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Physiological Factors of Female Runners with and without Stress Fracture Histories: A Pilot Study

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Statement: Female runners with low hip bone mineral density, menstrual changes during peak training, and elevated bone turnover markers may be at increased risk of stress fracture, and thus screening beyond what is commonly performed may be warranted.

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ABSTRACT

Background: Female runners are at increased risk of stress fractures (SF) compared to men. Literature is lacking in regard to best practice for preventing and treating SF in women. The purpose of the study was to compare physiological measures and running related factors between women with and without running-related SF histories of various ages and running abilities.

Hypothesis: Women with and without SF histories would differ in medical and menstrual history, bone health, body composition, nutrition, and running history.

Study Design: Prospective cohort study

Level of Evidence: 2b

Methods: Twenty female runners with SF histories were age and running-distance matched with 20 women without SF histories. Data included medical, menstrual, running, injury, and nutritional histories; blood histology related to nutritional, hormonal, and bone-related risk factors; and bone density, fat, and lean tissue using Dual Energy X-ray Absorptiometry. Paired t-tests were used to examine differences between women with and without SF histories, and Spearmen correlations were conducted to examine relationships between physiological factors.

Results: Women with SF histories had lower hip bone mineral density compared to women without SF histories ($p<0.05$). SF history was moderately correlated with menstrual changes during increased training times ($r=0.580$, $p <.0001$) but was not correlated with any other physiological factor. There was a moderate correlation within the SF group ($r=0.65$, $p=.004$) for bone markers for resorption and formation both increasing, indicating increased bone turnover.

Conclusion: Female runners with low hip bone mineral density, menstrual changes during peak training, and elevated bone turnover markers may be at increased risk of SF.

Clinical Relevance: Female runners need routine screening for risks associated with SF occurrence. As bone mineral density and bone turnover markers are not routinely assessed in this population, important risk factors may be missed.

Key Words: running, female, stress fracture, bone density

INTRODUCTION

Stress fractures (SFs) are non-traumatic incomplete fractures resulting from repetitive loading on normal bone or from normal loading on abnormal bone.[11] Running related SFs account for 69% of all SFs with 95% occurring in the lower extremities and pelvis.[11] Women have at least 2 times greater risk than men,[13,16] and more women than men are now running. In the 2018 National Runner Survey, runners were 54% female, 52% of all runners were between ages 35 and 54, and 60% considered themselves frequent fitness runners.[29]

The risk factors for SFs in women are multifactorial, and include differences in anatomy, body composition, metabolism, the cardiovascular system, hormonal status, and psychological status as compared to men.[16] Both intrinsic and extrinsic factors contribute to the occurrence of SFs. Intrinsic factors are physiological[11] and include bone structure and density, decreased fat in relation to lean tissue, and nutritional, hormonal, and bone-related health status. Menstrual irregularities and energy deficiency due to an imbalance between nutritional intake and activity are often present.[22] Women also have greater risks due to the female athlete triad, a negative energy balance between nutritional intake and activity that can lead to menstrual issues and decreased bone mineral density, showing the inter-relationships of these factors.[20] Both pre-menopausal and post-menopausal women are at risk.[20,26] Extrinsic factors include training intensity, training surfaces, diet, and footwear.[11]

The literature is lacking in regard to best practice for preventing and treating SFs in women. Surprisingly, few studies[4,27] directly evaluate women with and without a history of SFs to assist in better assessing risk and developing preventative strategies. There are several articles related to risk factors,[11,13,16,20,23] a few case reports with female runners,[3,10,12,18] and a few observational[15] and experimental studies.[4,21,27,30] These studies examine various factors including bone density, nutritional status, biomechanics, and menstrual status. Overall these studies show some relationships between these factors. Some limitations include small sample sizes in most studies, inclusion of only high level adolescent or young female runners, and mixed populations (male/female or different sports). Due to these limitations and the increased SF for women, there is a significant need to better understand issues related to SFs to prevent and properly treat these injuries to optimize return to running, overall health, and participation. The issue is not limited to women of a specific age as hormonal issues affect all women runners, thus making it important to not limit studies to young elite runners. Therefore, the objective of this study is to compare important physiological measures between women with and without running-related SF histories of various ages and running abilities. The hypothesis was that there would be differences related to medical and menstrual history, bone health, body composition, nutrition, and running history.

METHODS

Female runners, age 18-65 years, with and without running-related SF histories were recruited over a 5 month time period via posted flyers and social media for this study held within an urban university hospital system. A variety of social media sites were identified to decrease possible selection bias. Women self-identified as runners, with no upper or lower limit set for running intensity, duration, or distance. To control for differences in age and running ability, after each woman with a SF history was enrolled into the study, a woman without a SF history was recruited who was age-matched within 5 years and running-distance-matched within 10 miles/week.[5,31] All enrolled women signed a written informed consent form approved by the governing Institutional Review Board. Women with SF were included if they had a SF at any time as runners. Women with and without SF histories were excluded if they had a neurologic diagnosis or any systemic medical condition that would impact bone, were pregnant, or were breastfeeding.

Data collection included background information and physiological measures. Participants completed an online questionnaire (Qualtrics, Seattle, WA) to collect demographics as well as medical, menstrual, running, injury, and nutritional histories. To examine physiological data on nutritional, hormonal, and bone related risk factors,[8] the following non-fasting serum histological measures were collected and processed using standard medical laboratory procedures: complete blood count, vitamin D (25-(OH)D), calcium, albumin, parathyroid hormone, estradiol, testosterone, bone specific alkaline phosphatase (BALP, measure of bone formation),[6] and N-telopeptide (N-Tx, measure of bone resorption).[6] To examine bone, fat, and lean tissue, Dual Energy X-ray Absorptiometry (DXA)[9] was used to measure areal bone mineral density (aBMD) of the left hip and the lumbar spine, and full body composition using a Hologic Horizon A scanner (Hologic, Marlborough, MA). The DXA machine was calibrated prior to each testing session to decrease measurement error. A negative pregnancy test was required prior to conducting the DXA for all participants.

To examine differences between women with and without SF histories, paired t-tests were conducted using SPSS Statistics Version 25 (IBM Corporation, Armonk, New York). Cohen’s d was calculated to determine effect size. To examine possible relationships between group and physiological factors and among different physiological factors, Spearmen correlations were performed. Due to the lack of data available on medical and menstrual history, bone health, body composition, nutrition, and running history that span the age ranges included, a sample of 20 per group was chosen based on differences in bone turnover, body mass, and estradiol levels seen in study with 37 adolescent runners.[2] Effect sizes were thus calculated for measures in this study.

RESULTS

Forty nine women were screened for the study. Two women with SF histories were excluded due to thyroid disease, and five eligible women without SF histories were excluded as they did not match with a woman with a SF. Forty two women (35.0 ± 7.4, range 22-50 years) enrolled into the study. Two participants withdrew after signing the consent form due to time constraints, and data are complete for 40 participants or 20 matched pairs. Data were complete for all participants expect for 1 missing albumin value for the SF group and 2 missing N-Tx values for the non-SF group. These data and the matched pair's values were thus excluded from data analysis.

The oldest enrolled woman was 50 years old, and she was the only participant who was post-menopausal. Her match with a SF history was peri-menopausal. Women were highly educated and predominately white (Table 1). Women with SF histories were 2.2 ± 2.6 years post their most recent fracture (range 0.8-10 years) with 10 having fractured within the past year, 5 in the last 1-3 years, and 5 more than 5 years prior. Fracture sites included tibia (n=15), metatarsal (n=8), femur (n=5), cuneiform (n=1), and sesamoid (n=1) with 6 participants reporting having had 2 SFs, and 2 participants reporting 3 SFs.

Tables 2 and 3 show self-reported information for running and menstrual status, respectively, and there were no differences (p=0.57-1.00) between groups for these data. Groups were also evenly distributed in regard to birth control use and type, and for the number who had ever gone >3 months without a period other than during pregnancy (6 per group). However, 12 women who had a SF reported that their menstrual periods changed during increased training times, while only 1 reported this occurring in the non-SF group. Age when started running did not differ between groups, yet 9 women with SF histories started running at 18 years or younger, while only 4 without SF started this young.

In comparing physiological measures between women with and without SF histories (Table 4), the only statistical difference was in hip aBMD, with lower aBMD in the women with a SF history. But the effect size for this difference was low (0.19). The measure with the largest effect size of 0.61 was BALP, but the difference between groups was not statically significant. Correlational analysis showed that time post fracture was unrelated to bone markers (BALP, N-Tx) and that hip aBMD was unrelated to any other physiological factor. SF history was moderately correlated with menstrual changes during increased training times (r=0.580, p <.0001) but was not correlated with any other physiological factor. While there was a low correlation between BALP and N-Tx when looking at all participants together (r=0.34, p=.03), there was a moderate correlation within the SF group (r=0.65, p=.004) with BALP and N-Tx increasing together (Figure 1), indicating increased bone turnover.

DISCUSSION

The main results from this study were that women with a SF history had lower hip aBMD than their matched counterparts without a SF history, and that women with a SF history had alterations in their typical menstrual cycles during more intense training times even though current estradiol levels did not differ between groups. The study was conducted during the months of March to June, which represented mainly off to early season training for the included women. Within the SF group, there was a correlation between bone formation and resorption that was not seen within the non-SF group, indicating increased bone turnover.[17] Of note, DXA for bone density and blood histology to examine bone resorption and formation markers are not routinely performed in this population, thus important information may be missed clinically in these women. As DXA is a relatively inexpensive with low radiation exposure, performing DXA in this population may be cost-effective. The more expensive tests for bone resorption and formation markers may then be performed based on concerning findings via DXA. Asking female runners about any menstrual cycle changes during heavier training times may be an important addition to a patient interview. Women who had these changes reported lighter flow, shorter duration, increased spotting, irregularity, and missed cycles.

Several studies have examined menstrual dysfunction in relation to bone, but primarily in a younger population. Ackerman et al.[1] reported decreased spine and whole body aBMD and altered bone structure in 14-25 year old female athletes with oligoamenorrhea (6 cycles or less in prior year), with greater changes seen in participants with more than 1 SF. In a study that included collegiate cross-country runners, Tenforde et al.[30] reported that oligoamenorrhea or amenorrhea and a prior SF were predictors of subsequent bone stress injuries. A small percentage of participants had low aBMD, with more than half of them being runners. Nose-Ogura et al.[24] found a relationship between amenorrhea in the teenage years and aBMD in the 20's for female athletes that included distance runners, suggesting the need for intervention at a younger age. While these studies provide important information for female runners in these younger age groups, women older than 25 years represent a large number of runners. As bone mass starts to decline between 20 and 30 years of age for women,[7] issues specific to these women must also be addressed. Micklesfield et al.[22] studied 613 long distance (half-marathon and ultramarathon) female runners ages 16-62 years, of whom 17.3% had sustained a bone stress injury, but found no differences between these women and the women without these injuries for age, weight, BMI, or menstrual function. They also found that over half of all 613 women reported menstrual dysfunction. Thus, further study is needed to better understand the risks. These studies that relate menstrual status and aBMD as well as the results of this current study indicate the need to evaluate and treat female runners for these issues early and to continue to evaluate changes over time.

While there were no differences in estrogen levels between women with and without SF histories, some women in the study had very low estrogen levels. The low end of the normal range for estrogen levels is 24 pg/mL. Four women with SF histories and eight without had very low values (<5 pg/mL), and two in each group had low values (8-23 pg/mL). The significance of these low values is difficult to determine in this small sample as the women with and without SF histories were equally impacted. Estrogen levels fluctuate during the menstrual cycle,[28] and data were not collected regarding menstrual phase in this study. To gather cyclical data on female runners would require measures of estrogen levels to be collected throughout the menstrual cycle to identify patterns.[28] Assessing estrogen levels across the menstrual cycle is thus recommended for future studies.

The bone turnover markers of N-Tx and BALP as measured in this study are not routinely assessed in female runners but may play a role in assessing risk. While these measures were not statistically significant different between groups in this study, there was a correlation between increased bone formation and resorption in the SF group, indicating increased bone turnover.[17] In a literature review of studies of post-menopausal women by Vasikaran et al.,[32] several studies reported that an increase in bone turnover markers led to an additive effect on the risk for fractures, and that increased bone turnover markers may predict fracture risk independently of aBMD. While the population in Vasikaran et al.[32] differs from the women runners in this study, the use of these markers may be beneficial and more research is warranted. In a sample of adolescent female cross-country runners, elevated bone markers were associated with a lower BMI, menstrual irregularities, and lower estradiol and Vitamin D levels.[2] In contrast, Fujita et al.[14] measured bone resorption (urine N-Tx) twice per year in a small sample of female runners ages 19-34, and found while N-Tx values were normal during training, they increased when a SF occurred. These findings suggest that N-Tx may be a non-invasive way to identify SFs and monitor healing. A review article by Papageorgiou et al.[25] reported that short term low energy availability can also elevate bone markers, thus several factors need to be considered when using bone markers to guide diagnosis and return to running post SF. Finally, there is mixed opinion as to the effect of increased turnover. While increased formation temporarily increases bone porosity and decreases stiffness, it may also induce microdamage repair following bone stress.[19] Thus, more research is needed on the interpretation of these bone markers clinically.

In this study, a physical therapy examination was not performed as the goal was to gather physiological factors rather than specific musculoskeletal impairments. Koprelainen et al.[21] reported that the risks of recurrent SFs across multiple sites may include a high weekly training mileage, a leg length difference, a high longitudinal arch of the foot, and forefoot varus in addition to menstrual dysfunction. Thus, these factors may be important to consider in the examination of runners clinically along with the measures collected in this study. As the current study controlled for running distance through matching of subjects, the impact of mileage cannot be determined. Other factors to consider are impact forces and kinematics, which are not easily collected clinically. Popp et al.[27] reported that women who fractured had less bone strength and greater impact forces than women without fractures,[27] and Becker et al.[4] reported different kinematic patterns between runners with and without navicular SFs.

CLINICAL SIGNIFICANCE

For female runners ages 20-50 years of age with varying running abilities, it is recommended that screening of intrinsic and extrinsic risk factors be performed to determine potential risks for SF. Based on the research of others, these factors include nutritional, hormonal,[11] menstrual irregularities, energy deficiency,[22] training intensity, training surfaces, diet, and footwear.[11] Testing of aBMD is also recommended based on this study and others,[11] especially for those women who report menstrual changes as intensity/frequency/duration of running increase. While women with these changes may be at increased risk, DXA is encouraged for all female runners to better inform them about potential increased risks and educate them on prevention. Histological measures of bone turnover should also be considered for those with increased risk.

LIMITATIONS

In this study, a physical examination was not performed as the goal was to gather physiological factors rather than specific musculoskeletal impairments. Koprelainen et al.[21] reported that the risks of recurrent SFs across multiple sites may include a high weekly training mileage, a leg length difference, a high longitudinal arch of the foot, and forefoot varus in addition to menstrual dysfunction. Thus, these factors may be important to consider in the examination of runners clinically along with the measures collected in this study. As the current study controlled for running distance through matching of subjects, the impact of mileage cannot be determined.

Other study limitations include the small sample size, which could potentially impact the ability to obtain statistical significance. Matching women based on age and running distance likely reduced some of the impact of small sample size. The sample was also one of convenience and thus may not represent the population of female runners as a whole. The women in this study also spanned a wide age range. But despite this heterogeneity of age, differences were found between groups.

CONCLUSION

Based on the results of this study, measurement of aBMD, bone turnover markers, and menstrual change data during training may be important additions to the clinical examination of female runners. More research is needed on the role of bone turnover markers in assessing risk of SFs and return to running post SF.

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TABLE 1. Participant demographics

Item	Item Choices	Stress Fracture Group (n)	Non-fracture Group (n)
Age	Years	35.1 ± 7.2	34.4 ± 7.7
Highest Educational Degree	Bachelor's	7	7
	Master's	6	9
	Doctoral	7	4
Race	Asian	0	3
	Hispanic	1	1
	White	19	16

TABLE 2. Running status

Item	Item Choices	Stress Fracture Group (n)	Non-Fracture Group (n)	p-value
Days per week	2	0	1	0.96
	3	11	7	
	4	4	4	
	5	2	5	
	6	2	1	
	7	1	2	
Miles per week	0-10	1	1	0.88
	11-20	6	9	
	21-30	6	6	
	31-40	4	2	
	41-50	1	1	
	>50	2	1	
Average running pace (min/mile)	<6	1	0	0.98
	6-7	0	1	
	7-8	6	2	
	8-9	2	6	
	9-10	7	4	
	10-11	4	5	
	>11	0	2	
Age when started running	<10	3	1	0.96
	11-18	6	3	
	19-25	2	9	
	26-33	5	7	
	34-40	3	0	
	>40	1	0	

No differences between group (p>0.05) using Chi-square.

TABLE 3. Menstrual status

Item	Item Choices	Stress Fracture Group (n)	Non-Fracture Group (n)	p-value
Age at first menstrual cycle	9-10 years	1	2	1.0
	11-12 years	9	8	
	13-14 years	6	8	
	15-16 years	4	2	
Menstrual cycle length	29 days or less	11	13	1.0
	30-35 days	2	1	
	36 days or more	1	1	
	Irregular	6	4	
	Absent	0	1	
Menstrual cycle length	N/A	0	1	0.57
	1-2 days	1	2	
	3-4 days	9	9	
	5-6 days	8	4	
	7-8 days	0	3	
	8 days or more	0	0	
	No answer	2	1	

No differences between group ($p>0.05$) using Chi-square.

TABLE 4. Blood histological, bone density, and body composition results

Measure	Normal range	Stress Fracture Group	Non-Fracture Group	p-value	Effect size
Albumin	3.2 - 4.9 g/dL	4.3 ± 0.3	4.4 ± 0.2	0.21	0.40
Vitamin D	18 - 72 pg/mL	51.0 ± 10.0	51.8 ± 21.6	0.88	0.04
Calcium	8.5 - 10.3 mg/dL	9.3 ± 0.3	9.3 ± 0.3	0.73	0.11
Estradiol	12.5 - 498 pg/mL†	76.1 ± 105	50.6 ± 67.0	0.35	0.29
Testosterone	2-45 ng/dL	18.8 ± 8.2	19.1 ± 7.8	0.90	0.03
Parathyroid Hormone	11 - 67 pg/mL	36.7 ± 14.2	34.8 ± 9.2	0.64	0.16
Bone Specific Alkaline Phosphatase	5.0 - 18.8 mcg/L	9.9 ± 2.7	8.3 ± 2.4	0.09	0.61
N-Telopeptide	6.2 - 19.0 mg/dL	11.8 ± 5.0	11.1 ± 4.9	0.67	0.15
Spine Bone Mineral Density	N/A‡ gm/cm^2	1.0 ± 0.09	1.0 ± 0.11	0.15	0.44
Hip Bone Mineral Density	N/A‡ gm/cm^2	0.9 ± 0.1	1.0 ± 0.1	0.03*	0.19
Fat percent	N/A‡ %	31.2 ± 6.1	31.0 ± 5.0	0.94	0.02
Body Mass Index	18.5-24.9 kg/m2	22.4 ± 2.8	23.2 ± 2.9	0.36	0.28

***** Significant p-value
†Pre-menopausal, influenced by menstrual cycle phase
‡N/A as normal is based on age and percentiles.

Figure Caption

FIGURE 1. Bone turnover for each group. There was a moderate correlation within the stress fracture group between bone resorption (N-telopeptide) and bone formation (bone specific alkaline phosphatase) but not within the non-stress fracture group. This finding indicates increased bone turnover in the stress fracture group.