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Award Number: DAMD17-02-1-0219

TITLE: Leg Muscle Usage on Tibial Elasticity during Running

PRINCIPAL INVESTIGATOR: Peter P. Antich, Ph.D.

CONTRACTING ORGANIZATION: The University of Texas Southwestern
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REPORT DATE: January 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE January 2005	3. REPORT TYPE AND DATES COVERED Annual (15 Dec 2003 - 14 Dec 2004)	
4. TITLE AND SUBTITLE Leg Muscle Usage on Tibial Elasticity during Running			5. FUNDING NUMBERS DAMD17-02-1-0219	
6. AUTHOR(S) Peter P. Antich, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Southwestern Medical Center at Dallas Dallas, TX 75390-9105 E-Mail: Peter.Antich@UTSouthwestern.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) Tibial stress fractures (TSFs) are a substantial problem in military training, but a means of predicting their occurrence remains elusive. Bone strength is key to the resistance of TSF, but bone density, a determinant of strength, is known not to predict TSF occurrence. Elasticity is nearly as important as density in determining bone strength but has not been tested in TSF, or even studied in runners. These basic validation studies will determine if modulators of tibial stress, such as heel-strike mechanics and surface incline, also modulate bone elasticity during running. Because these modulators may operate on the tibia via the muscles, we have combined ultrasound characterization of tibial elasticity with MRI monitoring of muscle recruitment during a running (training) protocol in healthy volunteers. We hypothesize that elasticity will be profoundly altered by our training constraints and that differential muscle recruitment effects the changes in bone material, this permitting subsequent application in groups with higher risks for TSF. This hypothesis is consistent with Frost's Utah paradigm of bone remodeling. Because of significant delays due to change in Principle Investigators and Protocol/Consent Form revisions, subject recruitment and data collection is on-going.				
14. SUBJECT TERMS bone quality, ultrasound, stress fractures, MRI, muscle				15. NUMBER OF PAGES 7
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Table of Contents

Cover.....	1
SF 298.....	2
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	5
Reportable Outcomes.....	5
Conclusions.....	5
References.....	5
Appendices.....	6-7

Introduction

Tibial stress fractures (TSFs) are a substantial problem for military recruits, elite athletes, and adults transitioning from a sedentary lifestyle to an exercise regimen. Bone strength is key to the resistance of TSF, but it is evident that a better method of evaluating bone quality is needed, as the gold standard method (bone mineral densitometry) is known not to predict TSF risk. Furthermore, there is growing evidence that the influence of muscles on bone may be an important determinant of bone properties. This school of thought is embodied in Frost's Utah paradigm of skeletal physiology [1] where the load-bearing skeleton adapts to the voluntary mechanical loads induced by muscles. Ultrasound critical-angle reflectometry (UCR) is a novel modality developed in laboratory of Dr. Peter Antich that allows the complete anisotropic elastic properties of bone to be measured in vivo [2]. In this study, tibial stress will be modulated in subjects by varying running styles and inclination. Changes in bone elasticity will then be analyzed in relation to the muscle recruitment patterns as determined using magnetic resonance imaging (MRI).

Body

In September 2003, the Principle Investigator status for this study was transferred to Dr. Peter Antich. This was in response to the departure of the original PI for a position in private practice. At that time, it was learned that the Study Protocol and Consent Form had outstanding issues with the Human Subjects Safety Review Board (HSSRB) and had not been approved. In summary, although the UT Southwestern Medical Center Institutional Review Board (IRB) had rated this study Minimal Risk, it was determined by the members of the HSSRB that this study was Greater than Minimal Risk. For the time period December 2003 to May 2004, the Study Protocol and Consent Form were scrutinized by all parties, and significant revisions were submitted on several occasions. These changes culminated with a conference call between all co-investigators and the HSSRB on 12 May 2004.

In essence, the HSSRB concerns dealt with two issues: (1) what efforts were being taken by the co-investigators to minimize the Greater than Minimal Risk assigned to the transition from a sedentary lifestyle to moderate-to-high intensity exercise regimen, and (2) in particular, do the running style and inclination parameters in the study group arms present any additional risk of injury to the subjects.

To address issue (1), several key experts have joined this study as co-investigators. Peter Snell, Ph.D., a widely-respected exercise physiologist and elite track athlete, was enlisted to review and supervise all aspects of the treadmill training. Mark Perry, M.D., an orthopaedic surgeon specializing in the foot and ankle, has joined the study to provide medical oversight and to assess subjects for identified risks. In addition, as requested by the HSSRB, an independent Medical Monitor (Scott Pennington, M.D.) has been identified for reporting Adverse Events or Effects.

In regards to issue (2), an extensive literature search was performed along with consultation of external biomechanics experts to examine the relative risk of forefoot versus heel-strike running. In summary, there is no evidence in the literature that either study arm is at more risk than the other for acute injuries, although it was agreed that forefoot runners will be periodically evaluated for injuries to the Achilles tendon.

After all changes were submitted in written form, the Protocol and Consent Form were provisionally accepted by the HSSRB in July 2004, provided that local IRB approval for changes was obtained. Documentation for all changes was prepared in August 2004 and submitted to the UT Southwestern IRB in September 2004 at the time of annual review. Acceptance of all changes was received on 28 October 2004 and communicated to the HSSRB. Final HSSRB approval was dated 1 November 2004. Recruitment of subjects commenced in December 2004 and is on-going.

Key Research Accomplishments

Subject recruitment, training, and data collection is on-going. As per the original protocol, 40 subjects will be enrolled in total, with 5 groups of 8 subjects grouped for training efficiency. The first group will commence their study calendar on 1 February 2005, and the last group will finish their study calendar on 1 September 2005

Reportable Outcomes

No directly reportable outcomes are available at this time.

Although not directly supported by this grant, one paper based on data collected with the third generation clinical UCR device used in this study has been accepted for publication [3].

Conclusions

No conclusions can be drawn at this time. Data analysis will be complete in the next study year.

References

- [1] HM Frost. "The Utah paradigm of skeletal physiology: an overview of its insights for bone, cartilage and collagenous tissue organs." *J Bone Miner Metab*, 18:305-316, 2000.
- [2] PP Antich and S Mehta. "Ultrasound critical-angle reflectometry (UCR): a new modality for functional elastometric imaging." *Phys Med Bio*, 42:1763-1777, 1997.
- [3] E Richer, MA Lewis, CV Odvina, MA Vazquez, BJ Smith, RD Peterson, JR Poindexter, PP Antich, CYC Pak. "Reduction in Normalized Bone Elasticity Following Long-Term Bisphosphonate Treatment as Measured by Ultrasound Critical-Angle Reflectometry." *Osteoporosis International*, *In Press*, 2005.

Appendices

Letters of approval from UT Southwestern IRB and HSSRB.

SOUTHWESTERN

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Institutional Review Board

TO: Peter Antich, PhD
c/o Matthew Lewis, PhD
Radiology - 9058

FROM: *Kita Cathey for*
Darren McGuire, MD
Institutional Review Board 4 – Chairperson
IRB - 8843

DATE: October 28, 2004

SUBJECT: **Continuing IRB Review – Expedited Approval**
IRB File Number: 1101-555
Project Title: Leg Muscle Usage Effects on Tibial Elasticity during Running

The Institutional Review Board reviewed this research activity on an expedited basis. Your protocol and consent form(s) were approved for continuation for the period beginning 6 November 2004 and expiring on 5 November 2005. Your modification dated 9/17/04, for protocol, consent, and personnel changes, was also approved.

Please report to the IRB any unexpected or serious adverse events that occur during the study. Any proposed changes in this research must be submitted to the IRB for review and approval prior to implementation, except for immediate changes necessary to assure research subject safety, which must be reported to the IRB within two days.

This study will require continuing review from the IRB and a reminder will be mailed to you 60 days prior to the **expiration date of 5 November 2005**.

Important Note: You must use a photocopy of the attached IRB-approved and stamped consent form(s). Use of a copy of any consent form on which the IRB-stamped approval and expiration dates are replaced by typescript or handwriting is prohibited.

Should you have any questions, please telephone Kita Cathey in the IRB office at 214.648.3696.

DM/iw

Subject: FW: A-11101, Approval Memo (Proposal Log Number 01356012, Award Number DAMD17-02-1-0219)

From: "Tuzson, Tibor Mr USAMRMC" <Tiberiu.Tuzson@DET.AMEDD.ARMY.MIL>

Date: Tue, 2 Nov 2004 08:48:29 -0500

To: "Peter Antich" <Peter.Antich@UTSouthwestern.edu>

CC: "Matthew Lewis" <Matthew.Lewis@UTSouthwestern.edu>

Dear Dr. Antich,

The below notification of HSRRB approval was sent to the Contract Specialist and Grant Manager, who should notify you shortly of the release of funding for this project. Please don't hesitate to contact me with any concerns.

Best regards,
Tibor

Subject: A-11101, Approval Memo (Proposal Log Number 01356012, Award Number DAMD17-02-1-0219)

SUBJECT: HSRRB Approval of Protocol "Leg Muscle Usage Effects on Tibial Elasticity During Running," Submitted by Peter Antich, M.D., Ph.D., The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, Proposal Log Number 01356012, Award Number DAMD17-02-1-0219, HSRRB Log Number A-11101

1. The revised version of the protocol, consent form and supporting documents received 28 July 2004, have been reviewed and found to comply with recommendations made at the 24 March 2004 meeting of the Army Surgeon General's Human Subjects Research Review Board. Documentation of the IRB of Record's approval of this version of the protocol and consent form was received on 1 November 2004.
2. There are no outstanding human subjects protection issues to be resolved. This greater than minimal risk protocol is approved for implementation.
3. The Use of Human Subjects Clause and the Use of Human Anatomical Substances Clause should be entered into the Assistance Agreement for this grant.
4. Submission of the Volunteer Registry Data Base sheet is not required for this study.
5. In accordance with 32 Code of Federal Regulations 219, a continuing review report must be submitted to the local Institutional Review Board. According to our records, the continuing review report is due to the University of Texas Southwestern Medical Center IRB on or before 5 November 2005. A copy of the continuing review report and the University of Texas Southwestern Medical Center IRB approval of that report, is to be forwarded to the Acting Chair, HSRRB, as soon as possible after local approval is obtained.
6. Any protocol modifications (including but not limited to changes in the principal investigator, inclusion/exclusion criteria, number of subjects to be enrolled, study sites, or procedures) must be submitted as a written amendment for HSRRB review and approval before implementing the change.
7. The point of contact for this approval is Mr. Tibor Tuzson at 301-619-6192.

Signature Authenticated by Approve?
Approved by: LAURA R. BROSCH,

LAURA R. BROSCH, PhD
COL, AN
Acting Chair, Human Subjects
Research Review Board