less external rotation. These results correlated only with tibial stress fractures in male recruits.

Hormonal Factors: Effects on Bone Health

Delayed Menarche

There is a paucity of information regarding the long-term effects of exercise-associated delayed menarche on bone. There are a few studies, however, that implicate osteopenia, stress fractures, and scoliosis as potential complications of delayed menarche. Scoliosis and stress fractures have been observed in female ballet dancers with delayed menarche,[123] and female track and field athletes with a history of stress fractures have been found to be significantly older at menarche.[4] Hypoestrogenic primary amenorrhea of varying origin has also been associated with significant osteopenia in other studies of nonathletic women.[120] More research is needed to assess the effect of delayed menarche on bone.

Hypothalamic Hypoestrogenic Amenorrhea

It was not until the mid-1980s, that scientists linked a decrease in BMD of the lumbar vertebrae in premenopausal athletes with amenorrhea.[26, 67, 76, 92, 124] In the early 1990s it was demonstrated that this bone loss was not only limited to the lumbar spine in the amenorrheic and oligomenorrheic athlete, but was also noted in the proximal femur and femoral mid shaft, as well as the whole body,[88] with menstrual history being a significant predictor for BMD at these sites.[25, 89]

Site-specific increases in bone density have been demonstrated in athletes with menstrual dysfunction involved in higher-impact sports at specific skeletal sites, suggesting that a threshold of mechanical loading may exist that partially offset the adverse skeletal effects of estrogen deprivation on bone.[76, 109, 114, 129] These findings support the mechanostat theory, proposed by Frost,[32] where high mechanical loads serve to lower the physiologic set points for bone modeling and remodeling and estrogen deprivation serves to increase the set points. In a low estrogen environment, such as that seen in the amenorrheic athlete, higher me-

chanical loads are then necessary to increase bone mass. The magnitude of the forces on bone seem to result in a greater stimulus to bone than do lower loads of greater frequency.

Much of the data linking hormonal and nutritional abnormalities with stress fractures in the female athlete is derived from retrospective studies. Myburgh found that athletes (participating in running and aerobics) with stress fractures had lower bone density, lower calcium intake, current menstrual irregularity, and lower oral contraceptive use, with no increased risk of stress fractures noted in those with a family history of osteoporosis.[89] Others have also shown that female runners with a stress fracture history are more likely to have a history of oligomenorrhea or amenorrhea,[2, 4, 59, 69, 76] and female ballet dancers with a stress fracture history have had a significantly longer duration of amenorrhea and a heavier training schedule.[59]

Cann[13] noted that bone loss resulting from athletic amenorrhea of longer duration (>3 years) may not be entirely reversible. Evidence exists that some bone may be regained if the athlete resumes normal menses,[27, 68] although the amount of bone gain may be limited. The increase in bone mass may occur, however, before the return of normal menses, especially if there is associated weight gain.[58]

There are no prospective published longitudinal studies to date that demonstrate an increase in BMD with exogenous estrogen in the young athlete with hypoestrogenic amenorrhea and associated bone loss. Preliminary studies following women with hypothalamic amenorrhea for 2 years on postmenopausal doses of premarin and provera have shown no difference in treated versus nontreated women.[125] Only those women who gained weight demonstrated an increase in BMD.

Ovulatory Disturbances

Although most scientists agree that the hormonal culprit contributing to loss of BMD in athletes is primarily a low estrogen environment, others postulate that low progesterone levels in the young athletic women is associated with bone loss.[100] Prior and colleagues[100] postulate that many young athletic women with ovulatory disturbances have low progesterone levels, and that it is the low progesterone levels that are associated with bone loss in the lumbar spine.

In a randomized, double-blind, placebo-controlled trial, Prior and colleagues[99] administered cyclic medroxyprogesterone treatment for 1 year in young (ages 21–45 years old) premenopausal women with a history of amenorrhea or ovulatory disturbances and documented low progesterone levels. There were small numbers in each group, however, and there was no known decrease in fracture noted. There is need for

further research assessing the effects of medroxyprogesterone on bone health before this treatment regimen is recommended in the young athlete with low BMD.

The effects of luteal-phase dysfunction on bone are not entirely known at this time. What is known is that athletes with regular menses and normal cycle lengths may have ovulatory disturbances.[100] It may be that the negative effects of ovulatory disturbances (such as luteal-phase dysfunction) on bone occur, but to a lesser degree than in the athlete with hypoestrogenic amenorrhea. A recent study[127] suggested that lower estrogen levels, especially during the early follicular phase, is associated with lower whole-body calcium per kilogram of soft lean tissue, (measured by DEXA) and lower spinal BMD. This study does not support Priors findings that lower progesterone levels during the luteal phase are associated with a decreased lumbar spine BMD. Further studies are needed to assess the effects of ovulatory disturbances on bone health and risk for stress injury in athletes with normal cycle lengths.

Oral Contraceptive Pills

Although oral contraceptive pills (OCP) have not been shown, in longitudinal prospective studies, to significantly increase BMD in the athlete with a history of hypoestrogenic amenorrhea and associated bone loss, there have been numerous studies assessing stress fracture risk, mostly in runners, that implicate a protective effect in those athletes with a history of oral contraceptive pill use.[2, 4, 69, 76] These studies have found an association with stress fracture history and less use of OCP in female athletes. It is possible that estrogen may be improving the bone "quality" and microarchitecture, and reducing risk of fracture without significant effect on BMD. In young anorectic patients with OCP exposure, BMD of the lumbar spine was higher compared with young anorectic patients not on OCP,[112] with no protective effect noted in the femoral neck.

There has been one pilot study suggesting a beneficial effect of OCP on spine BMD in young women with hypothalamic amenorrhea (compared to controls) followed for 1 year;[46] however, the numbers were small in each group, and the control group included women who received progesterone monthly. Longitudinal studies are clearly needed to evaluate the efficacy of OCP in the young amenorrheic athlete.

Testosterone

Recent studies in male endurance athletes have found that excessive exercise may result in negative effects on bone.[49, 115] In one study, male long-distance runners were found to have reduced bone mineral content in the lumbar spine, proximal femur, distal forearm, and total body

compared with nonrunner controls, as well as a higher bone turnover;[49] however, no correlation was noted with testosterone levels or other sex hormones. Other studies[126] have shown that reduced serum testosterone and prolactin levels have been noted in male distance runners, but BMD was not assessed. Adult men with a history of delayed puberty have been found to have decreased radial and spinal BMD, suggesting that the time of puberty is important in determining peak BMD in men.[29] These findings in the male athlete may parallel those in the female athlete, and may involve similar, as yet unknown, mechanisms.

Nutritional Factors: Effects on Bone Health

Calcium Effects

One of the most important preventive interventions contributing to optimal bone health in the child and young adult is adequate calcium nutrition. Bone mineral status of children ages 2 to 16 years old has been found to be positively associated with dietary calcium intake.[18] Calcium supplementation was found to enhance the rate of increase in BMD of the radius, femoral neck, and spine in prepubertal white children (boys and girls) in a 3-year, double-blind, placebo-controlled trial,[54] although no significant difference in BMD was noted in puberty or postpuberty, suggesting that hormonal influences on bone during puberty may overshadow the influence of calcium intake. Lloyd and colleagues[71] have noted an increase in BMD of the lumbar spine and total body in adolescent white girls with calcium supplementation.

Calcium supplementation may also be beneficial in the postmenopausal women. Supplementation of 1000 mg of calcium per day significantly slowed axial and appendicular bone loss in normal postmenopausal women,[104] and has been found to be most effective in postmenopausal women who are greater than 5 years after menopause.[24]

Studies on the effects of dietary calcium in the athletic population have shown that a positive linear correlation exists with dietary calcium and spinal trabecular bone density in amenorrheic and eumenorrheic elite female athletes (ballet dancers, rowers, and runners) in their 20s.[129] Myburgh and colleagues[89] found that athletes with stress fractures had lower intakes of calcium compared to athletes without stress fractures. It may be that dietary calcium and physical activity interact to influence BMD. Although more controlled studies are needed to assess the effects of calcium supplementation on bone health in the athletic setting, the authors suggest following the National Institutes of Health (NIH) guidelines for calcium needs by age group,[73] with the added recommendation of 1500 mg/day recommended in the athlete with a history of oligomenorrhea or amenorrhea.

Vitamin D Genetics

The skeletal effects of vitamin D include stimulation of osteoblasts, increasing calcium transport, decreasing parathyroid hormone (PTH), and potentiating androgen conversion to estrone, as well as other effects that contribute to bone health. Many of these metabolic functions are postulated to be mediated by vitamin D receptors present in the nucleus of many target cells.

Recent advances in osteoporosis research have focused on the strong genetic influence of bone density and evidence that a vitamin D receptor gene allele may predict differences in BMD that may account for some of the genetic variability on BMD in healthy women.[28, 30, 50, 85] These twin studies have demonstrated that the genotype associated with lower BMD was overrepresented in postmenopausal women with BMD over two standard deviations below the mean values for young normal women.[85] Support for an association between low BMD of the femoral neck and lumbar spine and certain genotypes has also been demonstrated in racially mixed, premenopausal women, suggesting that this genotype may limit peak BMD and that racial differences in BMD may be independent of the gene.[30] Individuals with specific haplotypes have been found to be more prone to fractures,[20] although larger epidemiologic studies are needed. Preliminary data following women in early and late menopause for 2 years with the susceptible allele suggest that calcium supplementation may be beneficial in increasing BMD at the femoral neck.[61]

Although the research regarding the role of vitamin D receptor alleles and risk for osteoporosis are controversial and recently questioned, recent studies support the use of vitamin D supplementation in fracture prevention in certain populations of postmenopausal women. Supplementation with vitamin D3 (cholecalciferol) 800 IU/day and calcium 1200 mg/day for 18 months reduced the risk of hip fractures by 43% and other nonvertebral fractures by 32% in elderly ambulatory women, and resulted in an increase in proximal femur BMD.[19]

Higher doses of vitamin D in the form of synthetic 1,25 dihydroxyvitamin D3 (calcitriol) have been used in the treatment of postmenopausal osteoporosis,[34, 119] and has been associated with increases in spine BMD and total body calcium and a decrease in fracture rates by some.[119] These higher doses of vitamin D need careful monitoring as hypercalcemia and hypercalciuria are potential complications. Lowering the dose of supplemental calcium is often recommended to avoid these potential adverse effects. Japanese studies using calcitriol have been promising, revealing a decrease in incidence of vertebral fractures in Japanese women,[95] even in the absence of significant effects on bone density. These results suggest a positive effect on bone microarchitecture that may not be measurable with standard techniques for measuring BMD.

Further studies are needed, however, using vitamin D or vitamin D analogues in the premenopausal population to assess effects on bone health and prevention of fractures.

Disordered Eating and Inadequate Calories

Disordered eating patterns and energy deficit states, not uncommon in the athletic setting, can lead to profound bone loss and place young athletes at risk for stress injury to bone. Disordered eating, amenorrhea, and osteoporosis are often interrelated in the young female athlete, and referred to as the *female athlete triad*.[90, 130]

Retrospective analysis assessing risk factors for stress fractures have demonstrated that young adult female track and field athletes with a history of stress fractures scored higher on the EAT-40 test and were more likely to engage in restrictive eating patterns and dieting.[4] Young female ballet dancers with a stress fracture history were similarly found to have a higher incidence of disordered eating behaviors.[33]

Nelson and colleagues[92] found that amenorrheic athletes with lower lumbar spine BMD had lower daily energy intakes. Inadequate caloric intake relative to the energy expenditure through exercise, a relative "energy drain,"[70] has been implicated as a mechanism by which intense athletic training predisposes young women to menstrual dysfunction (characterized by a decrease in gonadotropin-releasing hormone, low levels of gonadotropins, and secondary reduction of estrogen and progesterone) and potential detrimental effects on bone.

The majority of studies linking disordered eating to low BMD have been in young female athletes who are also underweight and with significant energy deficit. There are less data on the effects of bulimia nervosa on bone. BMD of the lumbar spine and radius in female patients with normal weight bulimia nervosa have been found to be normal in most studies,[16, 23] but below normal in those with anorexia.[16, 23] There have been fewer reported fractures in bulimic versus anorexic patients.[16] More research on the effects of bulimia nervosa on bone is needed.

Anorexia Nervosa

The effects of anorexia nervosa on bone may be profound, and little evidence exists that this loss is reversible. Several studies have demonstrated a significant reduction in BMD in women[107, 108] as well as adolescent girls[1] with anorexia nervosa, with nearly 75% of adolescent anorectic girls having BMD of more than 2 standard deviations below the normal value for age.[1] Body mass index was found to be an important predictor of reduced BMD in adolescents[1] as well as adults.[112]

Anorexic patients with primary amenorrhea and illness of earlier onset have been found to have greater deficits in lumbar spine and

femoral neck BMD. These deficits are hypothesized to be more likely the result of bone loss than low peak bone density, although both mechanisms probably contribute,[112] especially in the adolescent female during her years of growth and development.

A cross-sectional, long-term, follow-up study (11.7 years) found that anorectic patients with a good disease outcome had significantly less reduction of lumbar and radial BMD than those with a poor disease outcome, with relative estrogen exposure (for lumbar spine) and years of anorexia (for radial BMD) being the best predictors of BMD.[48] This reduction in BMD in anorectic individuals places them at an increased risk for fractures,[107] especially in those women who overexercise as an additional means to keep thin. Vigorous exercise in anorectic women, however, has been shown to increase BMD at the femoral neck (compared to sedentary anorectic women), but not in the lumbar spine.[112] Oral contraceptive use in anorectic women has been found to be protective for lumbar spine, but not proximal femur,[112] suggesting that the spine may be more sensitive to the effects of estrogen than the femur. Others have found that oral contraceptive use in the presence of persistently low body weight (<20% ideal) is of limited benefit for BMD and apposition.[63]

Other Risk Factors for Stress Injury

Other possible risk factors for stress injury that have not been well documented in the female athlete, but are known risk factors for osteoporosis in adults, include smoking, excessive alcohol, immobilization, certain medications (glucocorticoids, excess thyroid medication, certain anticonvulsant and antipsychotic medication, and chemotherapy), and some underlying metabolic diseases. A thin physique and low body weight have been previously mentioned to be independent risk factors for low bone mass in the adolescent as well as postmenopausal female.

Diagnosis

The diagnosis of stress injury to bone is made by a careful history, and a physical exam, and is confirmed by appropriate radiologic studies, as outlined in the article by Maitra and Johnson. Of additional concern, however, in the diagnostic workup is the evaluation of osteopenia and osteoporosis in the female athlete with hormonal and nutritional risk factors for stress injuries.

BONE DENSITY ASSESSMENT

There is no consensus as yet regarding guidelines for bone density assessment for young athletes with hypothalamic hypoestrogenic amen-

orrhea. Bone density assessment should be considered in individuals with prolonged amenorrhea or oligomenorrhea (>6–12 months), disordered eating and low weights, repeated stress fractures, and individuals with additional risk factors, as well as individuals hesitant to undergo treatment or implement preventive strategies. If specific treatments are to be instituted, a baseline BMD may be helpful to monitor effectiveness of the treatment. Many at-risk female athletes also tend to become more compliant after receiving a personal BMD assessment. DEXA is presently the state-of-the-art method for assessing bone density. Given the precision error of BMD assessment of approximately 1% to 2% by DEXA (at research or major institutions), repeating BMD before 1 year may not be beneficial. In the at-risk individual receiving treatment for low BMD, reassessment at 1 to 2 years in the initial period of treatment may prove beneficial.

If bone density loss appears to be out of proportion to the individuals history and risk factor assessment, a metabolic workup should be considered. Possible laboratory work up may include a chemistry panel to assess alkaline phosphatase, calcium, phosphorus and creatinine, a complete blood count, thyroid stimulating hormone, parathyroid hormone, and a vitamin D 25-OH if indicated. Serum and urinary markers for bone formation and resorption may also be beneficial in some circumstances. Serum osteocalcin and bone alkaline phosphatase measure bone formation, where urinary pyridinium crosslinks and N-telopeptide are markers for increased bone turnover or resorption. Further tests are needed if the patient is amenorrheic, oligomenorrheic, or has disordered patterns of eating and has not had a diagnostic workup.

Prevention of Bone Injury

Health care providers must realize that much of the treatment of stress injury to bone and true fracture lies in prevention, and is based on understanding of the complex interactions between environmental factors and genetics. Through a better understanding of how mechanical, hormonal, and nutritional factors contribute to bone quality and BMD, optimal bone health and a reduction in fracture prevalence can be promoted.

Maximizing Peak Bone Mass/Prevention of Loss

Although attainment of peak bone mass is largely determined by genetics, a significant impact may be made through optimizing lifestyle factors, including adequate calcium, caloric intake, weight, and participation in regular weightbearing exercise during adolescent and adult years. Excessive exercise to the point of hypothalamic dysfunction and subsequent menstrual dysfunction, as well as other factors known to

have a negative effect on bone, such as smoking, should be avoided. Maintenance of reproductive hormone balance is important throughout growth and development, as well as during adulthood.

Screening and counseling patients of all ages, including high-risk groups, such as female athletes with menstrual dysfunction or disordered eating, is imperative in the prevention of stress injury. Physicians need to schedule time during the preparticipation physical examination for screening young athletes, especially those at risk. Athletes with stress fractures should be assessed for risk factors for osteoporosis and counseled accordingly.

Adherence to Sound Principles of Training

Athletes need to learn the principles of a healthy training program and importance of avoidance of abrupt changes in training intensity, frequency, and duration. Physicians, trainers, parents, and coaches need to increase their awareness of environmental and biomechanical factors with a focus on injury prevention.

Treatment

Exercise intensity, mechanical factors, weight, stress, disordered eating, inadequate calcium or caloric intake, menstrual dysfunction, and other factors that may be contributing to suboptimal bone health need to be addressed and modified in the prevention and treatment of osteoporosis as well as bone injury. In those with hypothalamic hypoestrogenic amenorrhea and bone loss, resumption of menses naturally is superior to exogenous estrogen therapy; however, exogenous therapy is often necessary early on whereas other factors, such as weight, nutritional patterns, and exercise intensity, are addressed and optimized.

Correction of Mechanical Factors

Attention to training regimens, footwear, terrain, and other biomechanical and mechanical factors that may have contributed to stress injury need to be attended to and modified accordingly. The athlete's coach and members of the athlete's healthcare team are often integral participants in the athlete's treatment program.

Hormone Replacement Therapy

No longitudinal data exist that postmenopausal doses of premarin and provera (which are much lower doses of estrogen and progesterone

than OCP) leads to gain of bone density or prevention of fractures in young women with hypoestrogenic amenorrhea or oligomenorrhea; however, until more is known about alternative treatment strategies, hormone replacement therapy in the form of cyclic premarin and provera or OCP may provide some benefit in maintenance of BMD or improvement in bone quality.

Because numerous studies suggest a protective effect of OCP on bone, it may be more prudent to use OCP as opposed to postmenopausal doses of premarin and provera; however longitudinal prospective studies are lacking regarding the effectiveness of this therapy. There may exist a dose-related phenomenon in the premenopausal athlete, where higher doses are needed to prevent bone loss, although more evidence is needed to support this hypothesis. Estrogen replacement therapy is an alternative treatment for young women with low BMD and athletic amenorrhea while correction or modification of lifestyle patterns are being addressed.

There are few controlled longitudinal studies demonstrating positive effects of progesterone alone on bone in individuals with athletic amenorrhea and oligomenorrhea. Although this is one alternative, estrogen replacement is probably preferable.

Testosterone

There are a lack of data in treatment of men with low BMD. Male long-distance runners or other endurance athletes with recurrent stress fractures may warrant further workup and BMD assessment, especially if they have risk factors for osteoporosis. If low BMD is observed, testosterone levels may be helpful in the work-up, although there are a lack of data to support testosterone treatment at this time. More research is needed in the area of nutritional and hormonal factors on bone integrity in the male athlete.

Nutritional Therapy/Body Composition

Sources of dietary calcium should be discussed with patients, and a total calcium intake of 1500 mg/day is recommended for young athletes with menstrual dysfunction. The new NIH guidelines for calcium[93] should be reviewed for optimal calcium intake in various age groups for women and men. Calcium supplements should be recommended if these requirements are not being met. Calcium supplements should be taken at different times throughout the day to enhance absorption.

Optimal vitamin D should be encouraged in the prevention and treatment of osteoporosis. Doses of 400 to 800 IU/day should be ade-

quate for most individuals, although select groups may benefit from higher doses. Many multivitamins provide 400 IU per day of vitamin D. Calcium-vitamin D combination tablets can be used to provide additional vitamin D. The role of vitamin D receptor alleles in predicting BMD and preventing and treating osteoporosis is in its infancy. More research is needed regarding the clinical applications of its use in screening high-risk individuals.

Adequate caloric intake is imperative, especially in athletes with higher energy expenditures. The "energy drain" that may occur in some athletes with hypoestrogenic amenorrhea and disordered eating[69] needs to be reversed to result in a positive energy balance to foster normal reproductive hormone function and minimize the negative effects on bone. Small, frequent meals should be encouraged. Nutritional counseling is helpful in situations where energy intake is not being adequately met or with disordered eating patterns (in conjunction with psychological counseling).

Role of Other Medications

In the postmenopausal woman there are more options for the treatment of known osteoporosis. With recent advances in the medical treatment for osteoporosis, a gain of bone density is now possible in addition to a decrease in risk for future fracture. Currently, estrogen, calcitonin, and the bisphosphonates are the most common medications used for the treatment of postmenopausal osteoporosis; these are all antiresorptive medications. Estrogen has been shown to decrease fracture risk significantly in the forearm, hip, and spine. Alendronate (fosamax), a recently approved bisphosphonate for the postmenopausal female, has been shown to increase BMD by 4% to 6% per year and decrease risk of future fracture.[66] Calcitonin has been shown to increase BMD in the spine, but it is not yet clear if there is a reduction in fracture risk.

Unfortunately, calcitonin and the bisphosphonates have not been studied extensively in premenopausal women, and are not approved for the treatment of premenopausal osteopenia and osteoporosis at this time. The bisphosphonates in particular should be used with caution in women of childbearing age. The half-life of alendronate, for example, is very long (several years) and has not been adequately studied in the premenopausal female at this time. Therefore, the bisphosphonates should probably not be used in the premenopausal female athlete who wishes to bear children until further studied.

Hormone replacement therapy, calcium, and vitamin D are the medications of choice at this time in the premenopausal female athlete, in conjunction with regular weightbearing exercise and weights for improving muscle mass. Correction of underlying medical problems,

such as disordered eating, amenorrhea, low body fat and weight, and other underlying medical problems, need to be addressed.

SUMMARY

Stress injury to bone exists on a continuum, involving mechanical as well as hormonal and nutritional factors. Risk factors for stress injury include genetics, female gender, white ethnicity, low body weight, lack of weightbearing exercise, intrinsic and extrinsic mechanical factors, amenorrhea, oligoamenorrhea, inadequate calcium and caloric intake, and disordered eating.

Prevention of stress injury to bone involves maximizing peak bone mass in the pediatric, adolescent, and young adult age groups. Maintaining adequate calcium nutrition and caloric intake, exercise and hormonal balance are important preventive measures in the adult years for optimizing skeletal integrity and preventing fractures.

There are no prospective longitudinal studies to date that demonstrate a treatment that will increase bone density in female athletes with hypothalamic hypoestrogenic amenorrhea or disordered eating that have low bone density. Advances in genetic research show promise for future preventive and treatment strategies. More research is needed in this area to determine other factors that may be contributing to bone loss in these individuals, as well as to assess other treatment options leading to improvements in bone density and integrity.

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Address reprint requests to
Aurelia Nattiv, MD
University of California at Los Angeles
Division of Family Medicine
Room 50-071 Center for Health Sciences
10833 Le Conte Avenue
Los Angeles, CA 90095–1683