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Case Series

The Impact of Blood Flow Restriction Training on Tibial Bone Stress Injury Rehabilitation: An Exploratory Case Series

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Background

Lower extremity bone stress injuries (BSI) are common injuries among athletes and military members. Typical management involves a period of restricted weightbearing which can have rapid detrimental effects upon both muscle and bone physiology. Few studies have investigated the effect of blood flow restriction (BFR) training on bone in the rehabilitative setting.

Purpose

The purpose of this study was to investigate the effects of lower extremity exercise with the addition of BFR upon bone mineral density, bone mineral content, and lean body mass in military members with tibial BSIs.

Study Design

Case series

Methods

Twenty military members with MRI-confirmed tibial BSI were recruited to complete lower extremity exercise with the addition of BFR twice per week for four weeks. The BFR cuff was applied proximally to the participant's involved limb while they performed gluteal, thigh, and leg resistance exercises. Outcomes were assessed at baseline and four weeks. The primary outcomes were whole leg bone mineral density (BMD), bone mineral content (BMC), and lean body mass (LM) as measured by dual-energy x-ray absorptiometry. Secondary outcomes included thigh and leg circumference measures and patient-reported outcomes, including the Lower Extremity Functional Scale (LEFS), Patient-Reported Outcomes Measurement Information System 57 (PROMIS-57), and Global Rating of Change (GROC).

Results

No significant differences were found in BMD ($p=0.720$) or BMC ($p=0.749$) between limbs or within limbs over time. LM was generally less in the involved limb ($p=0.019$), however there were no significant differences between or within limbs over time ($p=0.404$). For thigh circumference, significant main effects were found for time ($p=0.012$) and limb ($p=0.015$), however there was no significant interaction effect ($p=0.510$). No significant differences were found for leg circumference ($p=0.738$). Participants showed significant mean changes in LEFS (15.15 points), PROMIS physical function (8.98 points), PROMIS

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social participation (7.60 points), PROMIS anxiety (3.26 points), and PROMIS pain interference (8.39 points) at four weeks.

Conclusion

The utilization of BFR in the early rehabilitative management of tibial BSI may help mitigate decrements in both bone and muscle tissue during periods of decreased physical loading.

Level of Evidence

4

INTRODUCTION

Lower extremity bone stress injuries (BSI) are a common injury among athletic and military populations.[1-8] BSIs are most commonly associated with running activities and account for 4-16% of reported running injuries.[2,9-11] A systematic review on running-related musculoskeletal injuries found that lower extremity stress fractures encompassed 5.7% of 10,640 observed injuries.[10] Specifically, the tibia is the most common site for running-related BSIs.[1,12,13] A ten year surveillance program of collegiate athletes showed that 21.9% of 671 observed bone stress fractures involved the tibia.[1] Military service members are especially susceptible to BSI during their initial entry training as many trainees are faced with sudden increases in running, marching, and other training loads.[2,14] The cumulative incidence for lower extremity BSI during initial military training ranges from 0.9-5.2% for males and 3.4-21% for females.[2] In military populations, the tibia has again been shown the most commonly affected bone, accounting for 55-74% of stress fractures.[12,13] As the previously discussed studies report specifically on diagnosed tibial stress *fractures*, the prevalence of lesser grade tibial BSIs is arguably even higher. Concerningly, a BSI injury can result in significant repercussions for both athletes and military members. In collegiate athletes, 20.7% of BSIs were season-ending injuries, while in military members, 13% of BSIs resulted in discharge from military service before completing training.[1,4]

Most stress injuries are amenable to conservative management involving a period of activity modification and reduced weightbearing until the individual is pain-free with activities of daily living.[15] This period of decreased loading could range from days to weeks depending upon the site and severity of injury. Concerningly, an extended period of decreased loading can have detrimental effects upon both muscle and bone physiology. Muscle disuse can result in muscle mass loss, decreased strength, slow/fast-twitch fiber transition, and catabolic molecular responses.[16,17] In a study of young healthy men, one week of unilateral lower extremity non-weightbearing resulted in a 6.7% and 3.5% decrease in quadricep and hamstring muscle volume, respectively. Subjects also showed significant decreases in cross-sectional area of thigh musculature and significant decreases in maximal strength leg extension (18%), leg press (22%), and calf raise (8%).[18] Similarly, disuse osteoporosis can also result from reduction in mechanical stress on bone, characterized by decreased bone mineral density (BMD) and cortical diaphysis narrowing.[19] Bone mineral loss after injury can persist for considerable time even after an individual returns to full activity. In a study of 30 female athletes with tibial BSI, subjects demonstrated significant volumetric BMD (vBMD) deficits at six and twelve weeks, and in eight subjects, vBMD never returned to baseline by one year.[20] Similarly, in a study of individuals with acute knee injuries, participants who were permitted weightbearing as tolerated after injury showed a 10% decrease in bone mineral content (BMC) in the tibia at three months post-injury, and these BMC deficits remained unchanged at one year.[21]

Ideally, athletes and military members with BSI would have access to a rehabilitation program that would provide adequate stimulus to muscle and bone during the period of weightbearing restriction. Increasing evidence suggests that low-intensity training with blood flow restriction (BFR) may be a beneficial alternative training method for individuals who are unable to participate in high-intensity physical training, to include those who are injured, post-operative, elderly, or limited by a disease state.[22,23] BFR training involves the partial restriction of arterial blood flow and occlusion of venous blood flow in an extremity during a bout of exercise.[24] This occlusion is accomplished with the use of a specialized tourniquet system which is applied to a proximal extremity and then inflated to a personalized target occlusion pressure. Typical protocols prescribe an individual to perform resistance exercises at a load 20-50% of one-repetition maximum.[23] Several studies indicate that BFR helps mitigate muscle size and strength losses in those with lower extremity injury.[25,26]

Similar to the benefits observed in muscle, vascular occlusion treatment may also positively impact bone repair. Animal models have shown that intermittent pneumatic compression applied proximal or distal to a lower extremity fracture improved bone mineralization, BMC, BMD, callus formation, vascularity, and torsional strength of the healed bone.[27-30] Mechanistically, BFR has been proposed to potentially influence two key mechanisms of bone adaptation – bone interstitial fluid flow (indirectly measured by intramedullary pressure) and hypoxia inducible transcriptional factor (HIF).[31] Animal models have shown that hind limb venous occlusion caused an increase in tibial intramedullary pressure which was associated with greater periosteal bone formation and BMD.[29,30] Other animal studies have shown that the HIF pathway is activated during bone repair and upregulates under tissue hypoxia. Animals in which the HIF pathway was interrupted showed impaired angiogenesis and bone healing.[32,33] As these tissue-sample studies have not been replicated in humans, indirect measures of bone response to BFR have been measured through blood biomarkers. Bone-specific alkaline phosphatase (BAP) levels are considered to reflect osteoblastic activity and are used as an indirect measure of bone formation.[34] Subjects performing exercise with BFR have shown significantly increased acute BAP levels compared to control exercise groups.[35,36] In contrast, N-telopeptides (NTX) are markers of bone resorption and were acutely decreased in subjects after a single bout of exercise performed with BFR.[37]

Literature suggests that mechanical and/or chemical mechanisms related to pneumatic compression may positively impact bone healing and adaptation. To date, however, few studies have investigated the effect of BFR upon bone in the rehabilitative setting. The purpose of this study was to investigate the effects of lower extremity exercise with the addition of BFR upon whole leg BMD, BMC, and LM in military members with tibial BSIs. It was hypothesized that no significant changes would be observed in BMD, BMC, LM, or limb circumference measures in the injured extremity over four weeks of rehabilitation incorporating BFR training.

METHODS

PARTICIPANT CHARACTERISTICS

Participants were recruited from military physical therapy clinics at Joint Base San Antonio in San Antonio, TX from December 2021 to May 2023. All volunteers provided informed consent for participation in the study, which was approved by the Institutional Review Board at Brooke Army Medical Center, San Antonio, TX. Participants were required to be 18-40 years old with a tibial BSI confirmed with magnetic resonance imaging. The grade of tibial BSI was classified per Frederickson criteria.[34] All injury grades were eligible given the subject was formally restricted from normal military running activity for at least four weeks by the referring physical therapist. Exclusion criteria included pregnancy, open wound or malignancy in the region of cuff application, clinically diagnosed hypertension, suspected deep vein thrombosis, femoral neck stress injuries, and lack of English fluency.

PATIENT-REPORTED OUTCOMES

Following consent, participants provided demographic information to include age, gender, and details regarding BSI history. They then completed two self-report questionnaires: the Lower Extremity Functional Scale (LEFS) and the Patient-Reported Outcomes Measurement Information System 57 (PROMIS-57). The LEFS is a 20-item region-specific functional outcome measure that ranges from 0-80 points with higher scores indicating higher functional status. It has been found reliable and valid in patients with lower extremity dysfunction. The minimal clinically important difference (MCID) is nine points.[35] The PROMIS-57 is a patient-reported outcome measure developed by the National Institute of Health. It is a universal measure that assesses physical, mental, and social health across diverse conditions, to include orthopedic conditions. The PROMIS-57 questions cover seven health domains: physical function, anxiety, depression, fatigue, sleep, social, and pain. The physical function domain has been found reliable and valid in surgical foot and ankle conditions.[36,37] MCIDs for physical function and pain interference in foot and ankle conditions vary amongst studies but a value of eight points was deemed appropriate for both domains for this study.[38,39] The other domains have been less extensively studied but changes of two to six T-score points are reasonable estimates for MCID across domains.[40]

BIOMETRIC OUTCOMES

Biometric data were then collected in two manners: limb circumference measures and dual-energy x-ray absorptiometry (DEXA). Lower extremity limb circumference measurement has been shown reliable in healthy subjects.[41] Thigh circumference was measured twenty centimeters proximal to the superior patellar pole with the subject in the supine position. Leg circumference was measured at the estimated point of greatest circumference in the uninvolved limb with the subject in the prone position.[42] The distance of this point to the inferior fibular head was then recorded in order to repeat the measurement on the involved limb and at follow-up. DEXA is a radiological study that provides measures of BMD, BMC, and body composition (including bone, fat, and lean body mass). It is the gold standard assessment for BMD and is also valid for body composition.[43,44] In the presence of injury, DEXA can be used to compare bone and body composition between limbs and to monitor change over time.[45] For this study, regional measures of BMD, BMC, and LM were calculated for each independent lower extremity (Figure 1). The same GE® Lunar Encore-Based X-ray Bone Densitometer machine was used for all subjects. The "least significant change (LSC)" calculation represents the minimal detectable change value for BMD studies and is specific to each DEXA machine.[43] LSC of lower extremity BMD is not a commonly assessed parameter and was not assessed for this study. For comparison, however, this machine's calculated LSC with a 95% level of confidence was 0.022 g/cm^2 for the spine and 0.017 g/cm^2 for the femoral neck.

INTERVENTION

BFR exercise intervention was initiated after completion of the DEXA study. BFR was performed utilizing the Food and Drug Administration approved Delphi® Personalized Tourniquet System for BFR which determines personalized tourniquet pressures and auto-regulates pressures throughout an exercise session. Participants completed two BFR training sessions per week for a total of four weeks. Four weeks was selected due to schedule feasibility of the local eligible military trainee population and to permit adequate time for the mechanical/chemical responses previously discussed.[35] Participants completed four different

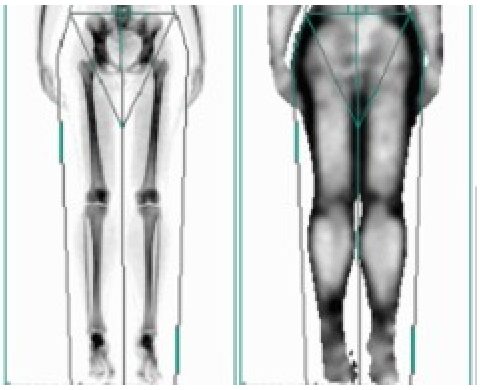

Figure 1. Sample DEXA image with isolation of left and right lower extremities.

lower extremity exercises per session – two press exercises, one pull exercise, and one leg exercise. Selected exercises varied by patient based on weight-bearing status and exercise tolerance. Exercises were progressed over the four weeks following the general progressions outlined in Table 1. Each exercise was performed for four sets with a target repetition scheme of 30-15-15-failure. The repetition goal for each exercise was 75 total repetitions, and the future exercise weight was adjusted depending upon the number of repetitions completed in the fourth set. Limb occlusion pressure (LOP) was calibrated to 80% of total occlusion pressure and was maintained for the duration of a single exercise, to include the 30-second rest periods between sets. Occlusion was fully released during a two-minute rest break between exercises. All exercise sessions were performed with supervision from a healthcare professional with specific training in BFR application.

Four weeks after the start of intervention, participants repeated the previous self-report outcomes, limb circumference measures, and DEXA study. They also completed the Global Rating of Change (GROC) scale to measure self-perceived change in their condition at the end of intervention. Participants then resumed further care with their evaluating physical therapist.

STATISTICAL ANALYSIS

Statistical analyses were performed using Stata Version 18 software (StataCorp LLC). Descriptive statistics were performed for demographic data and GROC and reported as means and standard deviations. Paired t-tests were performed for analysis of LEFS and PROMIS-57 outcome measures. DEXA and limb circumference outcomes were examined using linear mixed-effects models (LMM). Preliminary LMMs for each outcome included fixed effects for time, limb, and weightbearing (WB) status, all interaction effects (time x limb, limb x WB status, time x WB status, limb x time x WB status), and random effects for subject. WB status was included in preliminary models to investigate if this factor was associated with the outcome variables and to ensure it was not confounding the results. Alpha level was set to 0.05 for all analyses.

RESULTS

PARTICIPANT CHARACTERISTICS

Twenty-four participants consented to the study. Four participants withdrew from the study. Three withdrawals occurred before the first DEXA scan and first treatment. One withdrawal occurred after four treatments at which time the patient was referred back to the evaluating physical therapist due to worsening pain despite exercise and weightbearing modifications. All withdrawals were excluded from data analysis. Therefore, twenty participants completed the study. Demographic information is summarized in Table 2. The most common BSI classification was grade 3 (n=10). No participant had a previous history of BSI. The average time from start of activity modification to DEXA scan was 14.16 ± 5.69 days, excluding one outlier who reported 44 days. All participants were determined to have normal bone density at baseline and follow-up as compared to healthy population DEXA Z-scores. On average, participants completed 6.80 ± 1.15 treatments. The average time under occlusion for an individual treatment session was 21.34 ± 2.71 minutes. None of the participants reported serious adverse events or had to discontinue the study due to study-related procedures. Two participants reported temporary cuff-related discomfort during one exercise at a single treatment session which improved with changing exercises. Two participants required one unplanned rest period mid-exercise at a single treatment session due to leg discomfort; these participants were then able to continue treatment per protocol.

Table 1. BFR Exercise Progression Guidance Table

	Non-weightbearing	Progressive weightbearing	Full weightbearing
Press	Knee extension	Leg press machine Donkey kicks	Squats Static lunges Bulgarian split squats Step-ups
Pull	Hamstring curl Prone/quadruped hip extension	Supine hip bridges	Deadlift
Leg	Ankle PF/DF with TB	Heel raises on machine	Standing heel raises

Abbreviations: BFR (blood flow restriction); DF (dorsiflexion); PF (plantarflexion); TB (Theraband)

Table 2. Participant Demographics and Treatment Characteristics*

Age (yrs)	20.45 (range 18-27)	
BMI (kg/m^2)	23.9 ± 2.77	
Sex	11 males, 9 females	
BSI Grade† (count)	Grade 1	1
	Grade 2	5
	Grade 3	10
	Grade 4a	3
	Grade 4b	1
Number of Treatments	6.8 ± 1.15	
Average Occlusion Time per Session (min)	21.34 ± 2.71	

*Mean ± SD unless otherwise indicated; †Frederickson Classification
Abbreviations: BMI (body mass index); BSI (bone stress injury)

Table 3. Summary of the Linear Mixed-Effects Models for DEXA Outcomes

		Baseline *Mean ± SD*	4 weeks *Mean ± SD*	
BMD (g/cm^2)	Involved	1.28 ± 0.15	1.28 ± 0.15	p=0.366†
	Uninvolved	1.28 ± 0.14	1.27 ± 0.14	
		p=0.258*		p=0.720‡
BMC (g)	Involved	488.46 ± 117.13	488.79 ± 116.22	p=0.665†
	Uninvolved	489.64 ± 110.69	491.21 ± 108.19	
		p=0.904*		p=0.749‡
LM (kg)	Involved	18.97 ± 4.49	19.19 ± 4.84	*p=0.019†*
	Uninvolved	19.44 ± 4.59	19.43 ± 4.70	
		p=0.270*		p=0.404‡

*Main effect time; †Main effect limb; ‡Interaction effect
Abbreviations: DEXA (dual-energy x-ray absorptiometry); BMD (bone mineral density); BMC (bone mineral content); LM (lean body mass)

DEXA MEASUREMENTS

Table 3 summarizes the findings for DEXA outcomes. As the main effect of WB status and all interaction effects including WB status were found to be non-significant for all outcomes (p > 0.10), WB status was removed from subsequent models. The final LMMs for each outcome included the fixed effects of time and limb and the interaction of limb x time. For BMD, there were no significant main effects for time (p=0.258) or limb (p=0.366), and there was no significant interaction effect (p=0.720). For BMC, there were also no significant effects for time (p=0.904), limb (p=0.665), or interaction (p=0.749). For LM, there was a significant main effect for limb (p=0.019); however, the main effect for time (p=0.270) and interaction effect (p=0.404) were not significant. Percentage changes from baseline measures are included in Table 5 for study comparisons within the Discussion.

LIMB CIRCUMFERENCE MEASUREMENTS

Table 4 summarizes the findings for limb circumference outcomes. For thigh circumference, the main effects for time (p=0.012) and limb (p=0.015) were both significant; however, the interaction effect (p=0.510) was not significant. For leg circumference, no significant effects were found for time (p=0.089), limb (p=0.086), or interaction (p=0.738). Percentage changes from baseline measures are included in Table 5 for study comparisons within the Discussion.

SELF-REPORTED OUTCOMES

Table 6 summarizes all self-report outcomes. Participants showed a statistically and clinically significant improvement in LEFS from baseline to four weeks (mean change 15.15, 95% CI: 9.24-21.06). Participants also showed statistically and clinically significant improvement in PROMIS physical function (mean change 8.98, 95% CI: 5.58-12.37), pain interference (mean change 8.39, 95% CI: 5.95-10.83), and social participation (mean change 7.60, 95% CI: 3.69-11.50). Statistically significant improvements in anxiety (mean change 3.26, 95% CI: 0.54-5.98) may also be considered clinically significant depending upon MCID cutoff. The average GROC score at four weeks was 5.50 ± 1.82 points.

Table 4. Summary of the Linear Mixed-Effects Models for Limb Circumference Outcomes

		Baseline *Mean ± SD*	4 weeks *Mean ± SD*	
Thigh (cm)	Involved	54.61 ± 4.97	55.26 ± 5.16	$p=0.015^{\dagger}$
	Uninvolved	55.24 ± 4.71	55.65 ± 5.09	
		$p=0.012^{*}$		$p=0.510^{\ddagger}$
Leg (cm)	Involved	36.28 ± 2.98	36.54 ± 3.20	$p=0.089^{\dagger}$
	Uninvolved	36.54 ± 3.09	36.73 ± 3.43	
		$p=0.086^{*}$		$p=0.738^{\ddagger}$

[*] Main effect time; [†] Main effect limb; [‡] Interaction effect

Table 5. Percent Change Values for DEXA and Circumference Outcomes

		Percentage Change ± SD
BMD	Involved	-0.66 ± 2.01
	Uninvolved	-0.38 ± 1.99
BMC	Involved	0.11 ± 1.46
	Uninvolved	0.47 ± 1.63
LM	Involved	0.80 ± 3.99
	Uninvolved	-0.15 ± 3.68
Thigh Girth	Involved	1.21 ± 2.35
	Uninvolved	0.72 ± 2.17
Leg Girth	Involved	0.69 ± 1.55
	Uninvolved	0.45 ± 1.66

Abbreviations: DEXA (dual-energy x-ray absorptiometry); BMD (bone mineral density); BMC (bone mineral content); LM (lean body mass)

Table 6. Patient-Reported Outcomes

	Baseline *Mean ± SD*	4 weeks *Mean ± SD*	Mean Change (95% CI)	
LEFS	55.60 ± 16.65	70.75 ± 11.18	15.15 (9.24, 21.06)	
PROMIS[*]				
a) Physical Function	44.18 ± 9.11	53.15 ± 7.90	8.98 (5.58, 12.37)	$p<0.001$
b) Anxiety	45.32 ± 7.45	42.06 ± 7.04	3.26 (0.54, 5.98)	$p=0.022$
c) Depression	42.74 ± 5.43	40.57 ± 5.14	2.18 (-0.71, 5.06)	p=0.131
d) Fatigue	43.60 ± 10.83	42.99 ± 10.95	0.62 (-2.88, 4.11)	p=0.717
e) Sleep Disturbance	48.04 ± 8.57	47.43 ± 7.41	0.61 (-2.89, 4.10)	p=0.721
f) Social Participation	52.69 ± 9.19	60.28 ± 10.02	7.60 (3.69, 11.50)	$p<0.001$
g) Pain Interference	55.12 ± 6.65	46.73 ± 7.87	8.39 (5.95, 10.83)	$p=0.002$
GROC		5.50 ± 1.82		

[*] T-scores

Abbreviations: LEFS (Lower Extremity Functional Scale); PROMIS (Patient-Reported Outcomes Measurement Information System); GROC (Global Rating of Change)

DISCUSSION

After sustaining a lower extremity BSI, athletes and military members must commonly undergo a period of modified weightbearing and exercise restriction. This period of decreased physical loading is known to have detrimental effects upon both bone and muscle tissue. Various studies support the theory that pneumatic compression can positively impact bone adaption and healing.[27-37] This study adds to the scant literature investigating the potential effect of BFR training upon bone in the rehabilitative setting. Military trainees with a tibial BSI demonstrated no significant changes in BMD, BMC, LM, or limb circumference measures despite four weeks of restricted physical activity.

To the authors' knowledge, only one case study has described the utilization of BFR in the management of a BSI. A military trainee who sustained a grade III midshaft femoral BSI was rehabilitated with the inclusion of BFR over a six-week period. Despite a period of limited weight-bearing, the soldier increased thigh girth by 2.5 cm and returned to training 51 days after diagnosis with radiographic evidence of healing and no reported pain. The author reported that the clinic's average recovery period for similar injuries was 141 days, boasting a 50% reduction in return to duty timeline.[46]

The authors also believe only one other study has incorporated DEXA as a primary outcome measure to assess the impact of BFR training within injury rehabilitation. Jack et al[47] randomized 32 subjects who underwent anterior cruciate ligament reconstruction (ACLR) to a rehabilitative program with BFR training versus usual rehabilitation. Subjects participated in BFR training twice per week over 12 weeks. At six weeks post-operative, the BFR group showed non-significant decreases in distal femur (-2.8%) and proximal tibia (-1.9%) BMD compared to pre-operative values, while the usual rehabilitation group showed significant reductions in distal femur (-7.6%) and proximal tibia (-4.8%). At 12 weeks post-operative, both groups showed significant decreases in distal femur BMD, but this decrement was blunted in the BFR group (-4.9% vs -8.2%). Only the usual rehabilitation group showed a significant decrease in proximal tibia BMD at 12 weeks (-2.2% vs -8.0%). Additionally, involved leg LM significantly decreased over time in the control group at both six weeks (-6.64%) and twelve weeks (-4.67%), while the BFR group did not significantly decrease from baseline (-0.69% and 0.74%, respectively). Comparatively, the BSI subjects in the current study showed a mean involved limb BMD change of -0.66% and leg LM change of +0.80% (Table 5). These differences in change between studies are expected given the longer post-operative weightbearing and activity restrictions in the ACLR study. Also, BMD comparisons may be limited as the Jack study measured BMD at local femur and tibia sites compared to the global limb value used in this study. Both studies suggest that BFR may have a protective effect on bone and LM.

This potential protective effect on bone is important as the natural history of BMD after musculoskeletal injury appears variable. While BMD loss occurs readily with unloading, return to baseline BMD values seems less predictable. Kazakia et al[48] investigated changes in distal tibial volumetric BMD (vBMD) in 12 subjects who underwent six weeks of non-weightbearing after knee surgery (mostly ACLR or high tibial osteotomy). After the non-weightbearing period, the involved tibia showed a significant vBMD decrease of 1.2%. Even after resumption of weightbearing, the tibial vBMD still remained significantly decreased at six weeks (-2.0%) and 13 weeks (-2.5%).

Similar chronic BMD deficits have been found in athletes with tibial BSI. Popp et al[20] investigated the natural change in tibial vBMD over the course of one year in 30 female athletes recovering from tibial BSI. At six weeks post-injury, tibial vBMD was significantly decreased from baseline in both the injured and uninjured legs. At 12 weeks post-injury, tibial vBMD remained 0.94% decreased in the injured limb. These vBMD values did not return to baseline for 24-52 weeks, and in eight athletes, vBMD never returned to baseline values by one year. In comparison, the tibial BSI subjects in the current study showed non-significant decreases in BMD of 0.66% and 0.38% in the involved and uninvolved limbs (Table 5), respectively, which may suggest BFR training can positively impact early BMD changes after injury. Again, comparisons between these studies should be made with caution as the current study did not include longer term BMD reassessments and did not utilize HR-pQCT for isolated tibial vBMD measures.

Concerningly, these chronic BMD deficits may leave athletes at higher risk for recurrent BSI. Previous studies have reported conflicting results regarding associations between BMD scores and BSI injury risk, however most of these studies used spine or hip BMD measures as surrogate parameters for lower extremity BSI risk.[49-51] Beck et al[8] performed a large prospective observational trial in Marine trainees which instead measured BMD locally at the femur and tibia. They found that females who suffered BSI had significantly lower femoral and tibial BMD. Femoral and tibial bone strength was also significantly lower in individuals of both genders who sustained a BSI. Similarly, Kazakia et al[48] used finite element analysis to assess tibial microstructure and biomechanics in subjects after a tibia-related surgery. They determined that tibias with decreased vBMD also showed decreased stiffness and failure load even 13 weeks after subjects had returned to weightbearing. In the Popp study previously discussed, 33% of female athletes had a recurrence of BSI injury within one year. These athletes demonstrated significantly lower baseline cortical tissue mineral density, estimated stiffness, and estimated failure load. These findings raise concern over residual BMD deficits and their correlation with compromised mechanical properties in those returning to activity. BMD levels may return to normal with exercise but research suggests bone mass and BMD can only be enhanced over long periods of consistent high-intensity strength training and plyometric/impact activity.[52] Further research would need to assess potential impact of BFR upon protection against BSI recurrence.

As the goal of this study was to investigate the potential protective effect of BFR training upon early tissue decrement, the current data cannot speak to the radiological healing of the actual bone injury itself. However, healing can also be partially inferred from clinical signs and symptoms including decreased pain and progressive function. Participants demonstrated signs of meaningful healing through improvements in patient-reported outcomes. LEFS scores significantly improved statistically and clinically at four weeks (15.15 points). Participants also showed statistically and clinically significant improvements on the PROMIS physical function (8.98 points), pain interference (8.39 points), and social participation (7.60 points) domains. Participants showed statistically and likely clinically significant improvement in the anxiety domain (3.26 points) as general guidance suggests appropriate MCID values may range from two to six T-score points. Return to activity timelines for tibial BSIs depend upon the severity of injury, but reported timelines include 6-12 weeks,[20] 6-7 weeks,[53] and 4-9 weeks.[38] On average, the participants in this study returned to impact activity at 36.5 days (5.21 weeks). Given most participants (70%) were diagnosed with a grade three or higher tibial BSI, this return to impact timeline appears to fall on the earlier range of typical return timelines. Further studies with control groups will need to be performed to help determine if BFR training can indeed promote a more accelerated return to activity.

In addition to protective effects on bone, our results also suggest that BFR training may have a positive influence upon muscle in individuals with BSI. Despite four weeks of modified activity, participants showed no significant reduction in limb circumference or LM measures. Kubota et al[54] also showed that BFR may help mitigate muscle atrophy during periods of unloading. They investigated the effect of BFR upon muscle atrophy in young healthy males undergoing a two-week period of non-weightbearing with ankle cast immobilization. While the control group showed significant decreases in limb circumference (-2.7% thigh, -2.8% leg), the group treated with BFR showed non-significant decreases over time (-1.18% thigh, -1.08% leg). Interestingly, the BFR group was treated with a "passive" BFR approach where compression was applied for five cycles of 5 minutes on/3 minutes off without the participant actively exercising. This difference may highlight one of the reasons subjects in our study tended to show non-significant positive girth changes in the involved limb (+1.21% thigh and +0.69% leg) (Table 5). Growing evidence on ACLR rehabilitation also supports the notion that passive and active BFR can help mitigate early quadricep atrophy.[26] LM has also been shown to decrease over periods of modified loading. In young healthy males who underwent two weeks of unilateral knee cast immobilization, leg LM significantly decreased 1.4% at five days and 3.1% at 14 days.[16] Participants in the current study demonstrated a non-significant LM increase of 0.80% (Table 5).

Maintenance of muscle mass throughout the recovery period could play a vital role in prevention of BSI recurrence. Muscles are believed to play a protective role against bone stress as they serve to absorb impact shock and decrease the force transmitted to bone. Studies have shown that muscular fatigue induced by distance running and rucking results in increased tibial strain.[55] While the current study did not include muscular strength or endurance measures, it seems logical that maintenance of muscle mass would be an important precursor to maintenance of muscular capacity upon return to activity. Also, other studies have previously established the beneficial effects of BFR training upon lower extremity strength.[25,56] Therefore, the muscular effects of BFR training may play an important role in BSI recovery and prevention of reinjury.

This study has several strengths. To the authors' knowledge, this is the first case series to assess the impact of BFR training upon bone and muscle changes in individuals with lower extremity BSI. All BSIs were confirmed with MRI and graded by a radiologist. Participants were treated with a tailored and progressive exercise program to promote adaption over time. BFR was performed with a personalized tourniquet system which maintained more standardized LOP throughout the course of treatment and provided accurate data on treatment dosage.

At the same time, this study has several limitations that must be considered for appropriate interpretation. The subjects' BMD may have been impacted by other factors besides BFR training, to include participation in exercise outside of the study's treatment protocol, nutritional considerations, or other individual considerations (hormonal, genetic). Also, a control group was not included which would allow for comparison of the natural bone and muscle changes over time. While the uninvolved limb was utilized as a paired comparison, this comparison may lead to inaccurate conclusions as even the uninvolved limb could have experienced changes in bone and muscle secondary to the general decrease in loading activity or crutch use. At the same time, BFR training is known to produce systemic hormonal and metabolic responses which could have produced a crossover training effect for the uninvolved side.[57] Next, 14 of 20 participants in the study were prescribed crutches for unloading by their treating providers. Although all participants were placed on official military restrictions to avoid impact activities, 6 participants were full weightbearing for the duration of the study which may limit comparisons with studies investigating muscle and bone loss secondary to true limb unloading with crutches or bracing. Also, compared to other trials that utilized HR-pQCT or specialized DEXA studies to obtain local tibial BMD values, this study used BMD values which represented the lower extremity mean. This limits conclusions that can be made regarding changes in BMD within the tibia specifically. Lastly, several participants had already altered training before study enrollment which may have influenced baseline bone measurements.

Future studies should be designed to further explore the impact of BFR upon both clinical and radiological outcomes. As this study was exploratory in nature, it lacked a true control comparison group. Future research should compare clinical outcomes between a BFR treatment group to standard of care conservative management for lower extremity BSI. Outcomes should include similar bone density, body composition, and patient-reported outcomes, but could also compare return to activity timelines and longer-term reinjury rates. Future research should also focus upon the true physiological impact of BFR upon the fracture healing process. Fracture healing is typically indirectly monitored by improvements in pain and function or by conventional radiographs. Conventional radiographs are limited in early fracture evaluation, however, due to delayed detection of callus progression, inconsistent grading criteria, and two-dimensional analysis.[58] Computed tomography (CT) has been suggested as a useful tool in monitoring fracture healing in clinical trials. CT evaluates early fracture healing with high-resolution multi-planar imaging which can provide more detailed radiographic information regarding fracture line and gap, callus formation, bridging, and union.[58,59] Future studies that seek to assess the physiological impact of BFR upon bone healing should consider utilizing a radiological outcome like CT to provide more detailed quantitative assessment of fracture parameters.

CONCLUSION

The authors believe this is the first study to examine the effects of exercise with BFR upon BMD in individuals with tibial BSI. Despite four weeks of modified weightbearing and restricted exercise activity, participants did not show significant changes in injured limb BMD, BMC, LM, or limb circumference measures. The utilization of exercise with BFR in the management of tibial BSI may help mitigate decrements in both bone and muscle tissue during periods of decreased physical loading. As a result, athletes and military members recovering from lower extremity BSI may be physiologically more prepared for safe return to previous physical performance compared to standard rehabilitation management.

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DISCLAIMER

The views expressed in this manuscript reflect the results of research conducted by the author(s) and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government.

CONFLICTS OF INTEREST

The authors report no conflicts of interest related to this research.

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