Full Length Article

Bone strength estimates relative to vertical ground reaction force discriminates women runners with stress fracture history

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ABSTRACT

Purpose: To determine differences in bone geometry, estimates of bone strength, muscle size and bone strength relative to load, in women runners with and without a history of stress fracture.
Methods: We recruited 32 competitive distance runners aged 18–35, with (SFX, n = 16) or without (NSFX, n = 16) a history of stress fracture for this case-control study. Peripheral quantitative computed tomography (pQCT) was used to assess volumetric bone mineral density (vBMD, mg/mm^3), total (ToA) and cortical (CtA) bone areas (mm^2), and estimated compressive bone strength (bone strength index; BSI, mg/mm^4) at the distal tibia. ToA, CtA, cortical vBMD, and estimated strength (section modulus; Zp, mm^3 and strength strain index; SSIp, mm^3) were measured at six cortical sites along the tibia. Mean active peak vertical (pkZ) ground reaction forces (GRFs), assessed from a fatigue run on an instrumented treadmill, were used in conjunction with pQCT measurements to estimate bone strength relative to load (mm^2/N $*$ kg^{-1}) at all cortical sites.
Results: SSIp and Zp were 9–11% lower in the SFX group at mid-shaft of the tibia, while ToA and vBMD did not differ between groups at any measurement site. The SFX group had 11–17% lower bone strength relative to mean pkZ GRFs (p < 0.05).
Conclusion: These findings indicate that estimated bone strength at the mid-tibia and mean pkZ GRFs are lower in runners with a history of stress fracture. Bone strength relative to load is also lower in this same region suggesting that strength deficits in the middle 1/3 of the tibia and altered gait biomechanics may predispose an individual to stress fracture.

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1. Introduction

Stress fracture is an overuse injury to bone tissue that occurs with repetitive loading and is thought to result from an imbalance between microdamage-driven bone remodeling and bone repair [16]. Because stress fracture healing typically takes 6–12 weeks or longer, depending on the fracture grade and site [31], this injury is a concern among athletes [27], particularly runners [25,37]. The highest incidence of stress fracture is reported in members of track and field teams with rates from 10 to 31% per year [11,23]. Some research suggests that the incidence in women runners is twice that in their male counterparts [3].

Due to the risk of stress fractures among highly active populations, as well as the costly nature of the injury in terms of recovery time, it is important to understand the factors that cause an individual to be at greater susceptibility [25,37]. These factors generally fall into two categories: factors that affect bone strength (bone mineral density, bone geometry, age, genetics, nutrition, endocrine and hormonal status, exercise or loading history, and bone disease), and factors that influence the mechanical load on bone (gait biomechanics, changes in loading intensity and frequency, training surface, footwear, and body size and composition) [5,22,41].

Numerous studies addressing stress fractures have focused on examining surrogates of bone strength – particularly bone mineral density (BMD) – to better understand stress fracture risk. The most widely utilized method of measuring BMD is through dual x-ray absorptiometry (DXA), which provides a two-dimensional or areal BMD (aBMD). Findings from cross sectional studies have yielded controversial results with

some showing lower aBMD and some showing no difference or even higher aBMD in those with a history of stress fracture [4,8–10,13,14,19,30,39]. There is evidence through both cross-sectional and prospective research suggesting that low aBMD, as a risk factor for stress fracture, may be more common in women than men [8,10]. In a prospective cohort study, female track and field athletes diagnosed with a stress fracture had lower aBMD of the lumbar spine compared to those who remained healthy [10]. Importantly, although aBMD was lower in women who sustained a stress fracture, it was higher than or similar to bone density of less active women. This implies that women at risk of stress fracture in this cohort would not be identified as high risk based on normative DXA values.

Some findings suggest that geometric parameters (e.g. thinner cortices and narrow bones) may be more helpful for predicting stress fracture risk [1,6–8,18,28,35,39]. However, most of these studies have used bone geometry parameters also derived from DXA that fail to depict true bone tissue density and 3-dimensional geometry [17]. Studies using computed tomography (CT) or low radiation measurement techniques such as peripheral quantitative computed tomography (pQCT), and high resolution peripheral quantitative computed tomography (HRpQCT), which are capable of assessing volumetric bone mineral density (vBMD) and 3-dimensional bone geometry, are lacking.

pQCT and HRpQCT allow estimates of bone strength as well as muscle mass from cross-sectional geometry. In a previous study conducted in our laboratory, we found significant deficits in pQCT derived estimated bone strength in women runners with a history of stress fracture (SFX) compared to those with no history of stress fracture (NSFX) [35]. However, these differences disappeared after the estimated bone strength was adjusted for muscle size. Our findings suggested that bone strength was appropriately adapted to muscle size. Although there is a clear muscle-bone relationship, using muscle size alone as a measure of load imposed on bone eliminates factors of load that are affected by differences in gait mechanics between SFX and NSFX. Evaluating ground reaction forces (GRFs) during a run provides additional information with which to understand the biomechanical basis of stress fracture. If the bones adapt to loads imposed by habitual running [32], those runners who elicit higher vertical GRFs relative to body mass should theoretically have stronger bones. Vertical GRFs that occur during running are indicative of the load experienced by habitual runners [9]. These GRFs can be used in combination with pQCT measurements to estimate bone strength relative to the loads imposed and should be considered when assessing stress fracture risk. We are unaware of any studies that have used pQCT derived strength values, at multiple sites of the tibia, relative to an individual's vertical GRFs during a continuous run.

Thus the purpose of our study was to: a) determine differences in vBMD and bone geometry, and b) use a force sensing treadmill in conjunction with bone measurements to assess differences in bone strength relative to load in competitive women distance runners with and without a history of stress fracture. We hypothesized that women distance runners with a history of stress fracture would have smaller cortical bone area (CtA), lower estimated bone strength, and lower estimated bone strength relative to load, than runners with no history of stress fracture.

2. Methods

2.1. Participants

We recruited competitive women distance runners (ages 18–37) with (n = 16) and without (n = 16) a history of stress fracture from the Salt Lake City metropolitan area. "Competitive" was defined as having a competitive season(s) each year in which three or more races are completed. To be eligible for the study, athletes must run an average of 20 or more miles per week during their competitive season. Participants were recruited into a stress fracture group (SFX) and a non-stress

fracture group (NSFX) depending on whether or not they had a medically diagnosed stress fracture by diagnostic imaging tests (bone scan, MRI or X-ray) in any bones of the lower limbs in five years prior to the study. In a screening questionnaire, potential participants were asked a series of questions related to basic health, stress fracture history, competition and training status. Participants were excluded if they had a stress fracture during the 12 months prior to the study (n = 2), had a self-reported history of an eating disorder (n = 1), medication use (other than oral contraceptives) known to influence bone metabolism, or were pregnant at the time of the study. A pregnancy test was administered to all participants prior to pQCT scans. This study was approved by the Internal Review Board (IRB) of the University of Minnesota, the University of Utah, and The Orthopedic Specialty Hopsital (TOSH) in Murray, UT. All participants signed an informed consent form in accordance with IRB guidelines prior to participation in the study.

Participants were required to visit the University of Utah Hospital for approximately 1 h on one occasion. During this visit, following consent and anthropometry, bone health was assessed. Participants were required to make an additional visit to TOSH within one week of consent, for measurement of ground reaction forces during running.

2.2. Anthropometry

We measured participant height to the nearest millimeter using a wall-mounted stadiometer (Health O Meter, Rye, NY) and mass to the nearest 0.1 kg on a calibrated electronic scale (Seca Model 840, Hanover, MD). We measured tibia length to the nearest millimeter using an anthropometric tape. All measurements were taken twice, and the mean of two measurements used.

2.3. Questionnaires

We assessed training history, health history, sport-related injury, menstrual history and status, stress fracture history and past/current oral contraceptive use through questionnaires. The eating attitudes test (EAT-26) was used to screen for disordered eating and has been used in previous studies of runners [2,21,34]. These questionnaires were chosen to help assess whether there were group differences in factors known to influence stress fracture risk.

2.4. Bone measurements

We used peripheral quantitative computed tomography (pQCT, XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) to assess vBMD, geometry and estimated bone strength. Participants were required to sit with one leg extended for ~30 min for each limb. pQCT scans were taken at the distal region (4% of the tibia length) and along the midshaft (15%, 25%, 33%, 45%, 50%, and 66%) of each tibia. Each participant's leg was positioned using a customized leg holder (Bone Diagnostic Inc.). A Velcro strap was used to ensure each participant's leg remained stationary during scan acquisition. We determined the reference line by acquisition of a 30 mm planar scout view of the joint line. All pQCT analyses were based on a sampling resolution (voxel size) of 0.4 mm and a scan speed of 25 mm/s, according to the manufacturer's recommendations. To analyze the 4% site we used contour mode 3 (200 mg/cm^3), peel mode 5 (automatic) and cort mode 3 (200 mg/cm^3). This highly trabecular site of the tibia was assessed for total bone cross-sectional area (ToA, mm^2) and total vBMD (mg/mm^3). Bone strength was estimated using the bone strength index (BSI, mg/mm^4) calculated as ToA $*$ vBMD^2/100,000. The cortical regions (15%–66%) of the tibia were assessed using contour mode 1 (710 mg/cm^3), peel mode 2 (540 mg/cm^3), and cort mode 1 (710 mg/cm^3 and 480 mg/cm^3 for polar strength strain index (SSIp)). We calculated ToA, CtA (mm^2), and cortical vBMD (mg/cm^3). The

polar strength-strain index (SSI$_p$, mm^3) and section modulus (Zp, mm^3) were used to estimate bone strength. Muscle cross sectional area (MCSA) was measured at the 66% site as this is typically the area associated with the largest calf muscle belly [36]. Our assessment of MCSA included all lower limb muscles that are in the 66% cross-section of the tibia and was determined based on thresholds to define tissue borders of bone, skeletal muscle, and subcutaneous fat. We used contour mode 1 (−100 mg/cm^3), peel mode 2 (40 mg/cm^3) and cort mode 1 (710 mg/cm^3). Total exposure to ionizing radiation for each participant was 1.8 millirem.

One trained operator (KP) performed all measurements as well as the scan analysis. Quality assurance was performed daily using the cone phantom provided by the manufacturer. Because there are currently no standardized analysis protocols for pQCT studies analyzing the present target population, the modes and thresholds used in this study are based on the manufacturer's recommendations.

2.5. Fatigue run

We used a high-speed force-sensing motorized treadmill (Treadmetrix, Park City, UT) to collect ground reaction forces during an exhaustive treadmill run. This custom designed, lightweight treadmill has 3D force transducers (MC3A AMTI, Watertown, MA) at each corner that interface with amplifiers (MSA6 AMTI, Watertown, MA) allowing continuous measurements of ground reaction forces during multiple footfalls.

The exhaustive run was performed at each individual's predicted 5 km race pace, based on previous race performances. This is a pace that is assumed to be greater than anaerobic threshold pace and assumed to elicit fatigue [12,15]. Because experienced runners are accustomed to various types of warm-up runs and stretches, participants were allowed 15 min to complete a self-selected warm-up. Upon completion of the warm-up, the treadmill was set to each individual's predetermined pace. Participants were asked to run to volitional fatigue with a goal of reaching 9–10 on a Rate of Perceived Exertion scale (scaled from 1 to 10). To monitor fatigue, heart rate and Rate of Perceived Exertion were recorded once every minute for the duration of the run and blood lactate levels were collected immediately after the run. We used C-motion visual 3D motion analysis software (C-Motion, Inc., Germantown, MD) to manage and report outcomes. All GRFs were collected at 1000 Hz and lowpass filtered at 25 Hz using a 4th order Butterworth filter. The main variable of interest was active peak vertical (pkZ) GRF. We chose the active peak because it has been associated with the largest compressive and sheer loading of the posterior tibia [38]. pkZ GRFs were collected during the first 10 s (~20–24 footfalls) of each minute and normalized for body mass (N ∗ kg^{-1}). For each 10 second collection period, we calculated a mean pkZ GRF for both the left and the right leg (~10–12 footfalls each). In order to make between-participant comparisons throughout the duration of the run, we normalized collection points into a relative percent of the fatigue run (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%). To do this we used the mean pkZ GRF collected during the minute nearest to each 10% of the total run length (i.e. for a 17 minute run each 10% segment represents 1.7 min thus we used the mean pkZ GRF of minutes 0, 2, 3, 5, 7, 9, 10, 12, 14, 15, and 17 for analysis).

2.6. Bone strength relative to load

In order to assess tibia strength in relation to mean pkZ GRFs during running, we adapted Selker et al.'s theory regarding the scaling of long bone fracture strength with body mass [40]. Selker suggests, based on the beam theory, that in animals with different body sizes, the strength of a long bone generally scales as the section modulus over bone length. We adapted this equation and calculated the polar strength strain index (SSIp), which is a density-weighted section modulus. We divided this

by a surrogate for lever arm (the product of total tibia length and percent length of the tibia at which SSIp was calculated). This gives us a measure of bone strength. To express bone strength relative to load we divided bone strength by ground mean pkZ GRFs.

$$\text{relative bone strength} = \frac{(\text{SSI}_p\,(\text{mm}^3)/\text{LengthTibia(mm)} * \text{x})}{\text{mean pkZ GRF}_{(N*\text{kg}^{-1})}}$$

x = percent tibia length

2.7. Statistical analyses

Data were summarized by means (95% Confidence Interval) unless specified otherwise. Participant characteristics were compared using unpaired t-tests. Between-group differences in contraceptive use and menstrual cycles per year were compared using the Fisher's exact test. While SFX and NSFX groups reported similar miles run per week and years of training, they differed by age, body mass, and height. To control for these factors, bone outcomes were adjusted for age, body mass and tibia length. Differences in baseline bone parameters, regardless of left or right limb, were compared using a random-effects general linear model treating left and right measures as a pair of repeated measures and to adjust for age, body mass, and tibia length, wherein the individual participant specific intercepts were allowed to vary at random. Analysis of covariance (ANCOVA) was applied to compare differences in left limb and right limb baseline bone parameters and bone strength relative to load. In an additional statistical model, we added MCSA as a covariate to determine if differences in bone geometry and strength remained after MCSA was controlled for. Finally, to compare differences in left and right mean pkZ GRFs between SFX and NSFX groups throughout the duration of the fatigue run, we compared the means over time using random intercept longitudinal general linear model with variance component error structure. A two-sided p < 0.05 was considered statistically significant.

3. Results

3.1. Demographics and training history

Values for descriptive variables for the women in both the SFX and NSFX groups are displayed in Table 1. Two participants (one from

Table 1
Demographic characteristics of female runners with (SFX) and without (NSFX) a history of stress fracture. Values are Mean (95% Confidence Interval).

	SFX n = 15	NSFX N = 15	p-Value
Age (yrs)	27.0 (24.3, 29.7)	30.9 (28.2, 33.5)	0.05[*]
Height (cm)	164.8 (162.1, 161.7)	169.8 (167.1172.5)	0.04[*]
Body mass (kg)	54.8 (52.1, 57.4)	60.3 (57.6, 62.9)	0.004[*]
BMI (kg/m^2)	20.2 (19.3, 21.1)	20.9 (20.0, 21.8)	0.30
Tibia length (mm)	367.9 (356.8, 379.1)	375.9 (364.8, 387.1)	0.31
Average miles run per week	25.6 (18.3, 32.9)	28.1 (20.8, 35.4)	0.63
Plyometric training (hrs/wk)	0.4 (0.1, 0.8)	0.4 (0.1, 0.8)	1.00
Weight training (hrs/wk)	1.9 (0.8, 3.1)	1.8 (0.7. 2.9)	0.87
Years of training	14.7 (11.4, 18.0)	14.9 (11.6, 18.2)	0.89
Fatigue run speed (mph)	8.1 (7.5–8.6)	7.7 (7.1–8.3)	0.39
Time to fatigue (min)	18.7 (15.8–21.5)	16.0 (13.8–18.2)	0.12
Eat 26	4.3 (2.2, 6.4)	6.2 (4.1, 8.3)	0.21
Age of menarche	13.5 (12.6, 14.5)	13.5 (12.5, 14.4)	1.00
Contraceptives (yes/no)	12/3	12/3	1.00
Cycles/year			0.53
<4	1	2	
4–10	2	4	
≥10	12	9	

[*] Significantly different from stress fracture group (p < 0.05).

each group) were unable to complete the fatigue run. One became injured after completing pQCT measurements, the other overestimated her current fitness and only completed 3 min of the run. They were excluded from the analysis leaving us with 15 runners in each group. Participants ranged in age from 18 to 39 years, weighed 47.4–72.8 kg and had normal body mass index (17–24 kg/m^2). Participants had been running for 4–31 years and ran between 6.5–10 mph during the fatigue run. Mean values were similar between groups for most variables although the SFX group was slightly younger (4 years, p < 0.05), shorter (5 cm, p < 0.05), and lighter (5.5 kg, p < 0.01) than the NSFX group. There was no significant differences in Eat-26 scores between groups and no scores were indicative of eating disorders. Contraceptive use, age of menarche and menstrual status were similar between groups. Women in the SFX group self-reported stress fractures in the femur (n = 5), tibia or fibula (n = 25) and bones in the foot (n = 8). Nine women had a history of 2 or more stress fractures and eight had experienced a stress fracture on both their right and left limbs.

3.2. Bone

Bone strength indices in both the left and the right tibia were similar to findings of the combined left and right limb analysis. In the general linear model combined analysis the SFX group had significantly lower Zp at the 45% and 50% sites, SSIp at the 50% site, CtA at the 15% and 45% sites and MSCA (Table 2) compared to the NSFX group. In the separate right and left leg analysis (ANCOVA) bone strength was also significantly lower in the SFX group within the middle third of the tibia (45–

50% sites) for Zp (−9 to −12%) and (50% site) SSIp (−10 to −11%). We detected significantly smaller CtA at the 15% site in both left and right tibia (−7%) and at the 45% site (−7%) in the left tibia. Total bone area and vBMD did not differ or approach statistically significant differences between groups at any site. Muscle cross-sectional area (MCSA) of the right leg was 8% lower (p = 0.03) in the SFX group than the NSFX group but we saw no significant difference in MCSA in the left leg (p = 0.06). Because of differences found in both the combined and separate limb analyses, we added MCSA as a covariate to the models. After adjusting for MCSA, there were no longer significant differences between groups at any measured site in either analysis.

3.3. Ground reaction forces

Throughout the fatigue run, there were no significant within group differences in mean pkZ GRFs when comparing the beginning of the run to the end (Fig. 1). Each participant reached a blood lactate level of >4 mmol·l^{-1}, suggesting fatigue was achieved [33]. Differences in, mean pkZ GRFs in the SFX group were approximately 3% higher (p = 0.006) on the left leg (Fig. 1) and 4% higher (p = 0.001) on the right leg (data not shown) throughout the entire run compared to the NSFX group.

3.4. Relative bone strength

Because mean PkZ GRFs did not change in either leg or in either group throughout the duration of the run we chose to use the values

Table 2
Tibia bone volumetric density, geometry and estimated strength in female runners with (SFX) and without (NSFX) a history of stress fracture. Values are adjusted for age, mass, and tibia length and presented as mean and mean (95% confidence interval).

	Group								
Parameter		Delta[a]	p-Value[a]	SFX n = 15 mean* (CI)		NSFX n = 15 mean* (CI)		p-Value	
				Left	Right	Left	Right	Left	Right
4%	Total area (mm^2)	52.0	0.18	931.2 (870.0, 992.4)	926.7 (868.0, 985.5)	988.9 (927.7, 1050)	969 (910.8, 1028.3)	0.19	0.31
	BMD (mg/mm^3)	4.7	0.70	321.2 (303.9, 338.5)	325.9 (306.4, 345.5)	319.8 (302.5, 337.1)	322.1 (302.5, 341.6)	0.91	0.78
	BSI ((mg/mm^4)/1,000,000)	2.5	0.72	96.2 (86.2, 106.1)	98.7 (87.9, 109.0)	101.3 (91.4, 111.2)	101.1 (89.8, 111.1)	0.47	0.80
15%	Total area (mm^2)	15.9	0.41	391.8 (362.9, 420.7)	393.3 (363.4, 423.3)	405.9 (377.0, 434.8)	409.9 (379.5, 439.4)	0.48	0.45
	Cortical area (mm^2)	14.04	0.01*	173.9 (165.1, 182.8)	174.5 (165.8, 183.3)	187.8 (179.0, 196.7)	188.6 (179.9, 197.3)	0.03*	0.03*
	Cortical density (mg/mm^3)	8.1	0.13	1162 (1153, 1171)	1159 (1151, 1167)	1169 (1161, 1178)	1168.2 (1160, 1177)	0.26	0.12
	SSIp (mm^3)	119.6	0.13	1369 (1249, 1489)	13,589 (1239, 1478)	1485 (1365, 1604)	1476 (1357, 1596)	0.17	0.17
	Section modulus (mm^3)	117.3	0.13	1320 (1203, 1437)	1317 (1198, 1437)	1439 (1322, 1556)	1431 (1312, 1551)	0.16	0.18
25%	Total area (mm^2)	12.1	0.34	335.8 (316.6, 355.1)	337.5 (316.8, 358.1)	345.1 (325.9, 364.3)	352.8 (332.2, 373.4)	0.50	0.30
	Cortical area (mm^2)	13.2	0.09	229.1 (217.9, 240.3)	230.7 (218.2, 243.1)	240.0 (228.8, 251.2)	245.8 (233.3, 258.2)	0.17	0.09
	Cortical density (mg/mm^3)	1.0	0.91	1202 (1192, 1211)	1199 (1189, 1211)	1203 (1194, 1213)	1200 (1189, 1211)	0.80	1.00
	SSIp (mm^3)	76.1	0.29	1380 (1273, 1488)	1408 (1293, 1522)	1440 (1333, 1547)	1500 (1385, 1614)	0.43	0.26
	Section modulus (mm^3)	89.0	0.22	1325 (1221, 1430)	1357 (1241, 1473)	1392 (1288, 1496)	1469 (1353, 1585)	0.37	0.18
33%	Total area (mm^2)	13.9	0.24	348.4 (331.4, 365.3)	355.4 (336.1, 374.8)	363.3 (346.3, 380.3)	369.2 (349.9, 388.6)	0.22	0.31
	Cortical area (mm^2)	13.0	0.14	268.5 (256.1, 281.6)	273.7 (259.0, 288.5)	282.0 (269.2, 294.7)	286.9 (272.1, 301.7)	0.15	0.21
	Cortical density (mg/mm^3)	0.8	0.91	1203 (1194, 1212)	1198 (1186.6, 1210.3)	1203 (1194, 1212)	1196.9 (1185, 1209)	1.00	0.85
	SSIp (mm^3)	84.6	0.20	1493 (1399, 1588)	1519 (1408, 1629)	1583 (1488, 1678)	1602 (1492, 1713)	0.19	0.29
	Section modulus (mm^3)	99.5	0.16	1452 (1353, 1552)	1495 (1378, 1612)	1560 (1460, 1660)	1590 (1473, 1708)	0.13	0.26
45%	Total area (mm^2)	24.0	0.07	395.4 (376.3, 414.6)	398 (367.6, 419.4)	417.5 (398.4, 436.7)	423.2 (401.7, 444.6)	0.11	0.10
	Cortical area (mm^2)	22.8	0.05*	302.1 (285.1, 319.2)	304.1 (285.2, 322.9)	322.6 (305.6, 339.7)	328.9 (310.0, 247.7)	0.01*	0.06
	Cortical density (mg/mm^3)	0.7	0.93	1189 (1178, 1200)	1189 (1176, 1201)	1190 (1179, 1202)	1186 (1173, 1199)	0.86	0.71
	SSIp (mm^3)	163.8	0.06	1714 (1592, 1836)	1722 (1580, 1864)	1868 (1746, 1990)	1886 (1744, 2028)	0.08	0.12
	Section modulus (mm^3)	191.0	0.03*	1692 (1571, 1811)	1681 (1534, 1829)	1860 (1740, 1980)	1891 (1743, 2038)	0.05*	0.05*
50%	Total area (mm^2)	22.6	0.13	412.7 (390.2, 435.1)	420.8 (397.4, 444.2)	438.1 (415.7, 460.5)	441.1 (417.7, 464.5)	0.12	0.22
	Cortical area (mm^2)	22.8	0.07	306.8 (288.1, 325.5)	312.5 (292.5, 332.5)	329.9 (311.2, 348.6)	334.2 (314.2, 354.1)	0.09	0.13
	Cortical density (mg/mm^3)	2.0	0.78	1183 (1172, 1194)	1176 (1163, 1188)	1186 (1175, 1196)	1177 (1164, 1190)	0.75	0.90
	SSIp (mm^3)	240.7	0.03*	1753 (1571, 1935)	1810 (1645, 1976)	2038 (1856, 2220)	2023 (1837, 2169)	0.03*	0.04*
	Section modulus (mm^3)	203.3	0.04*	1790 (1645, 1934)	1820 (1666, 1975)	2011 (1866, 2156)	2006 (1852, 2161)	0.04*	0.05*
66%	Total area (mm^2)	23.4	0.25	518.0 (486.9, 549.0)	519.9 (488.1, 551.8)	545.4 (514.4, 576.4)	537.0 (505.2, 568.8)	0.22	0.45
	Cortical area (mm^2)	18.1	0.12	302.7 (284.6, 320.8)	307.2 (289.2, 325.1)	319.3 (301.3, 337.4)	325.8 (307.9, 343.7)	0.20	0.15
	Cortical density (mg/mm^3)	8.3	0.22	1158 (1147, 1169)	1154 (1143, 1164)	1163 (1152, 1174)	1165 (1154, 1175)	0.48	0.14
	SSIp (mm^3)	231.3	0.07	2257 (2069, 2446)	2254 (2054, 2454)	2493 (2304, 2681)	2445 (2245, 2645)	0.08	0.18
	Section modulus (mm^3)	197.4	0.16	2302 (2091, 2512)	2320 (2104, 2536)	2511 (2300, 2722)	2476 (2260, 2692)	0.17	0.31
	Muscle CSA (mm^2)	396.4	0.03*	4852 (4582, 5121)	4884 (4608, 5160)	5215 (4945, 5484)	5327 (5051, 5603)	0.06	0.03*

* Significantly higher than the SFX group (p < 0.05).
[a] Difference in the combined left and right limb means between the SFX group and NSFX group after adjusting for age, mass, and tibia length.
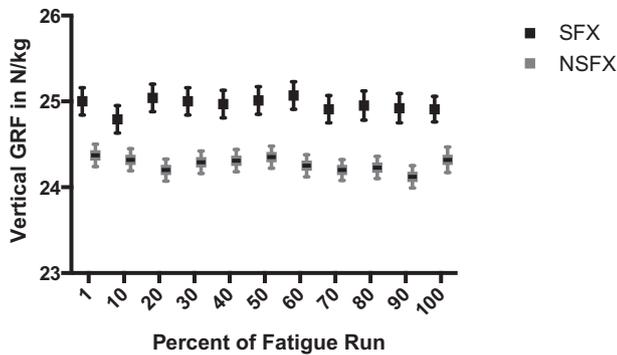
Fig. 1. Mean active peak vertical (pkZ) ground reaction forces (GRFs) between groups: Mean (SEM) pkZ GRFs (N) for the left limb, normalized by body mass (kg) measured at the beginning (0%) and at each 10% of a fatiguing run in women runners with (SFX) and without (NSFX) a history of stress fracture.

collected at the 50% time point in the fatigue run. Using the mean pkZ GRF at 50% of the run and SSIp at each cortical tibia site to calculate relative bone strength, there were no significant differences between SFX and NSFX groups at the three most distal tibial sites (15%, 25%, 33%). In contrast, the SFX group had lower bone strength relative to mean pkZ GRFs in both the left and right tibias at the 45% (−11%, to −13%), 50% (−16%) and 66% (−10%, to −12%) sites (Table 3). These between group differences were similar using the mean pkZ GRF at 0% and 100% of the run (data not shown).

4. Discussion

We assessed tibial vBMD, bone geometry (total and cortical bone area) and estimates of bone strength by pQCT in women distance runners with and without a history of stress fracture. We also measured mean pkZ GRFs during a fatiguing run using a 3-dimensional force-sensing treadmill. Our analysis found that women runners with a history of stress fracture had significantly lower measures of tibial bone strength at the 45% and 50% sites of the tibia. Consistent with our previous study on a separate group of runners [35], when adjusting for muscle size, bone strength was no longer significantly different between the groups with and without a history of stress fracture. However, bone strength relative to the mean pkZ GRF during running was substantially lower in the stress fracture group at the mid-shaft of the tibia.

4.1. Bone strength differences

A major finding of this study is that pQCT estimates of bone strength in the tibia tend to be lower in runners with a history of lower limb stress fractures compared to runners without a history of stress fracture. We used section modulus (Zp) and the polar strength strain index (SSIp) as indices of bone strength for this study. Those measures are highly correlated with 3-point bending strength in laboratory models

[26]. Both measures of bone strength outcomes were lower in the stress fracture group at one or more mid-shaft tibia sites. There were no differences in vBMD or total bone area at any measure site. However, there was a significant difference in CtA at the 15% and 45% sites. Our results are similar to findings of our previous research in which we found significantly higher CtA at the 45%, 50% and 66% sites, and SSIp at the 50% and 66% sites in the NSFX group [35]. While we were adequately powered to detect differences between groups in our primary research question, bone strength relative to load, we estimate we would have needed 29 runners in each group to detect a statistical difference in CtA at the 50% and 66% sites. Our findings are also consistent with studies from other laboratories that used 2-dimensional technology such as radiographs and DXA to estimate bone geometry by deriving cortical dimensions to estimate area moments of inertia [28]. In two separate studies, Beck et al. [7,8] found smaller cross sectional moments of inertia and section moduli at the femoral neck and tibia among male and women military recruits who experienced a stress fracture as well as thinner cortices in women fracture cases. In contrast, Bennell et al. [9] used computerized tomography (CT) to estimate bone strength differences in female running athletes with and without a stress fracture and found no significant differences in any bone strength or geometric outcome between groups. In that study, CT measurements were taken only at the 33% site of the tibia. By assessing multiple sites along the length of the tibia, our data show that differences in bone strength are smaller at the more distal sites of the tibia (below 45% site), which may explain the lack of difference in the paper by Bennell et al. [9].

4.2. Bone strength relative to load

While bone strength, structure and muscle size can be important in predicting stress fracture risk [8], perhaps even more important is the determination of bone strength relative to the external loads imposed. It is possible that individuals at risk for stress fracture have bone strength values that are similar to those who are not at risk. However, if bone is not adequately robust for the specific loads that are placed on it, strength may not be as important as strength relative to the applied load. Adjusting bone measurements statistically, based on muscle measurements is one method of estimating the strength relative to load relationship. After adjustment for muscle size, significant differences in bone strength were no longer apparent. This suggests that the strength and structure of bones of both groups are well adapted to muscle size. However, gait involves biomechanical measures such as joint moments, impact forces, GRFs and changes in GRFs due to muscular fatigue that are unaccounted for by static bone and muscle geometric measurements.

We chose to measure mean pkZ GRFs and changes in mean pkZ GRFs with fatigue as primary factors that are not accounted for from static measurements. pkZ GRFs are not a direct measure of the strain on bone, however they provide an approximation of the load acting on the tibia during gait [9,14,19,20] and are a more direct assessment of bone strain than muscle size alone. While we did not see a difference

Table 3
Relative bone strength $(mm^2/N*kg^{-1})$ in female runners with (SFX) and without (NSFX) a history of stress fracture, at six measurement sites (15%–66%) of the tibia. Values are Mean (95% Confidence Interval).

Group						
Site	SFX n = 15 mean* (CI)		NSFX N = 15 mean* (CI)		p-Value	
	Left	Right	Left	Right	Left	Right
15%	0.99 (0.89–1.09)	0.98 (0.88–1.07)	1.08 (1.00–1.16)	1.03 (0.98–1.17)	0.16	0.12
25%	0.60 (0.54–0.65)	0.60 (0.56–0.65)	0.63 (0.59–0.67)	0.66 (0.60–0.71)	0.37	0.11
33%	0.49 (0.45–0.52)	0.49 (0.46–0.52)	0.53 (0.50–0.55)	0.53 (0.50–0.57)	0.06	0.07
45%	0.41 (0.38–0.43)	0.40 (0.38–0.43)	0.46 (0.43–0.48)	0.46 (0.42–0.50)	0.006*	0.007*
50%	0.38 (0.34–0.41)	0.38 (0.36–0.41)	0.45 (0.41–0.49)	0.44 (0.40–0.48)	0.007*	0.02*
66%	0.37 (0.34–0.04)	0.37 (0.34–0.40)	0.41 (0.39–0.44)	0.42 (0.39–0.44)	0.03*	0.02*

* Significantly higher than the SFX group (p < 0.5).

with fatigue, our data indicate that mean pkZ GRFs were significantly higher (3–4%) in the SFX group than the NSFX group throughout the fatigue run. Similarly, bone strength relative to mean pkZ GRFs was significantly lower (−10 to −16%) in the SFX group than the NSFX at the mid-tibia sites (45–66%). This suggests that runners with a history of stress fracture at any lower limb site, experience greater loads at the tibia during running, and may help explain their predisposition to stress fracture. Importantly, these relationships are missed when static measurements alone are studied. Future studies regarding stress fracture risk should investigate additional dynamic gait indices in relation to bone strength. Several biomechanical factors have been associated with increased stress fracture risk in female runners. Recent evidence suggests higher rates of loading during early stance and higher free moments (a measure of torsion between the foot and the ground) are associated with stress fracture risk. Peak rearfoot eversion and peak hip adduction have also been shown to increase stress fracture risk. These high rates of loading, larger degrees of movement, and greater measures of free moment may result in increased load experienced by the tibia during running.

4.3. Site specific differences

Congruent with our previous study [35], we found site-specific differences in tibial bone strength, showing lower strength in the SFX group compared to the NSFX group at 45% and 50% sites. In both studies, bone strength was related to MCSA. Given this consistency between two separate cohorts of runners, we speculate that muscle size and strength are important factors in the development of stress fractures. Our current study extends those findings by showing that tibial bone strength is actually low in SFX relative to mean pkZ GRFs. Interestingly, we found no significant between-group differences at distal sites (15%, 25%, and 33%) in either study. The strength deficits in the SFX group at the mid-shaft correspond with the region of the tibia that is associated with the highest prevalence of stress fractures [29]. This pattern may point to an important region in the tibia to help identify individuals at high risk for tibial stress fractures and highlight the importance of assessing bone structure and strength relative to the loads placed on them when investigating skeletal pathologies.

4.4. Limitations and strengths

The cross-sectional, case-control design of this study is a limitation as data points were measured at only one point in time, and thus we are not able to examine causal relationships. The cases and controls were all very active in the running community and were recruited from the same geographic location. We did not control for nutrition, sleep, or training factors, other than weekly mileage, that may affect stress fracture risk. All but one participant was Caucasian, limiting the generalizability of our results to other races. Although age was slightly different between the groups, both groups had been training for a similar number of years, and achieved menarche ten or more years prior, and the number of cycles per year were similarly distributed between groups. We did not measure menstrual cycle or ovulatory status – both known to impact bone quality [24].

5. Conclusion

In conclusion, our data reveal that women runners with a history of stress fracture have lower bone strength in the middle third of the tibia and smaller muscle cross-sectional area. The difference in bone strength is not significant after adjusting for muscle size, suggesting a well-adapted muscle-bone relationship in both groups. However, women runners with a history of stress fracture have significantly lower bone strength relative to the loads they encounter during running, suggesting that suboptimal bone geometry and lower bone strength relative to load during running may predispose an individual to stress fracture. Further

research is needed to determine whether altering biomechanics to decrease pkZ GRFs is a viable solution to reduce injury risk in women with a history of stress fracture.

Disclaimer

The views, opinions, and/or findings in this report are those of the authors, and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Conflicts of interest

The authors have no conflicts of interest to disclose. The results of this study do not constitute endorsement by Bone.

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