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TITLE: Risk Stratification of Stress Fractures and Prediction of Return-to-Duty

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14. ABSTRACT

This first annual report reviews progress towards completing each of our three study tasks. Major accomplishments include IRB and HRPO approvals for all study protocols, hiring and training of staff at MGH, as well as the initiation of subject recruitment and enrollment. In study Task 1 we aim to determine the sex- and race-ethnicity-specific bone traits that may contribute to stress fracture risk in military recruits. We are ahead of enrollment projections, with 61 of 120 subjects enrolled to date (n= 40 White women, 14 White men, 6 Black women, 1 Black man). In study Task 2 we aim to quantify changes in bone structure and bone metabolism in recruits before and after Basic Combat Training (BCT). Enrollment (n=161) and data collection are complete, and data analysis is ongoing. Finally, for study Task 3 we aim to characterize recovery and predict bone-healing trajectories and develop return-to-duty guidelines. We hypothesize that changes in bone health during recovery from stress-fracture injury can be quantified and used to develop evidence-based RTD. Enrollment is underway, with 3 women with recent stress fracture enrolled.

15. SUBJECT TERMS
bone microarchitecture, HRpQCT, race, gender, sex, bone mineral density, vBMD, bone geometry, stress fracture

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Introduction:

Among the most common musculoskeletal injuries, lower extremity stress fractures remain a vexing problem for the military. Their occurrence leads to lost duty days and significant costs. This project involves three distinct studies aimed at improved understanding of pathophysiology of stress fractures and return to duty guidelines. The first (*Task 1*) is a cross sectional study aimed at identifying the bone properties that may be related to the well-known sex and race/ethnicity differences in risk for stress fracture. In this study, we will assess bone mineral density at the hip and spine, as well as bone microarchitecture at the distal tibia in young adult women (n=50 White and n=50 Black) and men (n=10 White and n=10 Black). We hypothesize Black individuals will have more favorable bone microstructure parameters than White individuals, and that men of both races will have more favorable bone microstructure parameters than women.

The second project (*Task 2*) is a longitudinal study that characterizes changes in bone structure and metabolism during Basic Combat Training (BCT). Specifically, the project team will measure serum markers of bone turnover and bone microarchitecture at the distal tibia in men (n=47) and women (n=114) before and after Basic Combat Training (BTC). We hypothesize that subtle changes in bone health during BCT (which may lead to eventual stress fracture) can be characterized by changes in micro-scale structural and functional bone measures and by changes in biochemical bone markers.

Our third study arm (*Task 3*) is longitudinal and designed to measure bone microarchitecture and serum markers of bone metabolism in female athletes (n=30) throughout their recovery from stress fracture of the tibia. Our collaborators will use these data to perform analyses and develop mathematical models to predict bone healing trajectories and return-to-duty (RTD) guidelines. We aim to quantify how bone properties change during recovery from stress fracture, leading to the development of predictive models for bone healing following stress fracture and RTD guidelines. We hypothesize that changes in bone microarchitecture and metabolism during recovery from stress fracture injury can be quantified and used to develop quantitative RTD guidelines. We assume that recovery after injury follows the reverse process of stress-fracture development. That is, bone health measures after recovery tend to revert back to "normal," pre-injury values after complete healing.

Table 1. List of objectives from statement of work and current status

	Objectives from Statement of Work	**Status**
Task #1	1) Obtain Institutional Review Board (IRB) approval [month 1-6]	**Done**
	2) Renew IRB protocol [month 13-18, month 21-36]	**Pending**
	3) Acquire and analyze high-resolution peripheral quantitative computed tomography (HR-pQCT) images for 120 subjects [100 female (50 Caucasian and 50 African-American) and 20 male; [month 7-28]	**Ongoing**
	4) Perform standard whole bone finite element analysis [month 7-28].	**Ongoing**
	5) Perform data cleaning and statistical analyses [month 7-30]	**Ongoing**
Task #2	1) Assist with all aspects of study, including planning study logistics, collection of HR-pQCT data, analysis of HR-pQCT images, data analysis and interpretation	**Ongoing**
Task #3	1) Obtain IRB approval [month 4-9]	**Done**
	2) Renew IRB approval [month 16-21 and 28-33]	**Ongoing**
	3) Acquire and analyze HR-pQCT images and blood samples during stress-fracture recovery for 30 female subjects [month 10-36].	**Ongoing**
	4) Perform data cleaning and statistical analyses [month 10-36].	**Ongoing**

Body

Task 1:   Characterize structural and functional differences in bone health that stratify high-risk (female; Caucasian) vs. low-risk (male; African-American) recruits [month 1-33]

Progress to date: We received Institutional Review Board (IRB) approval from Massachusetts General Hospital (MGH) in May 2015 and HRPO approval in August 2015 (task 1, objective 1). We will renew the IRB protocol in the spring of 2016, and yearly thereafter (task 1, objective 2). Our target recruitment for the first 15 months of the study was 30 subjects. We are currently ahead of schedule and have enrolled 61 subjects, including 42 Caucasian women, 6 African-American women, 12 Caucasian men, and 1 African-American man (Figure 1)(task 1, objective 3). Of the 61 subjects enrolled, we have completed the data entry and image analysis on 55 of the subjects (task 1, objectives 4 and 5). In addition, 24 subjects are already scheduled for study visits in the upcoming months.
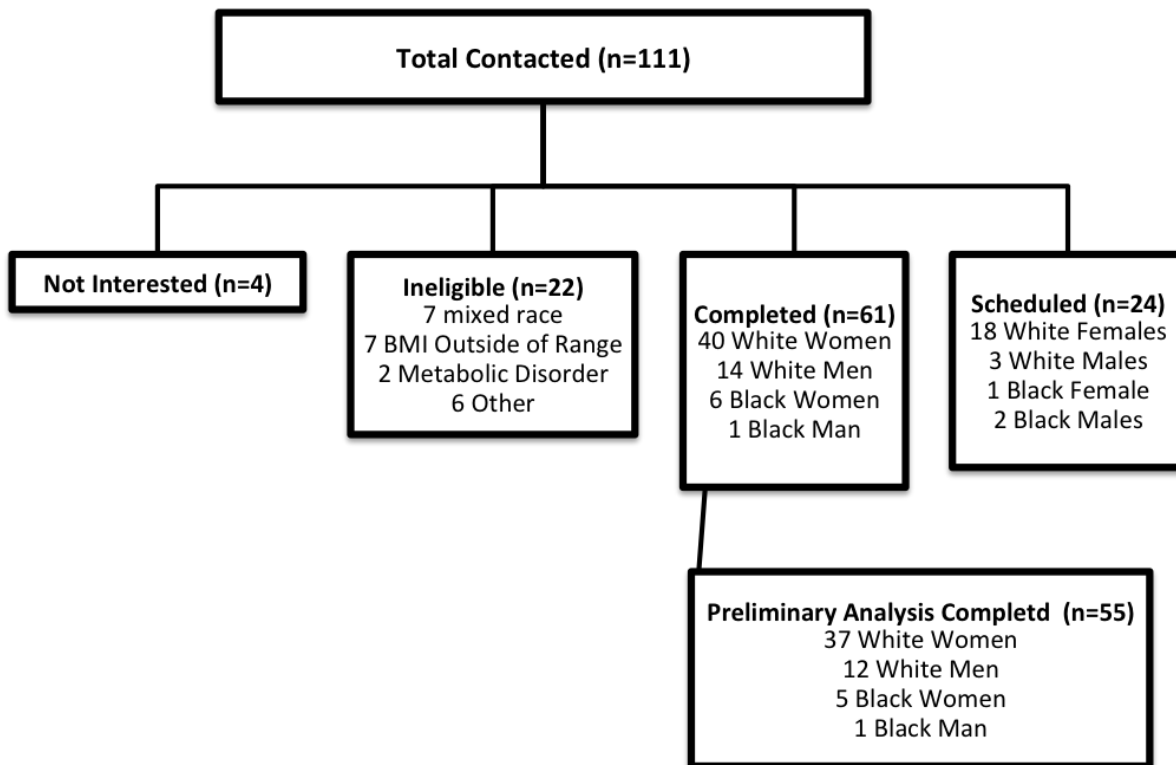

Fig 1. Recruiting efforts and enrollment for Task 1.

Preliminary data analysis (task 1, objectives 3-5): We have completed data entry, cleaning, and preliminary statistical analysis for 55 of our 61 enrolled subjects. For these subjects, basic demographics and selected bone parameters are presented in Table 2 and 3, respectively. Subjects range in age from 18.5 to 30 years, with body mass index from 18.3 to 30 kg/m^2. As the study completes enrollment, we will conduct formal statistical analyses to compare men to women and Blacks to Caucasians.

Table 2. Demographic characteristics of completed study subjects. Values are Mean (Standard Deviation, Range)

	White Women	White Men	Black Women	Black Men
n	37	12	5	1
Age (yrs)	24.1 (3.1, 18.5-30)	25.6 (2.55, 22.8-29.6)	24.7 (3.61, 19.6-29.6)	28.6
Height (cm)	163.27 (12.52, 106.3-184.5)	183.8 (8.23, 171.5-198.4)	163.4 (9.28, 152.3-177.7)	182.88
Weight (kg)	62.98 (10.16, 47.2-86.3	79.9 (13.08, 67-108.6)	70.8 (19.86, 52.5-95.0)	86.6
BMI $(kg/m^{2)}$	23.4 (2.91, 18.3-29)	23.6 (2.66, 19.4-28.0)	25.7 (4.46, 20.4-30)	25.9

Table 3. Selected results from high-resolution peripheral computed tomography (HRpQCT) scans at the tibia and dual-energy x-ray absorptiometry (DXA) results at the femoral neck, total hip and lumbar spine. Values are Mean (SD)

	White Women n=37	White Men n=12	Black Women n=5	Black Men n=1
HRpQCT Results				
Total Bone Density ($mgHA/cm^3$)	261.81 (39.52)	279.30 (57.54)	283.60 (38.55)	250.6
Cortical Bone Density ($mgHA/cm^3$)	792.78 (42.17)	762.70 (32.79)	857.58 (40.05)	848.1
Cortical Perimeter (mm)	115.31 (8.70)	137.68 (9.3)	114.28 (4.95)	132.8
Trabecular Bone Density ($mgHA/cm^3$)	196.71 (30.51)	222.48 (47.51)	201.10 (27.10)	182.9
Cortical Tissue Mineral Density($mgHA/cm^3$)	939.41 (29.97)	922.65 (16.7)	969.60 (30.54)	971.54
Cortical Area (mm^2)	99.95 (20.64)	122.38 (18.84)	104.80 (23.30)	113.99
Total Area (mm^2)	938.14 (191.47)	1194.38 (171.33)	847.19 (69.20)	1108.35
Apparent Cortical Thickness (mm)	0.85 (0.17)	0.91(0.16)	0.95 (0.21)	0.9
Cortical Porosity (%)	4.81 (1.87)	7.04 (1.70)	2.90 (1.08)	3.23
Stiffness (kN/mm)	237 (59)	310 (48)	243 (40)	275267
Failure Load (N)	12121 (2913)	15876.3 (2265)	12282 (2057)	14024
DXA Results				
Femoral Neck Bone Mineral Density (g/cm^2)	0.85 (0.12)	0.95 (0.12)	0.89 (0.11)	0.80
Total Hip Bone Mineral Density (g/cm^2)	0.97 (0.10)	1.03 (0.14)	1.01 (0.11)	0.94
PA Spine Bone Mineral Density (g/cm^2)	1.04 (0.11)	1.05 (0.12)	1.07 (0.10)	1.24

Task 2:   Quantify changes in bone health before and after basic combat training (BCT) [month 1-33]

Progress to date: We assisted our colleagues at USARIEM in the successful enrollment and data collection for Task 2. The study was conducted at Fort Jackson, with 174 subjects completing baseline assessments and 161 subjects (65 White women, 49 Black women, 35 White men, 12 Black men) completing both the baseline and follow-up assessments.

We are currently assisting in ongoing efforts to complete the image analysis, data analysis and interpretation.

Task 3:   Characterize injury recovery and develop a model for predicting bone-healing trajectories and return to duty (RTD) [month 1-33]

Progress to date: We obtained IRB approval for the study from MGH in May 2015 and HRPO approval for the study in August 2015 (Task 3, objective 1). We will apply for IRB renewal in the Spring of 2016 (Task 3, objective 2). We are on track with enrollment, with 3 subjects enrolled to date. We are collaborating with local sports medicine physicians, coaches, and athletic trainers to continue recruiting effectively (Task 3, objective 3). We anticipate that enrollment for this task will be seasonal, with low enrollment in the winter (when running mileages generally drop) and higher enrollment during the spring, summer and fall. HR-pQCT and DXA images are being analyzed and entered as they are acquired. We are freezing and storing blood samples and plan to send these in batches to USARIEM for analysis (Task 3, objective 4).

Key Research Accomplishments:
- Obtained IRB approval from MGH for Task 1 and Task 3
- Obtained HRPO approval for Task 1 and Task 3
- Recruited, hired, and trained MGH study staff
- Completed enrollment for Task 2
- Completed data collection for Task 2
- Started data entry, cleaning, and analysis for Task 2
- Started recruitment and enrollment for Tasks 1 and 3
    - Target recruitment was 30 subjects by 3/1/16 and 60 by 8/1/16
    - As of 11/30/15 we have enrolled 61 subjects with an additional 24 subjects scheduled
- Started data entry, cleaning, and analysis for Task 1
- Started enrollment for study Task 3
- Started data entry and cleaning for Task 3
- Held and continue to hold bi-monthly study team meetings with USARIEM and BHSAI

Reportable Outcomes:
Not Applicable, as data collection is currently ongoing.

Conclusion:
This research is important to determine factors that predispose individuals to stress fracture as well as predict return-to-duty for those who have incurred a stress fracture. Recruitment, data entry, and analysis are in progress for Task 1. Task 2 enrollment and data entry are complete. Analysis is in progress. Recruitment and data entry are in progress for Task 3. We are currently investigating whether it is possible to hire a research assistant to assist with subject recruitment and data entry. We anticipate that we would be able to hire this new study staff without additional funds or changes to the scope of work. While recruitment has just begun for Task 3, we anticipate recruiting women within three weeks of a stress fracture diagnosis will require great persistence and communication with the local athletic community.

Personnel receiving pay:
Mary L. Bouxsein, Ph.D. – Principal Investigator
Kathryn Ackerman, M.D. – Co-Investigator
Kristin Popp, Ph.D. – Co-Investigator

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