PODCAST In-Depth

Changes in Volumetric Bone Mineral Density Over 12 Months After a Tibial Bone Stress Injury Diagnosis

Implications for Return to Sports and Military Duty

Kristin L. Popp,*†‡§ PhD, Kathryn E. Ackerman,†‡|| MD, Sara E. Rudolph,† MPH, Fjola Johannesdottir,‡¶ PhD, Julie M. Hughes,§ PhD, Adam S. Tenforde,‡# MD, Miriam A. Bredella,** MD, Chun Xu,†† PhD, Ginu Unnikrishnan,†† PhD, Jaques Reifman,†† PhD, and Mary L. Bouxsein,†‡¶ PhD
Investigation performed at Massachusetts General Hospital, Boston, Massachusetts, USA

Background: Bone stress injuries (BSIs) occur in up to 20% of runners and military personnel. Typically, after a period of unloading and gradual return to weightbearing activities, athletes return to unrestricted sports participation or military duty approximately 4 to 14 weeks after a BSI diagnosis, depending on the injury location and severity. However, the time course of the recovery of the bone's mechanical competence is not well-characterized, and reinjury rates are high.

Purpose: To assess the bone microarchitecture and volumetric bone mineral density (vBMD) over 12 months after a tibial BSI diagnosis.

Study Design: Case-control study; Level of evidence, 3.

Methods: We enrolled 30 female athletes from the local community (aged 18-35 years) with a tibial BSI (grade $\geq$2 of 4 on magnetic resonance imaging) for this prospective observational study. Participants completed a baseline visit within 3 weeks of the diagnosis. At baseline and 6, 12, 24, and 52 weeks after the BSI diagnosis, we collected high-resolution peripheral quantitative computed tomography scans of the ultradistal tibia (4% of tibial length) of the injured and uninjured legs as well as pain and physical activity assessment findings.

Results: From baseline to 12 weeks after the diagnosis, total, trabecular, and cortical vBMD declined by 0.58% to 0.94% ($P < .05$ for all) in the injured leg. Total and trabecular vBMD also declined by 0.61% and 0.67%, respectively, in the uninjured leg ($P < .05$ for both). At 24 weeks, mean values for all bone parameters were nearly equivalent to baseline values, and by 52 weeks, several mean values had surpassed baseline values. Of the 30 participants, 10 incurred a subsequent BSI during the course of the study, and 1 of these 10 incurred 2 subsequent BSIs. Participants who suffered an additional BSI were younger and had a later age of menarche, a greater incidence of previous fractures, and lower serum parathyroid hormone levels ($P < .05$ for all).

Conclusion: Bone density declined in both the injured and the uninjured legs and, on average, did not return to baseline for 3 to 6 months after a tibial BSI diagnosis. The observed time to the recovery of baseline vBMD, coupled with the high rate of recurrent BSIs, suggests that improved return-to-sports and military duty guidelines may be in order.

Keywords: female athlete; stress fractures; running; epidemiology

Bone stress injuries (BSIs), particularly in the tibia and metatarsals,[44,45] are common among distance runners[8,44,50] and military personnel,[25,43,48] with women experiencing a greater incidence of BSIs than men.[4,5,8,44] BSIs often require a prolonged recovery time and are accompanied by a risk of reinjuries, persisting morbidity, and failure to return to sports or military duty.[18,19,26,45,52] After a tibial BSI diagnosis, standard treatment consists of the cessation of load-bearing sporting activities, consideration for crutches and/or immobilization, and gradual return to activity until symptoms resolve. BSI recovery depends on both the location and severity of the injury.[6] Both general[3,15,39] and skeletal site-specific[46,51] grading classification systems have been developed to guide BSI management and provide a framework for expected return-to-sports timelines. Magnetic resonance imaging (MRI) grading has become the standard of care for diagnosing the injury and determining return to play, given the high rate of false-negatives results

The American Journal of Sports Medicine
2021;49(1):226–235
DOI: 10.1177/0363546520971782

with radiography and that MRI uses nonionizing radiation.[39] The typical time to return to unrestricted athletic participation after nonsurgical treatment ranges from 4 to 14 weeks but may require up to 6 months, depending on the severity and location of the injury, with pain used as a proxy for healing in clinical management.[15,39,44]

Although the majority of BSIs heal with nonoperative treatment, approximately 1 in 5 athletes will have a recurrent BSI.[44] Moreover, a previous BSI is among the strongest risk factors for future BSIs.[7,28,50] Cross-sectional studies suggest that female runners with a history of BSIs have a smaller bone cross-sectional area and lower trabecular bone density and/or less favorable bone microarchitecture compared with female runners with no previous BSIs.[42,47] However, it is unclear whether these differences exist before an initial BSI or occur as a result of a BSI and resultant changes in weightbearing physical activity. To that end, it is well-established in both animal and human studies that bone strength, mineral density, and microarchitecture respond to physical activity and disuse, with improvements in these bone properties with physical training and the converse with disuse.[1,2,22,36,49,53,59] For example, collegiate gymnasts gained an average of 3.5% areal bone mineral density (aBMD) as shown by dual-energy X-ray absorptiometry (DXA) at the spine during an 8-month competitive season and lost 1.5% aBMD during a 4-month off-season.[49] Similarly, in a study using high-resolution peripheral quantitative computed tomography (HR-pQCT) among female soldiers, 8 weeks of Basic Combat Training elicited an increase in trabecular thickness (Tb.Th), number (Tb.N), and volumetric bone mineral density (vBMD; Tb.vBMD) as well as cortical thickness (Ct.Th) and total vBMD (Tt.vBMD).[22] Little is known about the skeletal response to BSI management, or whether the injured and uninjured legs respond differently, given that patients often remain weightbearing and may continue partial- and full-weightbearing exercises during BSI recovery. This information may be important in determining optimal return-to-sports and return-to-duty guidelines that minimize the subsequent injury risk. To our knowledge, there have been no studies assessing changes in global or site-specific bone health as a result of BSIs and related changes to physical activity. Further, it is unknown whether skeletal changes that occur during BSI recovery and subsequent return to activity persist beyond BSI healing and subsequent return to activity.

TABLE 1
Abbreviations

Abbreviation	Term
aBMD	Areal bone mineral density
BSI	Bone stress injury
Ct.Ar	Cortical area
Ct.Po	Cortical porosity
Ct.Th	Cortical thickness
Ct.TMD	Cortical tissue mineral density
Ct.vBMD	Cortical volumetric bone mineral density
DXA	Dual-energy X-ray absorptiometry
FN	Femoral neck
HR-pQCT	High-resolution peripheral quantitative computed tomography
LMM	Linear mixed model
LS	Lumbar spine
μFEA	Micro–finite element analysis
PTH	Parathyroid hormone
Tt.Ar	Total cross-sectional area
TH	Total hip
Tt.vBMD	Total volumetric bone mineral density
Tb.N	Trabecular number
Tb.Sp	Trabecular separation
Tb.Th	Trabecular thickness
Tb.vBMD	Trabecular volumetric bone mineral density
vBMD	Volumetric bone mineral density

Thus, through a year-long, multiple follow-up, prospective longitudinal study, we sought to characterize changes in tibial bone properties in female athletes throughout recovery from a tibial BSI. We hypothesized that (1) the vBMD and microstructure at the tibia would incur initial deficits before eventually returning to baseline values and (2) the injured leg would incur greater deficits in bone parameters compared with the uninjured leg.

A list of abbreviations used is provided in Table 1.

*Address correspondence to Kristin L. Popp, PhD, United States Army Research Institute of Environmental Medicine, 10 General Greene Avenue, Natick, MA 01760, USA (email: kpopp@mgh.harvard.edu).
†Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
‡Harvard Medical School, Boston, Massachusetts, USA.
§Military Performance Division, United States Army Research Institute of Environmental Medicine, Natick, Massachusetts, USA.
||Boston Children's Hospital, Boston, Massachusetts, USA.
¶Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.
#Spaulding Rehabilitation Hospital, Boston, Massachusetts, USA.
**Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA.
††Biotechnology High Performance Computing Software Applications Institute, Department of Defense, Frederick, Maryland, USA.
Submitted April 22, 2020; accepted August 13, 2020.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the United States Army, the Department of Defense, or The Henry M. Jackson Foundation for the Advancement of Military Medicine Inc (HJF). Any citations of commercial organizations and trade names in this report do not constitute an official United States Army, Department of Defense, or HJF endorsement of approval of the products or services of these organizations. This article has been approved for public release with unlimited distribution.

One or more of the authors has declared the following potential conflict of interest or source of funding: Support was received from the United States Department of Defense, Defense Health Program, and Joint Program Committee (W811XWH-15-C-0024) and a National Institutes of Health Shared Instrumentation Grant (S10 RR023405). AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

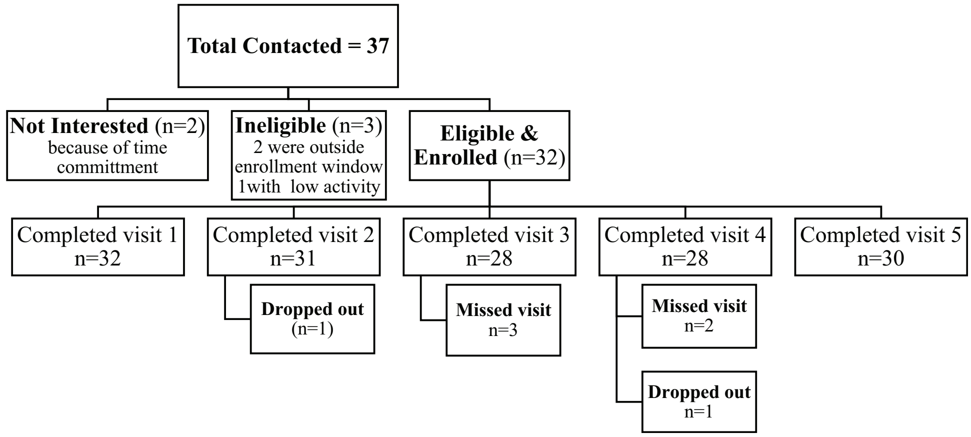

Figure 1. Screening and enrollment diagram for women enrolled in this 5-visit, 12-month longitudinal study.

METHODS

Participant Characteristics

We recruited female runners from the local community between the ages of 18 and 37 years between October 2015 and October 2017 for this prospective observational study. Participants were enrolled within 3 weeks of an MRI-diagnosed tibial BSI of grade $\geq$2 (of 4).[39] MRI grading was performed by 2 fellowship-trained radiologists. To be included in the study, participants needed to be engaged in a minimum of 4 hours of self-reported weightbearing exercise per week for at least 6 months before the injury. Exclusion criteria were underlying medical conditions (eg, diagnosed eating disorder, hyperparathyroidism, celiac disease) or the use of medications (eg, oral steroids, bisphosphonates, lithium) known to affect bone health. We screened 37 potential participants for this study; 5 did not participate in the study, including 2 who were not interested, 2 whose diagnosis of BSI was outside of the 3-week enrollment window, and 1 who did not meet physical activity requirements. Also, 2 enrolled participants dropped out during the study. A total of 30 women completed the study, although 4 participants missed $\geq$1 visits (Figure 1). This study was approved by the institutional review boards of participating institutions. Informed written consent was obtained from each woman before participation.

Clinical History and Anthropometric Measurements

At baseline, we assessed health history, fracture history, menstrual status, contraceptive use, and physical activity history through questionnaires. Self-reported nonweightbearing or partial weightbearing physical activities, such as swimming, cycling, and elliptical machine, were categorized as low-impact physical activities. Full weightbearing physical activities, such as running, dancing, and aerobic exercises, were categorized as high-impact physical activities. We assessed self-reported pain (scaled 1-10) during palpation of the tibia, ambulation, and running. We drew fasting morning blood for 25(OH)D, parathyroid hormone (PTH), iron, and ferritin. Height (to the nearest mm) was obtained using a wall-mounted stadiometer. Weight (to the nearest 0.1 kg) was measured on a calibrated electronic scale. Body mass index (BMI) was calculated as mass (kg) divided by height squared (m^2). We measured tibial length from the medial tibial plateau to the distal edge of the medial malleolus to the nearest millimeter using anthropometric tape. All leg length measurements were taken twice, and the mean of 2 readings was used. At the 4 follow-up visits (6, 12, 24, and 52 weeks from BSI diagnosis) over the next 12 months, we assessed weight; self-reported changes to physical activity; and perceived pain at rest, with palpation, and during ambulation.

Areal Bone Mineral Density

We used DXA (QDR45000A; Hologic) to assess bone mineral density (g/cm^2) at the lumbar spine (LS), femoral neck (FN), and total hip (TH) at baseline. Quality control was maintained through daily measurements of a Hologic DXA anthropomorphic spine phantom and visual review of every scan by an investigator experienced in bone densitometry.

Bone Microarchitecture

We used HR-pQCT (XtremeCT; Scanco Medical) (isotropic voxel size, 82 μm) to measure cortical vBMD (Ct.vBMD) and Tb.vBMD and the microarchitecture of the right and left distal tibias at each of the 5 study visits. Starting at 4% of tibial length (distal), the scan region extended proximally for 110 slices (9.02 mm). The 4% site was distal to the diagnosed BSI in all 32 participants.

Using Scanco Medical analysis software (Version 5.11), we directly measured Tt.vBMD (mg HA/cm^3), Tb.vBMD (mg HA/cm^3), and Tb.N (1/mm). Trabecular separation (Tb.Sp; mm) and Tb.Th (mm) were then calculated. Cortical and trabecular bone regions within a defined region of interest were identified automatically using a threshold-based algorithm. To differentiate cortical from trabecular bone, the system software determines a threshold by assuming that trabecular bone is one-third of the apparent Ct.vBMD.[30] The HR-pQCT system software then segments the cortex using gray-scale images and a Gaussian filter and threshold, as previously described.[30] We performed extended cortical analysis to measure total cross-sectional area (Tt.Ar; mm^2) along with cortical area (Ct.Ar; mm^2), Ct.Th (mm), Ct.vBMD (mg HA/cm^3), tissue mineral density (Ct.TMD; mg HA/cm^3), and porosity (Ct.Po; %). We also used 3-dimensional HR-pQCT images to perform linear micro–finite element analysis (μFEA) to estimate tibial metaphyseal stiffness and failure load under axial compression, as previously described.[40,41]

Quality control was maintained with daily scanning of the manufacturer's phantom. All scans were reviewed for motion artifacts and were repeated up to 2 times if significant motion artifacts were noted. Short-term reproducibility (with repositioning) for HR-pQCT measurements at the tibia in our laboratory ranged from 0.2% to 1.7% for density parameters, from 0.7% to 8.6% for microarchitecture parameters, and from 2.1% to 4.8% for μFEA parameters. Two-dimensional image registration based on Tt.Ar was performed for baseline and all follow-up scans. We required a minimum of 80% overlap for all scans for a given participant (6 scans were excluded because of insufficient overlap).

Statistical Analysis

Data were reported as the mean ± SD unless otherwise noted. Data were checked for normality. We used t tests and Pearson chi-square tests to determine differences in baseline characteristics, including baseline HR-pQCT measurements, between those who did and those who did not incur an additional BSI during the study period. When comparing HR-pQCT parameters at baseline, we averaged measurements from both legs for participants enrolled with bilateral BSIs at baseline. For these comparisons, we excluded 2 participants missing baseline scans on the uninjured leg (1 participant did not and 1 participant did incur an additional BSI). The percentage difference was calculated using the following formula: $\frac{|V_1-V_2|}{\frac{(V_1-V_2)}{2}} \times 100$, where V_1 equals the mean baseline bone parameter of the no additional BSI group and V_2 equals the mean baseline bone parameter of the additional BSI group.

Linear mixed models (LMMs) were used to analyze the average longitudinal change in the bone microarchitecture during the 12 months, stratified by injured and uninjured legs. We excluded those who had bilateral stress fractures (n = 3) at baseline in this analysis. The models accounted for between-participant variations and adjusted for within-participant correlations between the repeated measurements. Because we identified that the bone microarchitecture was lowest at visit 3, we fitted 2 LMMs (baseline to visit 3 and visit 3 to visit 5) for each variable to be able to assess both loss and recovery. We performed the regressions on variables in units of measurement with and without adjusting for age at enrollment, and results were reported as the percentage change from the baseline measurement. The programs R 3.2.5 (R Foundation for Statistical Computing) and Stata 15.1 (StataCorp) were used for statistical analyses.

RESULTS

Participant Characteristics

We enrolled 30 women (mean age, 24.7 ± 5.3 years) who completed this study. Participants had a grade 2 (n = 17), grade 3 (n = 10), or grade 4 (n = 3) BSI. On average, participants had a normal BMI (22.1 ± 3.0); were primarily White (93%); and had normal DXA Z scores at the LS (–0.45 ± 0.86), TH (0.35 ± 0.78), and FN (0.26 ± 0.80), although 5 participants had a Z score below –1 at the LS and 2 at the FN. Overall, 33% of participants had a fracture history, while 50% had a history of BSIs. During the 12-month study period, 10 of the participants incurred an additional BSI. Of the 10 participants who suffered an additional BSI, only 1 of those was in the same location as the initial BSI. The most common location for an additional BSI was in the opposite tibia. Of the 10 women who incurred an additional stress fracture, 1 participant had a BSI occur between weeks 1 and 6, one between weeks 6 and 12, three between weeks 12 and 24, and 4 between weeks 24 and 52; and 1 participant experienced more than 1 additional BSI between weeks 12 and 52. Notably, participants who suffered an additional BSI were younger and had a later age of menarche, a greater incidence of previous fractures, and lower serum PTH levels ($P < .05$ for all) (Table 2), although no difference in aBMD or MRI grade at the initial BSI diagnosis was noted.

Pain and Return to Activity

Ultimately, 23 of 30 participants resumed running by 12 weeks (visit 3). When asked to rate their activity on a scale from 1 to 10, where 1 is inactive and 10 is back to full preinjury athletic activity, the mean response was 5.8 ± 2.4 at 12 weeks and increased to 8.3 ± 2.5 by 1 year after the BSI diagnosis (visit 5) (Figure 2A). Pain with tibial palpation (scaled 1-10) decreased throughout the study (Figure 2A). Low-impact activity increased from baseline to 6 weeks before gradually declining, whereas high-impact activity began to increase at approximately 6 weeks and continued to increase throughout the study period (Figure 2B). Physical activity for those with no additional BSI during the study period followed a similar trend to the entire cohort (Figure 2C), while those who experienced an additional BSI had a more varied return to physical activity (Figure 2D).

Volumetric Bone Density and Microstructure of the Tibia

Baseline HR-pQCT values of the uninjured leg were reported for the whole cohort (Table 3) and were largely similar between those with and without an additional

TABLE 2
Baseline Participant Characteristics[a]

	Whole Cohort (N = 30)	No Additional BSI (n = 20)	Additional BSI (n = 10)	*P* Value
Age, y	24.7 ± 5.3	26.1 ± 1.3	21.9 ± 1.0	**.04**
Height, cm	165.1 ± 6.1	165.4 ± 6.6	164.6 ± 5.6	.8
Weight, kg	60.2 ± 7.0	61.8 ± 6.8	57.1 ± 6.6	.07
BMI	22.1 ± 3.0	22.6 ± 0.6	21.1 ± 1.0	.2
Race/ethnicity, n (%)				.6
White/non-Hispanic	28 (93)	19 (95)	9 (90)	
Mixed/non-Hispanic	1 (3)	0 (0)	1 (10)	
Mixed/Hispanic	1 (3)	1 (5)	0 (0)	
12-mo physical activity history				
High impact/running, h/wk	4.1 ± 2.3	3.6 ± 2.0	5.1 ± 2.7	.1
Low impact, h/wk	4.3 ± 3.4	4.9 ± 3.6	3.2 ± 2.7	.2
Age of menarche, y	13.1 ± 1.5	12.6 ± 0.2	14.1 ± 0.6	**.01**
Oral contraceptive use, n (%)	17 (57)	12 (60)	5 (50)	.9
Duration of oral contraceptive use, y	3.8 ± 1.5	3.8 ± 1.5	3.8 ± 1.6	>.99
Fracture history, n (%)	10 (33)	4 (20)	7 (70)	**.006**
BSI history, n (%)	15 (50)	10 (50)	5 (50)	>.99
Serum 25(OH)D, ng/mL	36.4 ± 11.2	34.4 ± 2.0	40.6 ± 4.5	.2
Serum PTH, pg/mL	27.8 ± 15.6	32.4 ± 3.7	18.7 ± 2.7	**.02**
Iron, ug/mL	103.9 ± 46.4	102.0 ± 10.0	107.8 ± 16.4	.8
Ferritin, ng/mL	42.1 ± 26.5	43.3 ± 6.2	39.6 ± 8.0	.7
MRI grade, n (%)				.4
2	17 (57)	10 (50)	7 (70)	
3	10 (33)	8 (40)	2 (20)	
4	3 (10)	2 (10)	1 (10)	
DXA				
LS BMD, g/cm^2	0.981 ± 0.091	0.993 ± 0.108	0.956 ± 0.034	.3
LS BMD *Z* score	–0.45 ± 0.86	–0.36 ± 1.02	–0.63 ± 0.40	.4
TH BMD, g/cm^2	0.983 ± 0.096	0.984 ± 0.099	0.982 ± 0.095	>.99
TH BMD *Z* score	0.35 ± 0.78	0.36 ± 0.79	0.30 ± 0.81	.9
FN BMD, g/cm^2	0.873 ± 0.090	0.883 ± 0.086	0.853 ± 0.098	.4
FN BMD *Z* score	0.23 ± 0.80	0.33 ± 0.75	0.03 ± 0.88	.3

[a]Data are reported as mean ± SD unless otherwise specified. *P* value indicates the comparison between the no additional BSI group and the additional BSI group. Bold indicates statistical significance ($P < .05$). BMD, bone mineral density; BMI, body mass index; BSI, bone stress injury; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; LS, lumbar spine; MRI, magnetic resonance imaging; PTH, parathyroid hormone; TH, total hip.

BSI. However, those who suffered an additional BSI had significantly lower baseline Ct.TMD, estimated stiffness, and estimated failure load. All other bone parameters also tended to be worse among those who suffered an additional BSI (Figure 3), although differences did not reach statistical significance.

After adjusting for age at enrollment, Tt.vBMD, Tb.vBMD, and Ct.vBMD decreased significantly from baseline to visit 3 (–0.94% [*P* = .0005], −0.94% [*P* = .004], and −0.58% [*P* = .043], respectively) (Figure 4) in the injured leg before returning to or surpassing baseline values. The uninjured leg followed a similar pattern (Tt.vBMD: −0.61% [*P* = .0002]; Tb.vBMD: –0.67% [*P* = .0008]); however, the decrease in Ct.vBMD (–0.28% [*P* = .33]) did not reach statistical significance. Results were similar in the unadjusted model, with significant decreases from baseline to visit 3 in Tt.vBMD and Tb.vBMD in both legs as well as Ct.vBMD in the injured leg. Of note, of the 30 participants, 8 had Ct.vBMD, Tb.vBMD, and Tt.vBMD values that did not return to normal.

DISCUSSION

We used HR-pQCT to assess vBMD and bone microarchitecture changes in female distance runners throughout 12 months of recovery from a tibial BSI. We found that both the injured and the uninjured tibias experienced compromised bone properties during the initial 3 months after a BSI diagnosis. This suggests that reduced mechanical loading associated with the initial management of a BSI affects all weightbearing bones. Throughout the study, 10 of the 30 participants suffered ≥1 additional BSIs. Women who suffered an additional BSI tended to be younger and had lower baseline PTH levels, a later age of menarche, and a greater prevalence of previous fractures than those who did not sustain an additional BSI, suggesting that several predisposing factors may be important in understanding the BSI risk.

Bone changes lagged behind self-reported reduced weightbearing physical activity and again lagged behind gradual return to weightbearing activity. That is,

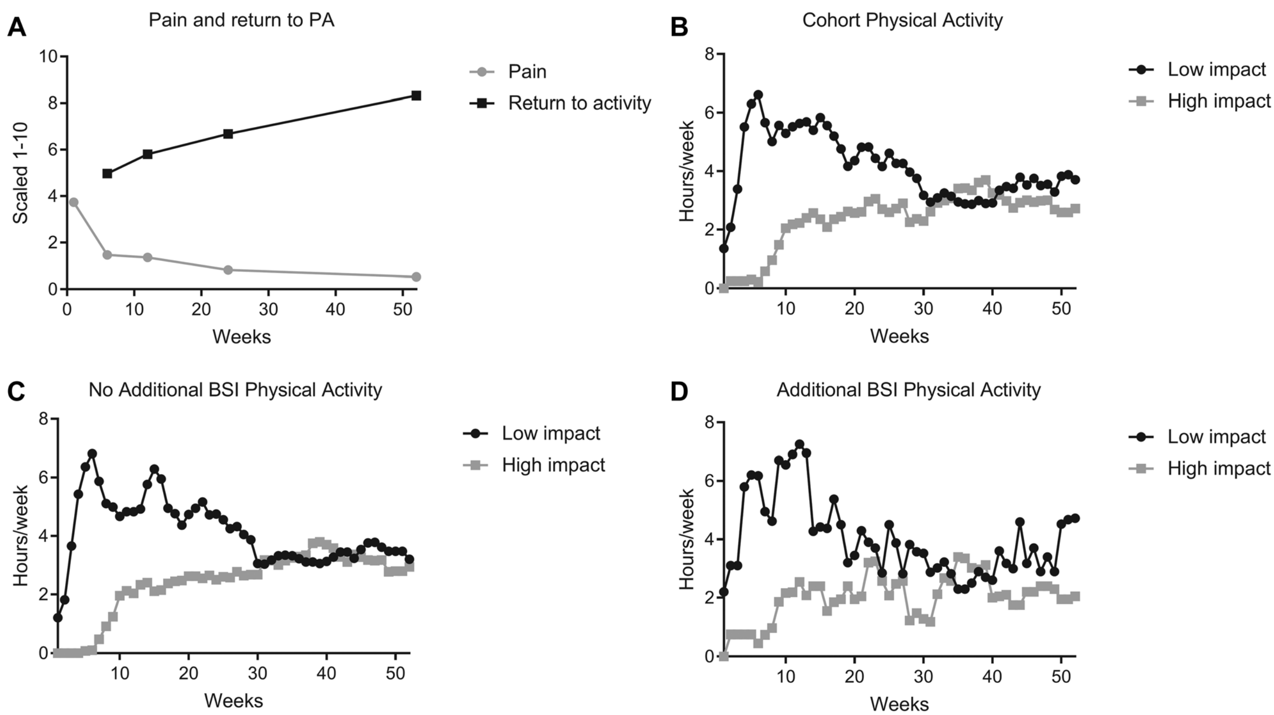

Figure 2. Mean changes in (A) perceived pain during tibial palpation and self-reported return to activity among the entire cohort (scaled 1-10), (B) hours of high-impact (gray line) and low-impact (black line) physical activities throughout 52 weeks after the bone stress injury (BSI) diagnosis among the cohort, (C) hours of high-impact (gray line) and low-impact (black line) physical activities (PA) throughout 52 weeks among those with no additional BSI, and (D) hours of high-impact (gray line) and low-impact (black line) physical activities throughout 52 weeks among those with an additional BSI.

weightbearing physical activity was lowest during the first several weeks of the study, while vBMD was lowest at 12 weeks (visit 3). Weightbearing activity increased steadily from approximately 7 to 20 weeks from baseline, while vBMD did not return to baseline until between visits 4 and 5 (24-52 weeks). This observation suggests that bone changes were influenced by physical activity patterns. Notably, because of the observational nature of this study, we did not dictate recovery strategies, although the majority of our participants wore a pneumatic walking boot or used crutches until they could ambulate without pain. Thus, the uninjured leg was exposed to more weightbearing than the injured leg during the initial phase of recovery.

Our findings of compromised bone properties in both the injured and uninjured legs during BSI recovery, followed by a gradual return to baseline, are supported by several human and animal studies examining the effects of weightbearing activity on the skeleton. It is well-documented that disuse, whether from hindlimb unloading,[10,31] casting,[54] microgravity,[17] or spinal cord injuries,[20] leads to bone resorption and decreased bone mass. At the same time, exercise intervention studies suggest that exercise leads to improved measures of bone strength and geometry in children and adolescents,[33,34] adult women,[55] and postmenopausal women.[58] However, the timing and extent of the skeletal response to partial or reduced weightbearing during injury recovery are ill-defined. To our knowledge, only 1 other study has used HR-pQCT technology in humans during recovery and return to sports after an injury, and this included a 6-week nonweightbearing period after anterior cruciate ligament reconstruction and did not include the uninjured leg.[27] Findings from the anterior cruciate ligament recovery study indicated decreased vBMD (–1.2%) after 6 weeks of nonweightbearing activity and additional decreases after 6 (–2.0%) and 13 (–2.5%) weeks of full weightbearing activity. Our findings of prolonged declines in vBMD after BSIs are similar in timing but smaller in magnitude in both the injured and the uninjured legs, suggesting that partial or full weightbearing allowance during BSI recovery prevents further decrements in vBMD. Interestingly, 8 participants sustained decrements in bone properties that did not return to baseline values (3 who suffered an additional BSI and 5 who did not). Of these 8 participants, 6 did not return to running during the study, 1 sustained 2 additional BSIs and thus was undergoing her third bout of disuse during the 12-month study period, and 1 returned to running but had reduced her running volume by approximately 80% compared with her running volume before study enrollment. Collectively, these observations are consistent with the notion that decrements in bone properties are caused by changes in physical activity patterns rather than the BSI itself.

There is no established protocol for return to running after a BSI diagnosis, although several programs have been proposed for lower limb BSIs.[16,21,57] Current

TABLE 3
Baseline HR-pQCT Measurements[a]

	Cohort Measured (n = 28)	No Additional BSI (n = 19)	Additional BSI (n = 9)	*P* Value
Size/morphology				
Tt.Ar, mm^2	827.0 ± 140.0	839.5 ± 156.0	801.2 ± 101.7	.5
Ct.Ar, mm^2	88.8 ± 14.1	91.6 ± 15.0	82.7 ± 10.4	.1
Ct.Ar/Tt.Ar	0.111 ± 0.028	0.113 ± 0.029	0.106 ± 0.026	.5
Microarchitecture				
Ct.Th, mm	0.80 ± 0.16	0.82 ± 0.17	0.75 ± 0.14	.3
Ct.Po, %	4.35 ± 0.13	4.45 ± 1.30	4.14 ± 1.30	.6
Tb.Th, mm	0.084 ± 0.012	0.086 ± 0.013	0.081 ± 0.009	.3
Tb.Sp, mm	0.379 ± 0.051	0.374 ± 0.057	0.387 ± 0.035	.5
Tb.N, 1/mm	2.18 ± 0.24	2.20 ± 0.27	2.14 ± 0.15	.6
Density				
Tt.vBMD, mg HA/cm^3	286 ± 44	294 ± 48	268 ± 32	.2
Tb.vBMD, mg HA/cm^3	220 ± 32	226 ± 35	207 ± 22	.1
Ct.vBMD, mm HA/cm^3	868 ± 41	876 ± 42	851 ± 35	.1
Ct.TMD, mg HA/cm^3	926 ± 34	935 ± 34	906 ± 26	**.03**
μFEA				
Stiffness, kN/mm	222 ± 32	231 ± 31	202 ± 24	**.03**
Failure load, kN	11.2 ± 1.5	11.6 ± 1.5	10.3 ± 1.2	**.03**

[a]Data are reported as mean ± SD. *P* value indicates the comparison between the no additional BSI group and the additional BSI group. Bold indicates statistical significance ($P < .05$). BSI, bone stress injury; Ct.Ar, cortical area; Ct.Po, cortical porosity; Ct.Th, cortical thickness; Ct.TMD, cortical tissue mineral density; Ct.vBMD, cortical volumetric bone mineral density; HR-pQCT, high-resolution peripheral quantitative computed tomography; μFEA, micro–finite element analysis; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; Tt.Ar, total cross-sectional area; Tt.vBMD, total volumetric bone mineral density.

strategies emphasize returning to full activity as soon as pain (as an indicator of BSI healing) allows, disregarding the overall skeletal response to the period of unloading necessary for BSI healing. Rest days are incorporated into most recommended progressions, and many recommend increases in weekly mileage by no more than 10%, although there is minimal evidence to support this advice as an effective strategy for preventing future injuries.[21,24] While healing of the pathological site is the primary concern, our data indicate that the skeleton remains compromised compared with baseline beyond BSI healing. It is not clear whether this suggests that a more gradual return to sports may be necessary to avoid subsequent BSIs by allowing time for the adequate recovery of bone strength or whether more aggressive loading interventions, particularly for the uninjured limb, might be more effective in preventing subsequent injuries. Further studies of different return-to-sports interventions will better inform the optimization of bone properties during BSI recovery.

The incidence of additional BSIs during the 12-month study period was higher than anticipated. One-third of our participants suffered at least 1 additional BSI during follow-up, most of which occurred in the opposite limb from the BSI at enrollment. Recurrent BSIs have been reported among military trainees. One study reported that recruits who suffered a BSI during basic training are at a higher risk of sustaining BSIs during subsequent training, with a 10.6% incidence within 1 year of the injury compared with 1.7% in injury-free recruits.[35] Among National Collegiate Athletic Association athletes, a recent report of BSIs suggests that 17.5% of female cross-country athletes and 26.3% of female track athletes with a diagnosed BSI experienced recurrent BSIs.[44] In that report, only injuries at the same anatomic location as the initial injury were noted as "recurring injuries." Although longitudinal studies of BSIs among runners are rare, 10.3% to 12.6% of cross-country and track and field athletes with a history of BSIs sustain a subsequent BSI (same or different anatomic site) over a 1- to 2-year time frame.[9,28] In the current study, it is unclear whether the observed trend in subsequent injuries occurring in the contralateral limb is primarily because of deconditioning of the musculoskeletal systems and/or changes in running biomechanics that might favor the previously injured leg. Moreover, because we did not design our study to discern differences between those with and without additional BSIs, we did not have adequate statistical power to determine differences in recovery strategies, return to physical activity, or bone density throughout the recovery time frame. Nevertheless, the high reinjury rate in our cohort, taken together with previous reports of multiple BSIs, suggests room for improved guidelines around BSI management and return-to-activity strategies. Our results indicating bone loss in both the uninjured and the injured legs may help clinicians better educate athletes on the importance of gradual bone loading.

Despite the high prevalence of recurrent BSIs in athlete and military populations, little is known about the characteristics of the bone and/or health history that may contribute to these injuries. At baseline, women in our study who incurred an additional BSI had significantly lower estimated failure load and stiffness as well as lower Ct.TMD.

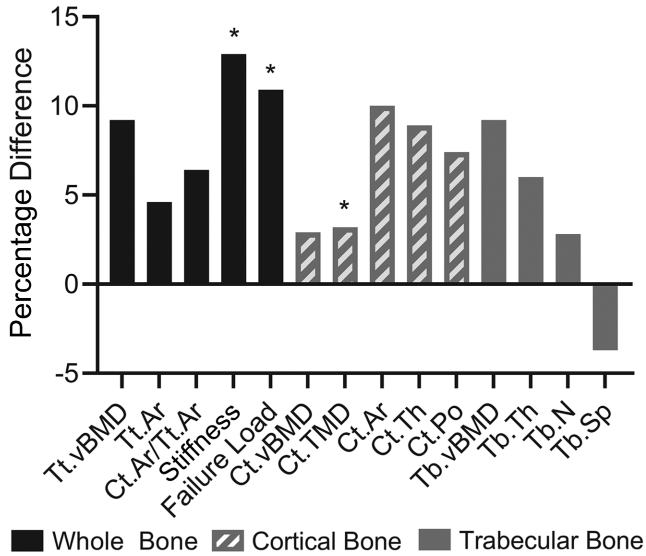

Figure 3. Percentage differences in baseline bone parameters between those who did not sustain an additional bone stress injury (BSI) and those who did sustain an additional BSI. Measurements include total volumetric bone mineral density (Tt.vBMD), total cross-sectional area (Tt.Ar), cortical area (Ct.Ar)/Tt.Ar estimated stiffness, estimated failure load, cortical vBMD (Ct.vBMD), cortical tissue mineral density (Ct.TMD), Ct.Ar, cortical thickness (Ct.Th), cortical porosity (Ct.Po), trabecular vBMD (Tb.vBMD), trabecular thickness (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp) measured by high-resolution peripheral quantitative computed tomography between those who did not sustain an additional BSI compared with those who did sustain an additional BSI during the 12-month study duration. *$P < .05$.

All other bone parameters tended to be worse at baseline in the women who sustained an additional BSI, although these did not reach statistical significance. Interestingly, BSI history before enrollment was not different between our 2 groups (Table 2), although 70% of women who suffered an additional BSI had a history of fractures compared with 20% of women who did not sustain another BSI. This finding is supported by a longitudinal study in adolescent runners that reported girls with a history of fractures had a 6-fold increased risk of BSIs compared with those without.[50] We cannot fully explain this finding, nor do we have a sufficient sample size to further investigate differences between those who have experienced multiple or recurrent BSIs and those who have not. Of note, the women who incurred an additional BSI had a later age of menarche compared with those who did not but no difference in history of amenorrhea, contraceptive use, or aBMD.

Younger age was also a risk factor for recurrent BSIs. Although not supported by the limited literature on athletes addressing age as a risk factor for BSIs,[23] our findings are consistent with several military studies,[11,29,32] including results from a cohort of 1.3 million soldiers reported younger age (<20 years) was associated with an increased BSI risk in

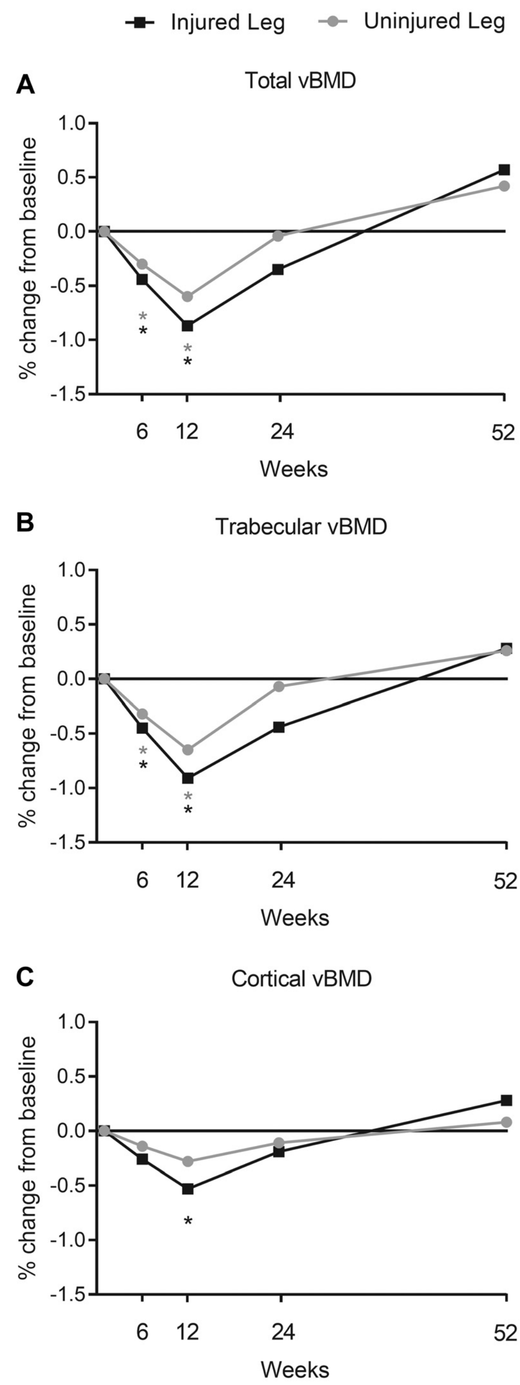

Figure 4. Estimated mean percentage change from baseline at each visit with adjustment for age at enrollment in (A) total volumetric bone mineral density (vBMD), (B) trabecular vBMD, and (C) cortical vBMD for both the injured and the uninjured legs. *$P < .05$ from baseline.

both men and women.[11] We also saw a trend for lower weight and BMI among those with an additional BSI. Low weight and BMI are well-established risk factors for a BSI,[14,37] although BMI in both groups in our study was still in the healthy range. Finally, women who incurred an additional BSI had significantly lower, but still normal, serum PTH levels at study entry compared with those who did not. Baseline levels of PTH have been assessed in previous cross-sectional[12,38] and longitudinal[13,56] reports of the BSI risk, and results are equivocal. While speculative, it is possible that the lower, but still normal, circulating PTH levels among the participants who sustained an additional BSI may reflect diminished bone remodeling activity that may lessen microdamage repair. Larger prospective studies are needed to further explore risk factors for multiple BSIs.

To our knowledge, this is the first study to assess skeletal sites during BSI recovery using HR-pQCT on both the injured and the uninjured legs, providing an indicator of overall skeletal health throughout BSI healing. All BSIs were diagnosed by MRI and graded by a radiologist. We collected detailed information on each athlete's physical activity and pain throughout the study. Despite these strengths, we acknowledge potential limitations of this study including the varied time frames from the onset of pain to the BSI diagnosis. While some participants reported pain for only 1 to 2 weeks before the diagnosis, others reported $\geq$1 month of pain and had altered training before seeking medical attention, which likely influenced "baseline" bone measurements. There was considerable time between the final 3 study visits, which were performed at 12, 24, and 52 weeks after the BSI diagnosis. Therefore, we can only estimate the time that it took for bone parameters to return to baseline. More frequent visits would have allowed a more precise understanding of changes in bone parameters over time. We did not anticipate that 10 participants would incur an additional BSI during the course of the study. While we were able to assess some differences between those who did and did not incur an additional BSI, we did not have the statistical power to adequately assess factors that indicate a greater risk of subsequent or recurring BSIs, nor did we design the study to capture extensive potential risk factors for multiple or recurrent BSIs. Finally, we did not include a control group of nonathletes or a group of athletes with no BSI history for comparison.

In summary, although BSIs are a common and debilitating injury for athletes and military recruits, return-to-activity guidelines are based on perceived pain and are often ambiguous. Our results indicated that vBMD did not return to baseline levels for 3 to 6 months after a BSI diagnosis. Moreover, one-third of our participants sustained $\geq$1 additional BSIs throughout the course of the study. Persistent decrements in bone parameters in both the injured and the uninjured legs, combined with the high rate of subsequent BSIs, suggest the need for improved return-to-sports and return-to-duty guidelines.

REFERENCES

1. Ackerman KE, Nazem T, Chapko D, et al. Bone microarchitecture is impaired in adolescent amenorrheic athletes compared with eumenorrheic athletes and nonathletic controls. *J Clin Endocrinol Metab*. 2011;96(10):3123-3133.
2. Ackerman KE, Putman M, Guereca G, et al. Cortical microstructure and estimated bone strength in young amenorrheic athletes, eumenorrheic athletes and non-athletes. *Bone*. 2012;51(4):680-687.
3. Arendt EA, Griffiths HJ. The use of MR imaging in the assessment and clinical management of stress reactions of bone in high-performance athletes. *Clin Sports Med*. 1997;16(2):291-306.
4. Armstrong DW 3rd, Rue JP, Wilckens JH, Frassica FJ. Stress fracture injury in young military men and women. *Bone*. 2004;35(3):806-816.
5. Beck TJ, Ruff CB, Shaffer RA, Betsinger K, Trone DW, Brodine SK. Stress fracture in military recruits: gender differences in muscle and bone susceptibility factors. *Bone*. 2000;27(3):437-444.
6. Behrens SB, Deren ME, Matson A, Fadale PD, Monchik KO. Stress fractures of the pelvis and legs in athletes: a review. *Sports Health*. 2013;5(2):165-174.
7. Bennell K, Matheson G, Meeuwisse W, Brukner P. Risk factors for stress fractures. *Sports Med*. 1999;28(2):91-122.
8. Bennell KL, Malcolm SA, Thomas SA, et al. Risk factors for stress fractures in track and field athletes: a twelve-month prospective study. *Am J Sports Med*. 1996;24(6):810-818.
9. Bennell KL, Malcolm SA, Thomas SA, Wark JD, Brukner PD. The incidence and distribution of stress fractures in competitive track and field athletes: a twelve-month prospective study. *Am J Sports Med*. 1996;24(2):211-217.
10. Bikle DD, Halloran BP. The response of bone to unloading. *J Bone Miner Metab*. 1999;17(4):233-244.
11. Bulathsinhala L, Hughes JM, McKinnon CJ, et al. Risk of stress fracture varies by race/ethnic origin in a cohort study of 1.3 million U.S. Army soldiers. *J Bone Miner Res*. 2017;32(7):1546-1553.
12. Carbon R, Sambrook PN, Deakin V, et al. Bone density of elite female athletes with stress fractures. *Med J Aust*. 1990;153(7):373-376.
13. Cosman F, Ruffing J, Zion M, et al. Determinants of stress fracture risk in United States Military Academy cadets. *Bone*. 2013;55(2): 359-366.
14. De Souza MJ, Nattiv A, Joy E, et al. 2014 Female Athlete Triad Coalition Consensus Statement on Treatment and Return to Play of the Female Athlete Triad: 1st International Conference held in San Francisco, California, May 2012 and 2nd International Conference held in Indianapolis, Indiana, May 2013. *Br J Sports Med*. 2014;48(4):289.
15. Fredericson M, Bergman AG, Hoffman KL, Dillingham MS. Tibial stress reaction in runners: correlation of clinical symptoms and scintigraphy with a new magnetic resonance imaging grading system. *Am J Sports Med*. 1995;23(4):472-481.
16. Fredericson M, Jennings F, Beaulieu C, Matheson GO. Stress fractures in athletes. *Top Magn Reson Imaging*. 2006;17(5):309-325.
17. Gerbaix M, Gnyubkin V, Farlay D, et al. One-month spaceflight compromises the bone microstructure, tissue-level mechanical properties, osteocyte survival and lacunae volume in mature mice skeletons. *Sci Rep*. 2017;7(1):2659.
18. Giladi M, Alcalay J. Stress fracture of the calcaneus: still an enigma in the Israeli Army. *JAMA*. 1984;252(22):3128-3129.
19. Giladi M, Milgrom C, Simkin A, Danon Y. Stress fractures: identifiable risk factors. *Am J Sports Med*. 1991;19(6):647-652.
20. Haider IT, Lobos SM, Simonian N, Schnitzer TJ, Edwards WB. Bone fragility after spinal cord injury: reductions in stiffness and bone mineral at the distal femur and proximal tibia as a function of time. *Osteoporos Int*. 2018;29(12):2703-2715.
21. Harmon KG. Lower extremity stress fractures. *Clin J Sport Med*. 2003;13(6):358-364.
22. Hughes JM, Gaffney-Stomberg E, Guerriere KI, et al. Changes in tibial bone microarchitecture in female recruits in response to 8 weeks of U.S. Army Basic Combat Training. *Bone*. 2018;113:9-16.
23. Iwamoto J, Takeda T. Stress fractures in athletes: review of 196 cases. *J Orthop Sci*. 2003;8(3):273-278.
24. Johnston CA, Taunton JE, Lloyd-Smith DR, McKenzie DC. Preventing running injuries: practical approach for family doctors. *Can Fam Physician*. 2003;49:1101-1109.
25. Jones BH, Cowan DN, Tomlinson JP, Robinson JR, Polly DW, Frykman PN. Epidemiology of injuries associated with physical training

among young men in the army. *Med Sci Sports Exerc*. 1993; 25(2):197-203.
26. Kaeding CC, Yu JR, Wright R, Amendola A, Spindler KP. Management and return to play of stress fractures. *Clin J Sport Med*. 2005; 15(6):442-447.
27. Kazakia GJ, Tjong W, Nirody JA, et al. The influence of disuse on bone microstructure and mechanics assessed by HR-pQCT. *Bone*. 2014;63:132-140.
28. Kelsey J, Bachrach LK, Procter-Gray E, et al. Risk factors for stress fracture among young female cross-country runners. *Med Sci Sports Exerc*. 2007;39(9):1457-1463.
29. Knapik J, Montain SJ, McGraw S, Grier T, Ely M, Jones BH. Stress fracture risk factors in Basic Combat Training. *Int J Sports Med*. 2012;33(11):940-946.
30. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998;6(5-6):329-337.
31. LeBlanc A, Marsh C, Evans H, Johnson P, Schneider V, Jhingran S. Bone and muscle atrophy with suspension of the rat. *J Appl Physiol (1985)*. 1985;58(5):1669-1675.
32. Lee D; Armed Forces Health Surveillance Center. Stress fractures, active component, U.S. Armed Forces, 2004-2010. *MSMR*. 2011; 18(5):8-11.
33. Macdonald HM, Kontulainen SA, Khan KM, McKay HA. Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls? *J Bone Miner Res*. 2007;22(3):434-446.
34. McKay HA, MacLean L, Petit M, et al. ''Bounce at the Bell'': a novel program of short bouts of exercise improves proximal femur bone mass in early pubertal children. *Br J Sports Med*. 2005;39(8):521-526.
35. Milgrom C, Giladi M, Chisin R, Dizian R. The long-term followup of soldiers with stress fractures. *Am J Sports Med*. 1985;13(6):398-400.
36. Mitchell DM, Tuck P, Ackerman KE, et al. Altered trabecular bone morphology in adolescent and young adult athletes with menstrual dysfunction. *Bone*. 2015;81:24-30.
37. Mountjoy M, Sundgot-Borgen J, Burke L, et al. The IOC consensus statement: beyond the female athlete triad. Relative Energy Deficiency in Sport (RED-S). *Br J Sports Med*. 2014;48(7):491-497.
38. Myburgh KH, Hutchins J, Fataar AB, Hough SF, Noakes TD. Low bone density is an etiologic factor for stress fractures in athletes. *Ann Intern Med*. 1990;113(10):754-759.
39. Nattiv A, Kennedy G, Barrack MT, et al. Correlation of MRI grading of bone stress injuries with clinical risk factors and return to play: a 5-year prospective study in collegiate track and field athletes. *Am J Sports Med*. 2013;41(8):1930-1941.
40. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone*. 2002;30(6):842-848.
41. Popp KL, Hughes JM, Martinez-Betancourt A, et al. Bone mass, microarchitecture and strength are influenced by race/ethnicity in young adult men and women. *Bone*. 2017;103:200-208.
42. Popp KL, Hughes JM, Smock AJ, et al. Bone geometry, strength, and muscle size in runners with a history of stress fracture. *Med Sci Sports Exerc*. 2009;41(12):2145-2150.
43. Rauh MJ, Macera CA, Trone DW, Shaffer RA, Brodine SK. Epidemiology of stress fracture and lower-extremity overuse injury in female recruits. *Med Sci Sports Exerc*. 2006;38(9):1571-1577.
44. Rizzone KH, Ackerman KE, Roos KG, Dompier TP, Kerr ZY. The epidemiology of stress fractures in collegiate student-athletes, 2004-2005 through 2013-2014 academic years. *J Athl Train*. 2017;52(10): 966-975.
45. Robertson GA, Wood AM. Return to sports after stress fractures of the tibial diaphysis: a systematic review. *Br Med Bull*. 2015;114(1): 95-111.
46. Saxena A, Fullem B, Hannaford D. Results of treatment of 22 navicular stress fractures and a new proposed radiographic classification system. *J Foot Ankle Surg*. 2000;39(2):96-103.
47. Schnackenburg KE, Macdonald HM, Ferber R, Wiley JP, Boyd SK. Bone quality and muscle strength in female athletes with lower limb stress fractures. *Med Sci Sports Exerc*. 2011;43(11):2110-2119.
48. Shaffer RA, Rauh MJ, Brodine SK, Trone DW, Macera CA. Predictors of stress fracture susceptibility in young female recruits. *Am J Sports Med*. 2006;34(1):108-115.
49. Snow CM, Williams DP, LaRiviere J, Fuchs RK, Robinson TL. Bone gains and losses follow seasonal training and detraining in gymnasts. *Calcif Tissue Int*. 2001;69(1):7-12.
50. Tenforde AS, Sayres LC, McCurdy ML, Sainani KL, Fredericson M. Identifying sex-specific risk factors for stress fractures in adolescent runners. *Med Sci Sports Exerc*. 2013;45(10):1843-1851.
51. Torg JS, Balduini FC, Zelko RR, Pavlov H, Peff TC, Das M. Fractures of the base of the fifth metatarsal distal to the tuberosity: classification and guidelines for non-surgical and surgical management. *J Bone Joint Surg Am*. 1984;66(2):209-214.
52. Torg JS, Moyer J, Gaughan JP, Boden BP. Management of tarsal navicular stress fractures: conservative versus surgical treatment. A meta-analysis. *Am J Sports Med*. 2010;38(5):1048-1053.
53. Umemura Y, Ishiko T, Yamauchi T, Kurono M, Mashiko S. Five jumps per day increase bone mass and breaking force in rats. *J Bone Miner Res*. 1997;12(9):1480-1485.
54. Uthoff HK, Jaworski ZF. Bone loss in response to long-term immobilization. *J Bone Joint Surg Br*. 1978;60:420-429.
55. Vainionpaa A, Korpelainen R, Sievanen H, Vihriala E, Leppaluoto J, Jamsa T. Effect of impact exercise and its intensity on bone geometry at weight-bearing tibia and femur. *Bone*. 2007;40(3):604-611.
56. Valimaki VV, Alfthan H, Lehmuskallio E, et al. Risk factors for clinical stress fractures in male military recruits: a prospective cohort study. *Bone*. 2005;37(2):267-273.
57. Warden SJ, Davis IS, Fredericson M. Management and prevention of bone stress injuries in long-distance runners. *J Orthop Sports Phys Ther*. 2014;44(10):749-765.
58. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR. High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. *J Bone Miner Res*. 2018;33(2):211-220.
59. Westerlind KC, Fluckey JD, Gordon SE, Kraemer WJ, Farrell PA, Turner RT. Effect of resistance exercise training on cortical and cancellous bone in mature male rats. *J Appl Physiol (1985)*. 1998;84(2): 459-464.