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Bone

Determinants of Stress Fracture Risk in United States Military Academy Cadets

Felicia Cosman [1,2], Jamie Ruffing [1], Marsha Zion [1], John Uhorchak [3], Stuart Ralston[4],

Sue Tendy[3], Fiona E A McGuigan[6], Robert Lindsay [1,2] , Jeri Nieves [1,5]

[1] Helen Hayes Hospital, West Haverstraw, New York 10993

[2] Department of Medicine, Columbia University, New York, NY 10032

[3] United States Military Academy, West Point, New York

[4] Molecular Medicine Centre, University of Edinburgh

[5] Department of Epidemiology, Columbia University,New York, NY 10032

[6]Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences

Malmo, Lund University, Malmo, Sweden

 Address Correspondence to:

Dr. Felicia Cosman

Regional Bone Center, Helen Hayes Hospital, West Haverstraw, New York 10993

ABSTRACT:

Background: Prior studies have identified some risk factors for stress fracture in athletes and military recruits.

Objective: To determine whether historical factors, physical measures, biochemical variables of skeletal metabolism, genetic factors, bone density (BMD) and bone size could predict risk of stress fracture over 4 years in physically fit cadets at the US Military Academy (USMA).

Methods: Baseline surveys, assessments of height, weight, scores on the Army Physical Fitness Test, and peripheral BMD were obtained in all cadets (755 men, 136 women), and central BMD in a subset. Blood samples were analyzed for variables of calcium homeostasis, bone turnover, and selected hormones and genetic factors. Stress fractures were adjudicated by review of orthopedic notes and imaging reports.

Results: 5.7% of male and 19.1% of female cadets had at least 1 stress fracture (58% metatarsal and 29% tibial), most within 3 months of entry to USMA. In males, risk of stress fracture was higher in those who exercised < 7 h per week during the prior year (RR 2.31; CI 1.29,4.12), and in those with smaller tibial cortical area (RR 1.12; CI 1.03,1.23), lower tibial bone mineral content (RR 1.11; CI 1.03,1.20) and smaller femoral neck diameter (RR 1.35, CI 1.01, 1.81). In women, higher stress fracture risk was seen in those with shorter time since menarche (RR 1.44 per year; CI 1.19, 1.73) and smaller femoral neck diameter (RR 1.16; CI 1.01, 1.33.).

Conclusion: Although prior physical training in men, length of prior estrogen exposure in women and leg bone dimensions in both genders played a role, the maximum variance explained by all of these factors was below 10%. We conclude these factors play a minor role in the development of stress fractures in physically fit USMA cadets.

INTRODUCTION

Stress fractures are mechanical loading injuries, which result from an imbalance between microdamage and bone remodeling and repair [1-2]. Stress fractures are common in athletes, dancers and military recruits [3-12], with incidence in the military ranging from 1–5% of males to 2–21% of females [5-10] and an estimated cost of $34,000 per soldier in the US [13]. Risk factors for stress fractures can be categorized as extrinsic or intrinsic, with only some modifiable [14-17]. Extrinsic factors include type of physical activity, prior training regimens, footwear and environment [3,18-20]. Environmental factors, such as running surface (treadmill vs. concrete) [3,21], techniques used for certain activities (bending legs during landing from a jump) [22-23] and quality of footwear can also contribute to the development of stress fracture [3]. Most athletes can identify a change in their training regimen as a precipitant to the development of a stress fracture, with sudden changes more likely to produce stress fractures compared with gradual changes in training [3]. Length of marching is a key determinant of stress fracture risk in the military and reducing march length has been shown to decrease stress fracture risk significantly [24].

Various intrinsic factors have also been reported to be associated with an increase in stress fracture risk. Females are at much higher risk than males [9], [25-31]. Women with the female athlete triad (oligomenorrhea or amenorrhea, osteoporosis and eating disorder with energy deficit) are at particularly high risk [15,32-34]. Disordered eating alone may reduce skeletal repair efficiency and increase stress fracture risk [35]. Bigger bones [36-38] and bigger muscles, particularly calf and thigh, appear to be protective [39]. Other potentially important skeletal features include leg-length discrepancy, degree of external hip rotation and foot shape [14,23,37,40-41]. In prior studies of military recruits, as in athletes, higher fitness levels are consistently associated with reduced stress fracture risk [3,8,28, 34, 42-43].

Several prior studies have shown an inverse relationship between bone density and stress fracture risk [7, 23, 33, 34, 44-45]. Valimaki studied a comprehensive list of endocrine factors possibly associated with stress fracture risk in male military recruits [43]. The only positive finding was a 60% higher median PTH level in those with fracture. In that

study, vitamin D and sex steroid levels did not differentiate fracture cases from others. In contrast, in young Finnish men, serum 25(OH)D levels were related to the incidence of stress fracture [46]. It is unclear whether calcium intake contributes to stress fracture risk; at least one study in military cadets found that calcium supplementation was ineffective at decreasing stress fracture risk [47], although a much larger study reported a significant reduction in stress fracture occurrence during basic training with calcium and vitamin D supplementation [48].

Although recruits to the United States Military Academy (USMA) are at potential risk for stress fractures as a result of multiple extrinsic factors, including footwear, physical activity, and long march durations, there have been no data published concerning whether intrinsic skeletal factors and modifiable lifestyle factors can affect risk of stress fracture risk in cadets at the USMA. This population is unique among military cohorts, with regard to baseline high physical fitness level [49], and it was hypothesized that in the setting of more homogeneous underlying fitness, other factors might emerge as significant. The goal of this study, therefore, was to determine if calcium intake, exercise, lifestyle, fitness, skeletal size, bone density, biochemical variables of skeletal metabolism or genetic profiles could predict risk of stress fracture prospectively over 4 years of study.

METHODS

This study was approved by the Institutional Review Board of Keller Army Hospital, USMA, West Point, NY. The USMA is a 4 year military college with strict entrance requirements that include academic and physical excellence. The first 6 weeks at the USMA is comprised of 6 weeks of cadet basic training to ensure that cadets are in adequate physical condition required for military readiness, and includes long marches in boots with heavy packs.

Study cohort

Prior to initiation of this investigation, each cadet of one entire incoming class of the USMA was mailed an overview of the study protocol and a consent form to review at

home. Upon arrival at the USMA, the class consisting of 1054 male and 192 female cadets, was briefed en masse by the investigators to overview the purpose of the study and the procedures involved in the investigation. 71.5% of these incoming cadets consented to participate (n = 891; 755 men, mean age 18.7 years; 136 women, mean age 18.4 years). Of the consenting male cadets, self identified racial distribution was 86.5% Caucasian, 5% Asian, and 8.5% Black. Of consenting females, 79.4% were Caucasian, 11% Asian, and 9.6% Black.

Baseline surveys for historical data

All cadets who volunteered to participate in the investigation completed baseline surveys, which included questions concerning prior clinical fractures, parental fracture history, age at menarche, and for the preceding 12 months: average daily calcium intake using the modified Block questionnaire [50], average weekly exercise duration, smoking history, alcohol ingestion and estimated number of menstrual cycles in female cadets over the year preceding matriculation into USMA. An Eating Disorders Inventory (EDI-2) was also completed during the last year in USMA in 311 men and 96 women [51]. Scores on the Eating Disorder Inventory have been shown to be stable in individuals of this age group, such that scores at the time the inventory was completed (during the last year) would be expected to correlate strongly with scores upon entry to USMA [51].

Physical measurements

All baseline physical measurements were obtained within days of cadet arrival at USMA. The physical education department obtained height and weight measurements from which body mass index was derived (weight divided by height squared). The army physical fitness test included individual scores for 2-mile run speed, number of push-ups in 2 min and number of sit-ups in 2 min, as well as a composite score of these three fitness variables [52].

Bone density and bone size measurements

Within the first two months of arrival to USMA, bone mineral density (BMD) of the calcaneus was measured by peripheral dual X-ray absorptiometry (pDXA, Lunar PIXI,

Madison, WI) and bone size and macroarchitecture of a single slice at the distal tibia was assessed by peripheral quantitative computed tomography (pQCT, Norland, Fort Atkinson, WI) in all cadets. To identify and standardize the distal tibial site, the tibial length was measured with the cadet seated in a chair with the knee flexed and length measured from the apex of the patella to the medial malleolus (to the closest centimeter). The pQCT measurement site was then determined in an automated fashion utilizing the entered tibial length to position at the 33% distal site from the starting point of above the medial malleolus. Bone mineral content (mg per 1 mm slice of bone), cortical thickness (mm), periosteal and endosteal circumferences (mm) were measured directly. Cortical thickness was derived using the circular ring model, which calculates a mean cortical thickness from measures of total bone area and cortical bone area. Central BMD was measured by DXA (Lunar DPX-IQ, Madison, WI) at the spine and hip in all 136 women and a randomly selected subset of male cadets (n = 146). Measurements of calcaneus BMD, tibial variables by pQCT and spine and hip BMD (in the selected subgroup) were repeated annually over the 4 years at USMA. The short-term coefficient of variation (CV%) for each machine was calculated by scanning ten individuals on each machine twice. The coefficients of variation for in vivo BMD measurements of the calcaneus, spine and total hip were 1.0%, 1.5% and 1.5%, respectively. The CV% was 2.2% for tibial mineral content and 3.2% for cortical thickness.

Bioelectrical impedance measurements

The Tanita 305 total body fat analyzer (Skokie, IL: Tanita Corporation of America, Inc.) was used to assess weight, impedance, percent body fat, fat mass, lean body mass and total body water. The primary variable of interest was percent body fat. The test retest correlation coefficient for percent body fat was 0.99.

Biochemical measurements

A single serum sample was collected on the third day after arrival at USMA on all study participants in July and participants were not fasting. Serum samples were analyzed for levels of 25-hydroxyvitamin D; intact PTH(1–84); ferritin; bone turnover [osteocalcin

(OC), crosslinked n-telopeptide (NTX), and C-terminal crosslinked telopeptide (CTX)]; hormones [luteinizing hormone (LH), estradiol (E2) and testosterone (TST) in men only, and sex-hormone binding globulin (SHBG) in all]. OC and NTX were measured by ELISA (Quidel, San Diego, Ca. for OC, and Osteomark, Princeton NJ for NTX). CTX, PTH, hormone levels and ferritin were measured on the Roche Elecsys (Bohemia NY). Level of 25(OH)D was measured by RIA (Diasorin, Stillwater, MN. Intraassay %CVs were 1.0–4.6% for the bone turnover markers, 0.8–2.2% for the hormones, and 8.6% for 25(OH)D. Interassay %CVs were 1.9–6.9% for turnover markers, 2.1–3.7% for hormones, and was 7.0% for 25(OH)D.

Genetic analyses

Genotyping for polymorphisms in the ESR1, COLIA1 and VDR genes was carried out on PCR amplified fragments of genomic DNA (dbSNP reference) extracted from peripheral blood leucocytes using the Nucleon II DNA extraction kit (Scotlab, Coatbridge, Lanarkshire, UK) according to the manufacturer's instructions. For the ESR1 polymorphisms ESR1—PvuII (rs2234693) and XbaI (rs9340799) genotypes were determined by DNA sequencing, using standard methods as previously described [53]. Genotyping for the COLIA1 Sp1 polymorphism (rs1800012) was carried out by TaqMan analysis as previously described [54]. For the VDR gene, genotypes at the Bsm1 polymorphism (rs1544410) were determined by allelic discrimination using the 5′ nuclease Taqman assay (Applied Biosystems, Foster City, CA, USA) as previously described [55]. All genotyping was performed blindly and 10% of all samples were repeated to ensure concordance of results.

Stress fracture incidence

Stress fracture diagnoses were made by orthopedists at the USMA over the 4 years, on the basis of symptoms, physical examination and radiologic imaging tests ordered by the orthopedist following standard protocols of the Keller Army Hospital. All cadets with a suggestion of bone pain, tenderness or swelling had an initial X-ray, as well as a follow up X-ray, radionuclide bone scan or MRI as deemed necessary by the orthopedist.

Investigators (FC, RL), blinded to subject characteristics, adjudicated results of orthopedic evaluation from both the clinic or emergency department notes and reports of imaging tests generated by Keller Army Hospital radiologists and orthopedists. Radiographic descriptions included focal periosteal bone formation and/or edema, endosteal callous, focal cortical lucencies, cortical cracks and focal sclerosis, with impressions consistent with a stress fracture diagnosis.

Statistical analysis

Baseline questionnaire data were analyzed with chi-square or Fisher's Exact tests. Skeletal measures and biochemical variables were analyzed with t-tests or Wilcoxon rank sum tests for non-normally distributed variables. Relative risks were calculated using log binomial models, with and without controlling for race. Genetic markers were analyzed with chi-square, and Cochran–Mantel–Haenszel tests. All analyses were performed with SAS version 9.2 (Cary, NC).

RESULTS

Stress fracture results are based on all cadets who consented to participate (n = 891; 755 men, mean age 18.7 years; 136 women, mean age 18.4 years). Over the 4-year prospective trial, 176 (20%) of the cadets enrolled in our study left the academy for personal reasons. This included 58 withdrawals during the first three months at USMA, where cadets undergo intensive basic physical training for 2 months, followed by the beginning of the academic program. Gender, age distribution, prior level of physical activity, prior milk intake, and fracture history were similar between those who left and those who remained. All fractures that occurred prior to withdrawal from the USMA were included in these analyses.

Fracture incidence and location

5.7% of males and 19.1% of females had at least 1 stress fracture (Fig. 1a) over the 4 years with a total of 98 stress fractures occurring in 69 cadets. Fourteen men (1.6%) and

8 women (5.9%) had 2 fractures, 3 men had 3 fractures (0.4%), and one woman had 5 fractures (0.7%). More than 50% of the stress fractures occurred within the first 3 months of matriculation to the USMA. Fig. 1b shows the site distribution of the fractures; the most common fractures for both genders were metatarsal (58% of all fractures) and the next most common site was the tibia (29%).

Historical and physical characteristics

Table 1 presents mean physical characteristics of the cohort by gender and stress fracture occurrence. Mean age was slightly lower in women with stress fracture than women without. Although women had a slightly lower BMI than men, percent fat by bioelectrical impedance (BIA) (first measured after 1 year at USMA) showed lower fat percent in males. There were no differences in height, weight, BMI or body fat by BIA in cadets with and without stress fracture. Results on the army physical fitness test, including time to run 2 mi (males 12 min, 28 s and females 14 min, 27 s) and number of pushups (males 55, females 32) revealed the high level of physical fitness in entrants to the USMA as compared to average military recruits (mean 2-mile run speed for males 14 min, 31 s and females 17 min, 24 s) and number of push-ups (males 45, females 22) [49]. However, none of the physical measures, including any part of the physical fitness test or the composite physical fitness score was different between fracture and non-fracture cadets for either gender.

A survey of self-reported characteristics revealed that 35% and 49% of the females and males, respectively, had had a prior clinical fracture, with no differences in this proportion seen between those who had a subsequent stress fracture versus those who did not. Almost all prior fractures (94%) were peripheral fractures likely related to typical childhood or sports related trauma. The majority of cadets consumed more than 1 glass of milk daily and there were no differences in milk intake between cadets with and without fracture for either gender.

Approximately 5% of males and 2% of females reported they smoked in the past year. Less than 10% of males and 1% of females had used chewing tobacco. Little or no alcohol intake was reported in 60% of males and 68% of females prior to entering

USMA. No alcohol use was permitted while at USMA. 75% of both male and female cadets exercised 7 or more hours weekly during the year prior to matriculation. For males, a higher incidence of stress fractures was seen in those cadets who exercised less than 7 h per week the year before entering the academy (44% of men with fractures vs. 24% of men without fractures; $p = 0.004$). Male cadets who exercised 7 or more hours per week prior to USMA entry scored 6% higher on the Army Physical Fitness Test upon entry ($p < 0.0001$) than those who did not. In female cadets, those who exercised > 7 h weekly prior to matriculation had a 16% higher score on the Army Physical Fitness Test ($p = 0.007$) as compared to those who exercised less than 7 h per week. However, prior exercise did not predict stress fractures in females.

Female cadets who had fractures had a later age of menarche compared with cadets without fractures (13.1 vs. 12.1 years; $p < 0.01$). 22% of the female population at the USMA had 9 or fewer menstrual cycles in the year prior to entry and 5.3% reported having 0 to 3 cycles in the year prior to USMA entrance, however, the prevalence of fewer than 10 menstrual periods or fewer than 6 menstrual periods in the year prior to entering the USMA was not higher in those who had subsequent stress fracture. Approximately 10% of cadets were on oral contraceptives at baseline and there was no difference in use between cadets with and without stress fracture. During the year prior to matriculation, those women who had > 9 menstrual periods did not differ in terms of weight, BMI, BIA, EDI or exercise history compared to those who had fewer menstrual periods.

Female cadets in the highest quartile of Eating Disorder Inventory scores had a mean total score of 38.5, similar to the score previously published for patients with anorexia nervosa [51]; however, there was no relationship between the Eating Disorder Inventory score and stress fracture risk. Furthermore, women in top quartile of Eating Disorder Inventory scores had higher BMI (23.7 vs. 22.4 in all other quartiles; $p = 0.02$), but no difference in BMD at any site or number of menstrual cycles prior to or after entering the USMA. However, female cadets who were in the top quartile of the EDI were more likely to have taken oral contraceptives ($n = 14$, 10.45%) at baseline.

Bone density, bone size and biochemical indices

Table 2A and Table 2B present selected mean variables of bone density, bone size and biochemistry. All were within normal ranges, though bone density levels were on average 1 standard deviation (SD) higher for men and 0.8 SD higher for women compared to standard age and gender matched reference populations (Lunar Reference Database; GE lunar, Madison WI).

For women, although there were no significant differences, average BMD level in those who had a stress fracture was 3.3% lower at the spine ($p = 0.13$), 3.9% lower at the total hip ($p = 0.09$), and 4.4% lower at the femoral neck ($p = 0.06$) compared to those who did not (Table 2A). In men, average BMD levels at all sites in those who had a stress fracture were similar to those who did not. Femoral neck diameter was smaller in both male and female cadets who had a stress fracture compared to those who did not ($p < 0.03$). Furthermore, in men, tibial cortical area and tibial BMC were both lower in those who had a fracture versus those who did not (both $p < 0.05$). BMD of the spine, femoral neck, total hip, calcaneus and tibia (both BMD and cross sectional cortical area) were all significantly higher in those who exercised more than 7 h weekly prior to entry to the Academy. In contrast, in women, there were no significant relationships between history of exercise > 7 h/weekly and BMD. In men, longer prior exercise history was associated with greater cross sectional area of the femoral neck. This relationship was not seen in women.

Levels of bone turnover were higher in males than females, but no differences were seen between cadets with and without stress fractures (Table 2B). As expected, mean serum SHBG level was higher in females, and mean levels of testosterone and ferritin higher in males. There were no differences in any of the biochemical variables of bone turnover, calcium homeostasis or hormone levels between fracture and non-fracture cadets for either gender.

Change in weight during USMA

During the time at the academy 6% of women lost greater than 5 lb of weight and 47% gained more than 5 lb, the remaining 47% stayed within 5 lb of their entry weight. During the time at the academy 4% of men lost greater than 5 lb of weight and 41% gained more than 5 lb, the remaining 54% stayed within 5 lb of their entry weight. There was no association between change in weight and stress fracture occurrence in either males or females.

Menstrual function during USMA

Menstrual function and contraceptive use were assessed prospectively during the 4 years at the USMA. During the first 3 months of USMA basic training, menstrual function was interrupted in many cadets. Of the 26 women who had stress fractures, 28.6% had no menstrual periods during the first 3 months and 21.4% had only 1 menstrual period. However, this interruption in menstrual function was similar in women who had no stress fractures (33.3% had no menstrual periods and 20% had only 1 menstrual period during the first 3 months).

Genetic factors

Table 3A and Table 3B present genetic analyses for four separate genes associated with BMD and/or fracture risk in other populations for both men (Table 3A) and women (Table 3B) [56]. Each of the genotypes was in Hardy Weinberg equilibrium. None of the genetic factors was associated with stress fracture incidence, whether or not analyses controlled for race.

Fracture risk predictors

Table 4 presents relative risks of stress fracture for significant risk factors. Men who exercised < 7 h per week in the year prior to USMA matriculation had a 2.3 fold increased stress fracture risk (CI 1.3–4.1) compared to those who exercised ≥ 7 per week. For women, fewer years since menarche was associated with increased risk, mean 4.9 years in fracture cases vs 5.8 years in nonfracture cases (1.4 fold, CI 1.2–1.7).

However, past history of amenorrhea or oligomenorrhea was unrelated to subsequent stress fracture risk. In addition, prospectively assessed amenorrhea during the basic training period (first 2 months at the USMA) was also unrelated to stress fracture occurrence during basic training or thereafter.

In males, each 10 mg decrease in tibial BMC increased fracture risk (RR 1.11, CI 1.03–1.2), but this relationship was not seen in women. Also, in males, each mm^2 decrease in tibial cortical area was related to increased fracture risk (RR 1.12, CI 1.03–1.2), but again, this was not seen in women. In both men and women, each mm decrease in diameter of the femoral neck was related to increased fracture risk for both men (RR 1.35, CI 1.01–1.81) and women (1.16; CI 1.01–1.33). In men, the relationship between femoral neck diameter and stress fracture risk was lost after controlling for race.

DISCUSSION

We have investigated a series of factors thought to be possible contributors to the development of stress fracture occurrence, including historical lifestyle factors, menstrual regularity, anthropometric indices, physical fitness, bone density, bone size, bone turnover markers, hormone levels, indices of calcium homeostasis and several genetic factors shown to predict bone density or fracture risk in other populations [14, 15, 37, 43, 46, 57]. In our study, the only significant factors shown to be predictive in men were lower levels of prior exercise, cortical tibial dimensions, tibial BMC (most likely a reflection of tibial size) and femoral neck diameter (though the latter was no longer significant after controlling for race). In women, stress fracture risk was associated with a shorter time since menarche and a smaller diameter of the femoral neck. The magnitude of risk variance explained by any one of these factors ranges from 0.9 to 2.6% in men and 3.7 to 4.8% in women. The amount of risk explained by all of the factors combined for men is only 7%, and for women only 10%.

Our study in this unique USMA population is consistent with studies in military recruits in some, but not all, respects. Although prior studies in military recruits have found lack of prior physical capability to be a major predictor of risk in females [9, 26, 28, 29], we did not find this association in females, as measured by self reported prior exercise or score on the fitness test on admission. Perhaps this is related to the overall high level of physical fitness for cadets entering the USMA compared to that of basic military recruits [49] or because of the limited sample size. However, lower level of prior exercise was a risk factor for stress factors in men in our study, though in all cadets, exercise duration prior to USMA matriculation was higher than average for age matched young men [58].

Our findings indicating a relationship between bone size (tibia in men, femoral neck diameter in both women and men) and stress fracture risk in USMA cadets, is consistent with findings of several other prospective investigations [25, 36, 40, 59, 60]. This is also clearly one of the major factors accounting for the consistently higher stress fracture risk in women compared with men in all populations where it has been studied [36]. It is possibe that these bone size measurements may be related to stress fractures that occur at more distal sites. Our study is also somewhat similar to other prospective studies showing at best a weak relationship between BMD and stress fracture risk [36, 43, 61, 62]. It is possible that with a larger group of cadets, significance might have been achieved with BMD as a predictor of stress fracture risk in women. It is also likely that the homogeneity of our cohort with respect to BMD level and the fact that overall our cohort had BMD levels that were very high compared to the average population explains why such a minimal difference was seen in women and none was seen in men. More importantly, though, since BMD was so high in our cohort, it is hard to invoke BMD as a major contributor to the development of stress fracture in our population. Furthermore, in studies such as that of Valimaki et al, BMD differences were seen only after multiple adjustments (age, height, weight, etc). Therefore, BMD is not likely to be useful in identifying those individuals likely to be at high risk of fracture [43].

Measurement of biochemical indices of bone turnover after stress injury has occurred is not particularly useful since stress injuries accelerate remodeling to repair the damage

and this is reflected in increments in serum and urinary markers of turnover [63]. Our study was the largest to investigate prospectively the role of baseline bone turnover as a predictor of stress fracture risk. We showed no relationship in either gender, consistent with the findings of Valimaki et al. in a smaller series [43]. We only measured indices at one time point, however, and fasting morning specimens were not possible, so variability due to dietary and diurnal influences on these measurements could not be mitigated [64]. Moreover, biochemical markers of bone turnover may be affected by heavy exercise the day before the sampling, and our study protocol did not take this into account [64]. Bone turnover levels are also affected by age and growth status, and it is possible that some of the cadets, particularly males, had elevated levels associated with continued linear growth [65].

Shaffer et al. found that lack of menstrual function during the year preceding military training was an important predictor of stress fracture risk, though lesser degrees of menstrual irregularity were not predictive. We had very few women with complete amenorrhea prior to entry into the USMA so were likely underpowered to see this relationship. We did find the number of years after menarche to be a significant risk factor in our study, though age of menarche was not predictive in the Shaffer study [9]. Our data are consistent with data from Gilsanz et al. [66] who found that later pubertal age (in both genders) was associated with lower BMD. Whether the slightly longer estrogen exposure could improve bone strength independently of the other factors measured (bone size, density, etc.) is unknown. No relationship between BMD or bone size with years from menarche was seen. Lappe et al. also found an association between amenorrhea during basic training and stress fracture risk [48]. In our study, however, there was no association between interrupted menstrual function during the first few months at the USMA and stress fracture incidence, but again, we were likely underpowered to see this relationship.

There are several limitations to this prospective cohort trial. The USMA used radionuclide scans primarily, rather than MRI to confirm stress fracture diagnosis when the study started. Not everyone was sent out for this procedure due to time required and cost of transporting cadets. Some of these individuals might have had stress fractures and some were even treated as such, but per our study protocol, only stress fractures with radiologic confirmation were included as cases. Therefore, we might have underestimated the number of fractures in our trial. Although this study was quite comprehensive, there are some factors that we did not consider. For example, we did not examine several intrinsic factors, such as foot structure, leg length discrepancy, or external hip rotation, all predictive in other populations [14, 23, 37, 40, 41]. We did not assess Depo-Provera use for contraception during the year prior to matriculation, a factor that has also been shown to be associated with risk of stress fracture [48].

In conclusion, our study indicates that intrinsic factors, other than gender, play little role in affecting the risk of stress fracture (explaining less than 10% of risk). Studies attempting to affect intrinsic factors with medical therapy to decrease risk of stress injuries are unlikely to be fruitful in a population, which is at baseline, so highly physically fit. Given that stress fractures are a substantial problem for military readiness, future studies concentrating on interventions affecting extrinsic factors should be evaluated for efficacy in reducing the incidence of stress fractures in this population.

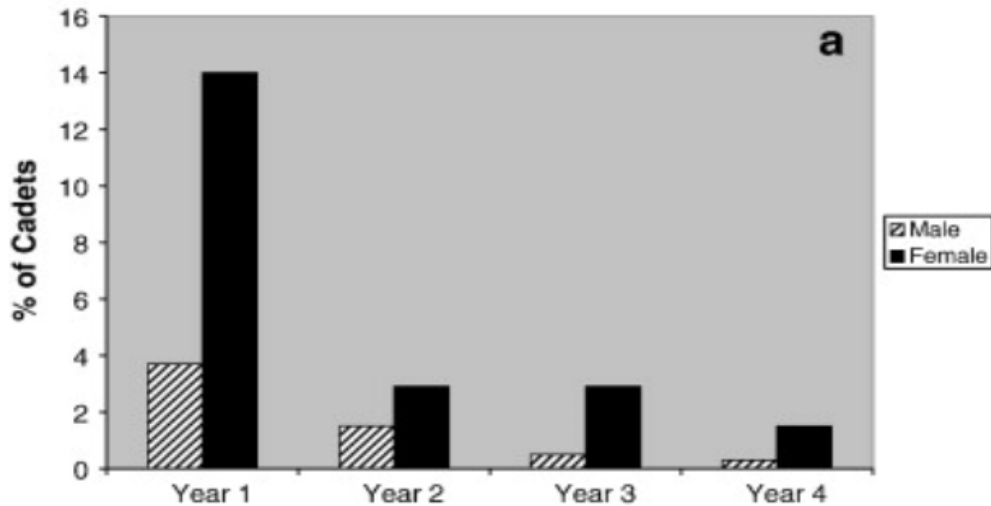**Figure 1. Stress fracture incidence and site distribution**

Percent of cadets with stress fractures by academy year

Number of stress fractures at each skeletal site
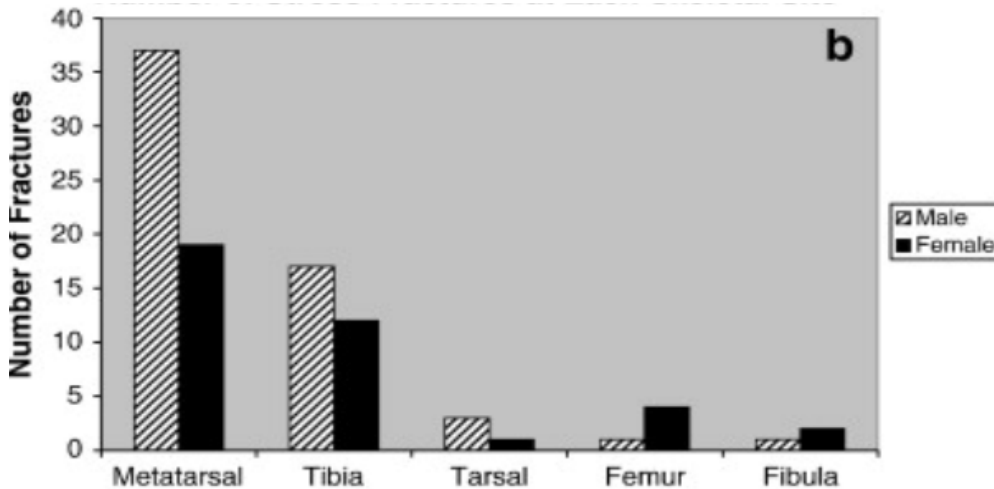
a. Percent of cadets with stress fractures by academic year, separately for males and females ■. Multiple stress fractures within a year were counted once, whereas multiple fractures occurring in different years were counted separately for each year. 60 fractures occurred in 43 men and 38 fractures occurred in 26 women.

b. Number of stress fractures at each skeletal site, for males and females ■.

Table 1: Baseline Characteristics in Cadets with and without Stress Fracture by Gender

Mean (sd) or n (%)	Males (n=755)		Females (n=136)	
	Stress Fracture (n=43)	No Stress Fracture (n=712)	Stress Fracture (n=26)	No Stress Fracture (n=110)
Age (years)	19 (0.8)	19 (1.0)	18 (0.5)	19 (0.8)
Height (m)	1.8 (0.1)	1.8 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kg)	77 (14)	78 (13)	64 (11)	64 (8)
BMI (mean,sd)	24 (4)	25 (3)	23 (3)	23 (2)
Percent body fat by bioimpedence	9 (3)	9 (3)	20 (3)	21 (3)
Army Physical Fitness Test [**]	215 (35)	215 (34)	200 (44)	210 (40)
Baseline Survey				
Prior fracture (n, %)	16 (37)	353 (50)	8 (31)	39 (36)
History of parental fracture (n, %)	13 (30)	158 (22)	5 (19)	24 (21)
Glasses of milk daily in past year (n,%)				
<1	9 (20)	159 (22)	8 (31)	47 (44)
1-2	23 (54)	333 (47)	13 (50)	49 (45)
≥ 3	11 (26)	218 (31)	5 (19)	12 (11)
Hours of exercise / week in past year (n, %)				
<7	19 (44)*	173 (25)	7 (27)	23 (22)
≥ 7	24 (56)	536 (75)	19 (73)	85 (78)
Years from menarche	-	-	4.9 (1.2)*	5.8 (1.4)
Menstrual cycles in past year (n, %)				
0-6			1 (4)	12 (12)
7-9	-	-	4 (16)	12 (12)
10-12			21 (80)	82 (76)
Smoked in past year (n, %)	2 (5)	39 (6)	0 (0)	4 (4)
Used chewing tobacco in past year (n, %)	5 (7)	64 (9)	0 (0)	2 (2)
Current oral contraceptive users (n, %)	-	-	3 (12)	11 (10)

** Maximum possible score = 300. Includes run score, push-up score, and sit-up score (Army age and gender standardized)

* p<0.05 Fracture vs. no fracture within gender

Table 2A: Baseline Bone Measures in Cadets with and without Stress Fracture

	Males (n=755)		Females (n=136)	
	Stress Fracture (n=43)	**No Stress Fracture** (n=712)	**Stress Fracture** (n=26)	**No Stress Fracture** (n=110)
Bone density & bone size	Mean (sd)			
Spine BMD (g/cm^2)[a]	1.29 (0.1)	1.28 (0.1)	1.2 (0.1)	1.27 (0.1)
Total hip BMD (g/cm^2)[a]	1.29 (0.2)	1.25 (0.2)	1.1 (0.1)	1.15 (0.1)
Femoral neck BMD (g/cm^2)[a]	1.26 (0.2)	1.31 (0.2)	1.16 (0.1)	1.11 (0.1)
Femoral neck diameter (mm)	33 (5)*	36 (3)	30 (2)*	32 (3)
Femoral neck cross-sectional area (mm^2)	254 (34)	243 (37)	179 (19)*	196 (27)
Tibial cross sectional area (mm^2)	443 (62)	460 (62)	364 (53)	372 (47)
Tibial circumference (mm)	78 (7)	81 (8.3)	70 (5)	72 (10)
Tibial cortical thickness (mm)	4.3 (0.6)	4.6 (0.9)	3.8 (0.5)	3.8 (0.6)
Tibial BMC (mg)	346 (41)*	367 (47)	289 (29)	293 (33)
Tibial cortex cross-sectional area (mm^2)	286 (34)*	305 (42)	235 (27)	235 (29)
Calcaneal BMD (g/cm^2)	0.70 (0.2)	0.72 (0.1)	0.58 (0.1)	0.59 (0.1)

Table 2B. Baseline biochemistry measures in cadets with and without stress fracture

Serum Biochemistry	Median (IQR)			
25(OH)-Vitamin D (ng/mL)	28 (10)	27 (11)	26 (9)	25 (8)
Parathyroid hormone (pg/mL)	34 (1)	30 (18)	32 (16)	30 (17)
Osteocalcin (ng/mL)	9.2 (3.4)	9.4 (2.5)	7.2 (2.1)	7.0 (1.8)
NTX (nM)c	16 (7)	17 (8)	12 (5)	12 (6)
CTX (µg/L)d	656 (282)	678 (302)	454 (246)	442 (204)
Estradiol (pg/mL))b	77 (39)	79 (32)	-	-
Testosterone (ng/mL)	8.4 (5.7)	8.0 (5.4)	1.9 (1.2)	1.9 (1.1)
Luteinizing hormone (mIU/mL)b	3.0 (2.5)	2.9 (2.5)	-	-
SHBG (nmol/L)	33 (20)	29 (13)	51 (31)	61.4 (40)
Ferritin (ng/mL)	73 (52)	79 (57)	42 (24)	39 (34)

[a] DXA was performed in a subset of men. 7 men with DXA had a stress fracture.
[b] LH and estradiol were not measured in women due to variation in menstrual cycle on the day blood was drawn.
[c] Cross-linked N-telopeptide of type 1 collagen
[d] C-terminal cross-linked telopeptide of type 1 collagen
[e] Sex-hormone binding globulin
* p<0.05 fracture vs. no fracture within gender

Table 3a: Genetic Factors in Men

Genotype	Stress Fracture			No Stress Fracture		
	1	2	3	1	2	3
COL1A1[a]	27 (67.5)	12 (30.0)	1 (2.5)	469 (67.6)	203 (29.3)	22 (3.2)
VDR[b]	8 (20.0)	18 (45.0)	14 (30.8)	97 (16.4)	321 (44.2)	273 (39.4)
ESR1 XbaI[c]	2 (5.0)	17 (42.5)	21 (52.5)	76 (11.0)	290 (41.9)	326 (47.1)
ESR1 PvuII[d]	6 (15.0)	19 (47.5)	15 (37.5)	142 (20.5)	341 (49.2)	209 (30.2)

[a]1=SS, 2=Ss, 3=ss   [b]1=BB, 2=Bb, 3=bb   [c]1=XX, 2=Xx, 3=xx   [d]1=PP, 2=Pp, 3=pp

Values are number (%). Not all cadets had all genetic analyses. There was no significant difference in genotype distributions between the fracture and no fracture groups for any marker.

Table 3b: Genetic Factors in Women

Genotype	Stress Fracture			No Stress Fracture		
	1	2	3	1	2	3
COL1A1[a]	21 (80.8)	4 (15.4)	1 (3.9)	65 (62.5)	33 (31.7)	6 (5.8)
VDR[b]	4 (15.4)	14 (53.9)	8 (30.8)	17 (16.4)	46 (44.2)	41 (39.4)
ESR1 XbaI[c]	3 (11.5)	13 (50.0)	10 (38.5)	15 (14.4)	40 (38.5)	49 (47.1)
ESR1 PvuII[d]	6 (23.1)	16 (61.5)	4 (15.4)	23 (22.1)	47 (45.2)	34 (32.7)

[a]1=SS, 2=Ss, 3=ss   [b]1=BB, 2=Bb, 3=bb   [c]1=XX, 2=Xx, 3=xx   [d]1=PP, 2=Pp, 3=pp

Values are number (%). Not all cadets had all genetic analyses. There was no significant difference in genotype distributions between the fracture and no fracture groups for any marker.

Table 4: Risk Factors for Stress Fracture in Men or Women**

Exposure	Men	Women
	Relative Risk (C.I.)	Relative Risk (C.I.)
Exercise< 7 hours / week in year prior to entry (<7 hours/week vs. > 7 hours/week)	2.31 (1.29, 4.12)*	1.27 (0.60, 2.74)
Years from menarche	-	1.44 (1.19, 1.73)*
Diameter of femoral neck (mm)	1.35 (1.01,1.81)*	1.16 (1.01, 1.33)*
Cross-sectional area of femoral neck (mm^2)	0.93 (0.75,1.56)	1.22 (1.06, 1.41)*
Tibial BMC (mg)	1.11 (1.03,1.20)*	1.03 (0.92, 1.16)
Tibial cortex cross-sectional area (mm^2)	1.12 (1.03,1.23)*	1.01 (0.89, 1.15)

* Confidence interval does not enclose 1.0 (p<0.05).
** Analyses were also performed controlling for race. Results were nearly identical, with the exception of femoral neck diameter in men, which was no longer statistically significant when controlling for race.

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