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TITLE: Effect of Isokinetic Strength Training and Deconditioning on Bone Stiffness, Bone Density and Bone Turnover in Military-Aged Women

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13. ABSTRACT *(Maximum 200 Words)*

For physically active military personnel, stress fractures are debilitating and costly. Female soldiers sustain twice the number of stress fractures compared to males. Exercise interventions for women are needed to promote military readiness in ways that enhance bone strength and reduce stress fractures. This study, currently in progress, is investigating the effects of 30 weeks of concentric Vs eccentric isokinetic resistance training on bone stiffness (mechanical impedance), quality (mineral density and content), and bone cell activity (biomarkers of turnover). Female volunteers (N = 120), 18-26 years of age are categorized into normal bone density (NBD, n = 60) and low bone density (LBD, n = 60) subgroups, based on whole body bone density measurements. Subjects then are randomly assigned within NBD and LBD subgroups for concentric (n = 30 LBD, n = 30 NBD) and eccentric (n = 30 LBD, n = 30 NBD) exercise training. Exercises are performed using non-dominant arms and legs, leaving dominant limbs as self-controls. Results of this study will enhance understandings of effects of specialized exercise training on bone adaptations among young adult females. This work has important implications for reducing stress fractures arising from combat-readiness activities and for preventing osteoporosis in women.

14. SUBJECT TERMS
Isokinetic exercise, MRTA, DXA, bone turnover, osteopenia

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INTRODUCTION

Physically active, female military personnel sustain twice as many stress fractures as their male counterparts. The purpose of this study is to evaluate a special form of high-load resistance exercise as an intervention to promote long bone structural integrity, thereby decreasing the incidence of these debilitating and costly bone injuries. The effects of 30 weeks of concentric vs. eccentric isokinetic resistance training on bone stiffness (mechanical impedance), bone quality (mineral density and content), and bone cell activity (biomarkers of turnover) are being measured in 120 female volunteers, 18-26 yr, categorized into normal bone density (NBD, n=60) and low bone density (LBD, n=60) subgroups. Each subgroup has been divided (n=30) and the halves randomly assigned for concentric (n=60) or eccentric (n=60) exercise training of non-dominant arms and legs, using the dominant limbs of each subject as a self-control. Results of this study will enhance our understanding of the effects of specialized exercise training on bone health and may lead to preventive measures for reducing stress fractures in military personnel. The latter has important implications for improving combat readiness, as well as preventing osteoporosis in women.

BODY

Our research group was unable to initiate research activities on 03/01/2000, as outlined in the approved original Statement of Work (Appendix A), due to post-award requirements of the USAMRMC Human Subject Research Review Board (HSRRB) to amplify human subjects' precautions in our protocol. Final approval for the protocol was received on 04/28/2000, and the contract awarded for an approved start date of 06/01/2000. Therefore, our updated Statement of Work (Appendix B) reflects actual dates for initiation and where applicable, completion of work tasks. Below are research accomplishments associated with Statement of Work tasks during this reporting period:

2000

Jun 1- Oct 30 Recruit and screen 150 female volunteers; purchase/install Biodex® isokinetic resistance training equipment, and Pentium desktop computer in War Memorial Hall training/lab facility.

Accomplishments Approximately 480 volunteers responded to solicitations for research subjects (i.e., electronic mail solicitations, direct mail solicitations, newspaper ads, and flyer postings). Subjects (n = 185) meeting inclusion/exclusion criteria completed screening interviews; of these, 114 agreed to participate and gave informed consent. The Biodex® isokinetic training units and Pentium desktop computer were purchased and installed in the Laboratory for Health and Exercise Science at Virginia Tech.

Problems Encountered The original proposal timeline called for utilizing the last 6 weeks of the 2000 spring semester at Virginia Tech to recruit and conduct health screening for enrollment of 120 subjects. With that scenario, when the enrolled subjects departed campus in early May for summer recess, all would have been ready for them to begin baseline testing and the exercise training treatment immediately upon return to campus for their start of the fall 2000 semester in mid-August. Unfortunately, it was not possible to secure final approvals from the HSRRB and

then authorization from the budget office until 10 weeks after our proposed start date, i.e. May 26, rather than March 16, 2000. The prospective subjects were gone for the summer, requiring that we solicit their participation via contact at their summer residences throughout the mid-Atlantic U.S. region (email list serves, mass mailings, newspaper advertisements).

Jun 1-Aug 15 Employ and train Graduate Research Assistants (GRA).

Accomplishments GRAs were recruited from the pool of students accepted for the Human Nutrition, Foods, and Exercise graduate program at Virginia Tech. Two Ph.D.-level graduate students funded through this project were trained to conduct isokinetic muscular strength testing, and mechanical response tissue analysis (MRTA) testing. In addition, the Ph.D.-level GRAs were trained to supervise isokinetic resistance training sessions. One MS-level graduate research assistant was trained to conduct isokinetic muscular strength testing, and assist with MRTA testing. In addition, the MS GRA was trained to supervise isokinetic muscular strength training sessions. One MS-level GRA was trained to conduct dietary analyses, dietary consultations, and assist with DXA scans.

Problems Encountered NONE

Jun 1-July 30 Document measurement protocols; complete final precision studies for MRTA, DXA, and Biodex®.

Accomplishments Measurement Protocols were finalized for MRTA, DXA, and Biodex®.

Problems Encountered NONE

Jun 15 Submit quarterly financial report to USAMRAA.

Accomplishments Not completed, as final approval for the protocol was not granted until 04/28/2000.

Problems Encountered Not applicable

Sep 10 –Nov 15 Baseline testing for isokinetic power; MRTA; biomarker assays; DXA; Biodex®; general health and physical activity history assessments; dietary records/nutrition analysis, counseling as needed; randomize NBD subjects to CON and ECC training groups; randomize LBD subjects to training; prescribe individual training regimens.

Accomplishments Subjects completed baseline isokinetic muscular strength testing (n = 71), mechanical response tissue analysis (MRTA) testing (n = 87), DXA scans (n = 108), nutrition analysis (n = 108), physical activity history assessments (n = 108), and blood draws for the biomarker assays (n = 114). There is a disparity in the number of subjects that completed the blood draws compared to the remaining baseline measures because blood draws for the biomarker assays were completed in conjunction with the blood draws for the screening measures (i.e. CBC w/differential) prior to the physical exam. A number of subjects elected to withdraw from

participation (dropouts) during the period when they awaited completion of the physical exam. Additionally, the muscular strength testing measures were the last procedures completed, before isokinetic training was begun with each subject; therefore, this number (n = 71) reflects the sum of attrition that occurred prior to initiation of the high-intensity resistance-training program. The number of subjects indicated for completion of the baseline measurements includes subjects entered into the study in the early fall of 2000 (n = 55), and a smaller late-starter group that entered the study in the late fall of 2000 (n = 16). The decision to enroll subjects beyond the original proposed date was communicated to the IRB at Virginia Tech, which granted approval, and then to the USAMRMC in early October 2000 (see Appendices C and D). Thereafter, several communications and a teleconference with staff and members of the HSRRB in late February 2001 led the investigators to design a protocol addendum for managing these "late starting subjects." The investigators now submit a protocol addendum to the HSRRB (Appendix H), which specifies how the late starters will be managed henceforth so that the scientific value of their data, their experience as human subjects, and investment of project resources are optimized. There are absolutely no changes in risk of harm to these subjects that arises from the proposed changes in their participation. The substantive changes proposed in the addendum will not affect the late starters until they return for final testing in October 2001, so an HSRRB decision on the addendum is needed by mid-September 2001. The investigators recently requested a re-review of this research protocol from the Virginia Tech IRB; our IRB gave original approval for the protocol on 05/05/2000, and required the re-review be conducted in 12 months. The required materials were submitted to our IRB. On 05/04/2001 the Chair, Dr. Moore, gave approval for a 12-month continuation of the protocol; these materials included an explanation of the protocol addendum for managing the late starter subjects and addendum to the standard informed consent for the protocol, which these subjects will be asked to complete before consenting to their final testing in October 2001 (Appendix I).

Problems Encountered The HSRRB required that we perform additional screening procedures before the subjects could be admitted to the study. The HSRRB required all candidates to complete screening blood chemistry tests with CBC, a urinalysis, and a physician-administered physical exam. Our original proposal called for acceptable results from a physical exam within the 5-year period prior to enrollment. The HSRRB required that candidates have a physical exam within the previous 12 months, or undergo one before admission to the study. Given that those who responded to our recruiting notices are young, asymptomatic, active, and apparently healthy women, it was unusual for them to have record of a physical exam within the past year. Consequently, we were restricted by the maximum rate at which the screening procedures, and physical exams could be completed. Generally, the screening process and physical exam required approximately 2 weeks to complete, and in extreme instances greater than 4 weeks. This was due in part, to the inability of subjects to arrange physical exam appointments that did not conflict with their academic schedules.

Recommendations Coordinate for physical exams to be conducted on campus for all subjects during one or two designated days.

Sept 15 Submit quarterly financial report to USAMRAA.

Accomplishments Completed by Ms. Pat Hobbs, Office of Sponsored Programs at Virginia Tech.

Problems Encountered NONE

Sept 18 Initiate supervised training for CON and ECC groups; promote adherence.

Accomplishment Adherence strategies were approved and implemented (Appendix E)

Problems Encountered None

Sept 18-Nov30 Analyze baseline data for muscular power, physical, and biochemical variables.

Accomplishment Baseline isokinetic muscular power tests were analyzed and stored in the database. Physical characteristic data were stored in the database. Statistical analyses have been conducted on a subset of data from the subject pool, for presentation at professional meetings. Abstracts for the presentations are in Appendix F.

Problems Encountered NONE

Dec 15 Submit quarterly financial report to USAMRAA.

Accomplishments Completed by Ms. Pat Hobbs, Office of Sponsored Programs at Virginia Tech.

Problems Encountered NONE

2001

February 5-14 Complete testing for mid-training interval (16 weeks); same measures as baseline, but no DXA scans; interview subjects to promote adherence and subjective responses to training; implement strategies to optimize subject adherence to study requirements and retention; analyze and store data.

Accomplishments Subjects completed mid-training at 15 weeks for isokinetic muscular strength testing (n = 50), mechanical response tissue analysis (MRTA) testing (n = 50), and blood draws for the biomarker assays (n = 50). The number of subjects indicated for completion of the mid-training testing series reflects only those subjects that began the high-intensity resistance training in the early fall of 2000.

Problems Encountered Five subjects dropped-out of the study in the time period between baseline testing and mid-training testing. The majority of these subjects indicated that the study commitment conflicted with their academic schedule for the spring semester.

Apr 13-May 3 Conclude isokinetic training; complete testing for immediate post-training interval (32 weeks); same measures as baseline; begin 36 week deconditioning period; analyze test results and store data.

Accomplishment Isokinetic training and immediate post-training testing was completed for 54 subjects on all variables of interest at a time point averaging 30 weeks after their baseline testing. The number of subjects indicated includes those that began the high-intensity resistance training program in the early fall of 2000 (n = 43), and the late starter group (n = 11). The muscular strength tests, and DXA scans were analyzed and stored in the study database. Venous blood samples were collected and stored at -80° C, and will be analyzed following the final testing series in January 2003 (no-cost extension has been requested for an additional one-year to replicate protocol for another group of <80 subjects over the period September 2001 – January 2003: (see Appendix G). MRTA measurements were completed, electronically stored, and now undergoing analysis to extract bone stiffness scores for each subject.

Problems Encountered Our research group is requesting a 12-month no-cost extension. This request is now being submitted to the USAMRAA contract officer for this protocol, Ms. Wendy Cockerman, (Appendix G) .

KEY RESEARCH ACCOMPLISHMENTS

- Development of an electronic database is now in progress. In the future, this will support statistical analyses related to the primary study objectives, as well as development of USAMRAA project reports and papers for scientific journals. To date, progress on this database includes storage of data for subjects who entered the protocol in fall 2001 and are scheduled to complete their final testing in the early winter of 2002:
    - All subject demographic and descriptive variables;
    - Baseline, mid-training and post-training test results for muscular strength measures, as well as training adherence information;
    - Baseline, and post-training test results for DXA measures;
    - Most baseline test results for tibial and ulnar bone stiffness variables. We have yet to complete mechanical response tissue analysis (MRTA) of the mid- and post-training bone stiffness scores. To speed our capacity to analyze the MRTA data, we now are installing new software and hardware that will allow batch analysis of the individual impedance response curves. Without batch analysis, extracting bone stiffness scores from the MRTA is manpower intensive, requiring computer analysis and quality assurance evaluation of 288 separate curves/subject;
    - Biochemical assays for biomarkers of osteoblast and osteoclast activity cannot be performed until all blood samples are available to batch analyze with the same assay kits, control sera, and calibration standards. These assays will be completed and stored on the database, when the last subjects have completed their final evaluations, i.e. after the post-deconditioning physical tests;

- Research questions, that indirectly support the main study objectives, were evaluated using data from the baseline testing of the women subjects. The findings from these studies are the key year one research accomplishments:

- In young healthy non-obese women similar in age to military recruits, the bending stiffness (mechanical strength) of a weight-bearing bone (tibia) is directly related to regional muscle mass and the bone mineral content of that bone; in a non-weight-bearing bone, such as the ulna, the bone's strength is influenced primarily by geometry of the bone (i.e. ulnar width);

- Simple body composition and dietary intake variables may be useful in identifying young-adult females with low tibial bone mineral density;

- Total-body BMD measures may be useful for screening young women for low or high lower-leg and tibial bone mineral density levels.

- Maximal isokinetic muscular strength was measured in both arms and legs of 77 women subjects at baseline testing; the women subjects then participated in either high-load concentric or eccentric isokinetic resistance training of one arm and one leg for 32 weeks, with 43 of these completing the training protocol and undergoing midpoint and post-training testing. This form of high-load resistance exercise was completed in these young military aged women without any observed or subject reported injuries.

REPORTABLE OUTCOMES

Manuscripts
None

Abstracts (See Appendix F)
Nickols-Richardson SM, Beiseigel JM, Zack MK, Wootten DF, Miller LE, Cross LH, Ramp WK, Herbert WG. Fat-free soft tissue mass predicts tibial bone mineral density in a group of young-adult females. *FASEB Journal*. 2001;15:A978. (Abstract # 751.7)

Zack MK, Nickols-Richardson SM, Beiseigel JM, Wootten DF, Miller LE, Cross LH, Ramp WK, Herbert WG. Bone mineral density (BMD) of the lower legs and tibias in young-adult females with low and high total body BMD. *FASEB Journal*. 2001;15:A978. (Abstract # 751.8)

Miller LE, Wootten DF, Zack MK, Beiseigel JM, Nickols-Richardson SM, Cross LH, Ramp WK, Steele CR, Herbert WG. Modeling contributors to bending stiffness of human long bones *in vivo*: Differentiating factors in weight bearing (tibia) vs. non-weight bearing (ulna) bones. American Society for Bone and Mineral Research Annual Meeting. 2001. Accepted for presentation in Phoenix, AZ, October 12-16, 2001.

Nickols-Richardson SM, Beiseigel JM, Zack MK, Wootten DF, Miller LE, Herbert WG, WK Ramp. Tibial bone mineral density is predicted by lean body mass and energy needs in a group of young-adult females. American Dietetic Association Annual Meeting. 2001. In review.

Presentations

Nickols-Richardson SM. The BONE Laboratory. Department of HNFE Advisory Board. Virginia Tech. Blacksburg, VA. 9/25/00.

Nickols-Richardson SM. The BONE Laboratory at Virginia Tech. College of Human Resources and Education Alumni Breakfast. Roanoke, VA. 7/25/00.

Herbert WG. A current view of the effects of exercise on bone and stress fractures. Continuing Medical Education Conference, sponsored by Montgomery Regional Hospital, Lewis-Gale Hospital, and Health Research Group, Inc. Blacksburg, VA. 5/6/00.

Herbert WG. The exercise prescription for skeletal health: The latest science and how to help clients? American College of Sports Medicine's Health and Fitness Summit 2001. Las Vegas, NV. 4/19/01

Patents and licenses applied for and/or issued

None

Degrees obtained that are supported by this award

Wootten DF. Dissertation: Short Term Time-Course Skeletal Response to High Intensity Physical Exercise. 04/27/2001. Ph.D. conferred in Summer 2001. (Dr. Wootten was supported, in part, by DAMD17-00-1-0114 during his final year of the doctoral program at Virginia Polytechnic Institute and State University.)

Development of cell lines

None

Tissue or serum repositories

The T.I.B.I.A.L. (Trial in Bone Injury Abatement for Ladies) serum repository has been established within the Department of Human Nutrition, Foods and Exercise at Virginia Polytechnic Institute and State University. This repository contains approximately 224 samples from participants of project #DAMD17-00-1-0114.

Infomatics such as databases and animal models

A database containing 475 study variables related to project participation to date has been established. This database is maintained by the research coordinator (David Wootten) in 213 War Memorial Hall, with backups maintained in the research coordinator office (215 War Memorial Hall).

Funding applied for based on work supported by this award

Herbert WG, Nickols-Richardson SM, Cross LH, Ramp WK, Wootten DF, Steele CR, Kelso TK, Miller LE. Efficacy of bone integrity markers for predicting lower-extremity stress fractures in female Army recruits during basic combat training. Amount requested: $1,010,612. Submitted to the U.S. Army Medical Research Acquisition Activity Program.

(Funding period: 08/15/01 - 06/30/03). Project designed to establish a battery of predictor variables centered primarily on appraisal of "bone structural integrity" of the tibia, to field test and refine this battery with 100 female college students, and to conduct a large prospective trial with 1,300 female Army recruits.

Nickols-Richardson SM, Herbert WG, Ramp WK, Cross LH, Wootten DF, Miller LE. Interactive effects of calcium intake and exercise on bone properties in young women and men of military recruitment age. Amount requested: $781,020. Submitted to the U.S. Army Medical Research Acquisition Activity Program. (Funding period: 02/01/02 - 08/31/04). Project designed to investigate the independent and interactive effects of daily dietary calcium supplementation and exercise training on bone properties, upper and lower body strength, growth factors, and biochemical markers of bone turnover in women and men of military recruitment age.

Employment or research opportunities applied for and/or received based on experience/training supported by this award

None

CONCLUSIONS

The experience gained thus far in conducting this protocol and the early findings generated from preliminary data analyses relating to ancillary issues, support the following conclusions:

- Slow-velocity high-load isokinetic resistance training of the arms and legs over 4 months increases muscular strength and power of the knee extensors and elbow flexors/extensors by 20-23 percent in young apparently healthy women of military age.
- Isokinetic exercise, even the eccentric-type, may be accomplished in young apparently-health young military-aged women unaccustomed to strength training, without adverse musculo-skeletal or cardiovascular consequences. Isokinetic eccentric exercise reportedly induces muscle damage when very high-repetition protocols are employed in studies aimed at modeling muscle damage and repair. When total repetitions are restricted to fewer than 30 for each exercise, there appear to be no significant untoward effects.
- Mechanical Response Tissue Analysis (MRTA) is capable of providing reliable measures of lateral bending stiffness for tibia and ulna. Procedural standardization for these measurements, achieved at the outset of this study, and ongoing data processing enhancements that will permit batch-analysis of MRTA data are improving the efficiency of this technology in the research setting.
- Evidence from our preliminary cross-sectional studies are leading to improved understanding of how bone mechanical properties are influenced by such factors as weight bearing, regional muscular strength, regional bone mineral density, and anthropometrics, e.g. height, body mass index, limb size.
- Excellent progress has been made in the first 12 months of this study, despite delays beyond the control of the investigators; the potential to successfully satisfy the main study objectives is very high, particularly upon approval of the one-year no-cost extension that the investigators are requesting.

REFERENCES

Not Applicable

Appendix A

Original Statement of Work

Statement of Work

2000

Mar 1-May 3	Recruit and screen 150 female volunteers; purchase/install Biodex® isokinetic training units and Pentium desktop computer for database in War Memorial Hall training/lab facility.
Mar 20-Aug 15	Employ and train Graduate Research Assistants.
May 22-July 30	Document measurement protocols; complete final precision studies for MRTA, DXA, and Biodex®.
Jun 15	Submit quarterly financial report to USAMRMC.
Sep 25 –Oct 9th	Baseline testing for isokinetic power; MRTA; biomarker assays; DXA; Biodex®; general health and physical activity history assessments; dietary records/nutrition analysis, counseling as needed; randomize NBD subjects to CON and ECC training groups; randomize LBD subjects to training; prescribe individual training regimens.
Sept 4	Initiate supervised training for CON and ECC groups; promote adherence.
Sept 1-15	Analyze baseline data for muscular power, physical, and biochemical variables.
Sept 15	Submit quarterly financial report to USAMRMC.
Nov 27-Dec 6	Complete testing for mid-training interval (16 weeks); same measures as baseline, but no DXA scans; interview subjects to promote adherence and subjective responses to training; implement strategies to optimize subject adherence to study requirements and retention; analyze and store data.
Dec 15	Submit quarterly financial report to USAMRMC.

2001

Mar 15	Submit midterm report to USAMRMC, with summary of scientific issues and accomplishments; submit quarterly financial report to USAMRMC.
Apr 13-May 3	Conclude isokinetic training; complete testing for immediate post-training interval (32 weeks); same measures as baseline; begin 36 week deconditioning period; analyze test results; store data.
May 7-Aug 12	Investigator meetings at 4 week intervals to review data, write preliminary reports, and prepare abstracts.
Jun 15	Submit quarterly financial report to USAMRMC.
Sept 15	Submit quarterly financial report to USAMRMC and an interim scientific report on findings from the training phase of the study.
Dec 15	Submit quarterly financial report to USAMRMC.

2002

Jan 21-Feb 1	Complete testing for post-deconditioning interval (36 weeks after cessation of training); same measures as baseline; administer survey instruments to establish subjects' physical activity patterns over deconditioning interval; analyze test results; store data.
Feb 4-Mar 15	Investigators meet to review findings, including deconditioning test results and complete final scientific reports for USAMRMC.
Mar 15	Submit final scientific and financial reports to USAMRMC; prepare two three manuscripts for publication in scientific journals, to be submitted by August.

Appendix B

(Updated) Statement of Work

Updated Statement of Work

2000

Jul 15-Oct 30	Recruit and screen 150 female volunteers; purchase/install Biodex® isokinetic training units and Pentium desktop computer for database in War Memorial Hall training/lab facility.
Jun 1-Aug 15	Employ and train Graduate Research Assistants.
Jun 1-July 30	Document measurement protocols; complete final precision studies for MRTA, DXA, and Biodex®.
Jun 15	Submit quarterly financial report to USAMRMC.
Sep 10-Nov 15	Baseline testing for isokinetic power; MRTA; biomarker assays; DXA; Biodex®; general health and physical activity history assessments; dietary records/nutrition analysis, counseling as needed; randomize NBD subjects to CON and ECC training groups; randomize LBD subjects to training; prescribe individual training regimens.
Sept 18	Initiate supervised training for CON and ECC groups; promote adherence.
Sept 18-Nov 30	Analyze baseline data for muscular power, physical, and biochemical variables.
Sept 15	Submit quarterly financial report to USAMRMC.
Dec 15	Submit quarterly financial report to USAMRMC.

2001

Feb 5-14	Complete testing for mid-training interval (16 weeks); same measures as baseline, but no DXA scans; interview subjects to promote adherence and subjective responses to training; implement strategies to optimize subject adherence to study requirements and retention; analyze and store data.
Mar 15	Submit midterm report to USAMRMC, with summary of scientific issues and accomplishments; submit quarterly financial report to USAMRMC.
Apr 13-May 3	Conclude isokinetic training; complete testing for immediate post-training interval (32 weeks); same measures as baseline; begin 36 week deconditioning period; analyze test results; store data.
May 7-Aug 12	Investigator meetings at 4 week intervals to review data, write preliminary reports, and prepare abstracts.
Jun 15	Submit quarterly financial report to USAMRMC.
Sept 15	Submit quarterly financial report to USAMRMC and an interim scientific report on findings from the training phase of the study.

Dec 15	Submit quarterly financial report to USAMRMC.

2002

Jan 21-Feb 1	Complete testing for post-deconditioning interval (36 weeks after cessation of training); same measures as baseline; administer survey instruments to establish subjects' physical activity patterns over deconditioning interval; analyze test results; store data.
Feb 4-Mar 15	Investigators meet to review findings, including deconditioning test results and complete final scientific reports for USAMRMC.
Mar 15	Submit final scientific and financial reports to USAMRMC; prepare two three manuscripts for publication in scientific journals, to be submitted by August.

Appendix C

Request for Protocol Modifications

October 2000

Virginia Tech

Research Office for T.i.B.I.A.L. Trial at Virginia Tech

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Laboratory for Health & Exercise Science
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MEMORANDUM

TO: Mr. Danny L. Laspe, USAMRAA Contract Office and
Ms. Louise Pascal, USAMRAA Office for Human Subjects Board

VIA: David M. Moore, DVM, Chair, Virginia Tech IRB

CC: Ms. Pat Hobbs, Contracts and Grants Administrator, Virginia Tech

FROM: William G. Herbert, Ph.D., Professor, Lab for Health & Exercise Science
Principal Investigator, USAMRAA Protocol DAMD17-00-1-0114

DATE: 10/6/2000

SUBJECT: Request for Approval of Modifications to Research Protocol

I am writing to request your support to implement certain changes in our protocol, which our research team believes are necessary to maintain the scientific integrity of our study. The primary reasons for these changes were summarized in my Memorandum to Mr. Laspe of September 11, 2000 (see attachment 1). As explained in that memo, enrollment has been slowed considerably. Therefore, we believe it is essential to continue entering subjects through the last week of October 2000. To date, we have completed almost all baseline testing for 64 subjects. Over the next 1-2 weeks, these individuals will begin high-intensity exercise training. Given this situation, our current concerns are to:

1) Achieve sufficient numbers of subjects in our protocol;
2) provide an adequate period between baseline and our training midpoint testing to allow early physiologic adaptations to be expressed;
3) increase the numbers of potential training sessions available to subjects, despite the occurrence of university recesses that will occur during the training period;
4) implement new strategies to promote adherence and minimize potential for dropout.

Therefore, we request your support for the following changes:

1) **Extend subject enrollment through the end of October 2000.** *This will enable us to approach a final baseline sample size of 100 subjects. Our proposal called for 120 subjects. The competing considerations affecting this decision are adequacy of sample size, safeguarding against potential dropout that would compromise statistical power, Vs a further shortening of the overall training period that would occur were we to extend enrollment beyond October 31, 2000.*
2) **Delay our mid-training evaluation dates by ~10 weeks, from the period November 27-December 6, 2000 to February 5-14, 2001.** *This change would provide a "true" mid-point evaluation, given our new timeframe for training resulting from the delays explained in my memo of September 11th. Now, we expect to do more to promote optional training sessions for our subjects during Thanksgiving and the fall-spring semester recess. This may improve our goal of sustaining the training stimulus over the Holidays. Also, even subjects not available or not inclined to train over the Holidays in our lab will have returned to campus in January and resumed formal training for at least 3 weeks before their February mid-training evaluations would be administered.*

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3) **Providing and Encouraging Training Sessions.** *During the 2000-2001 Holiday Periods. As indicated in item 2) above, we will offer optional formal training sessions to subjects who wish to participate during the periods that the University is in recess, i.e. Thanksgiving (November 18-26, 2000) and between fall and spring 2000 semesters (December 15, 2000 - January 14, 2001). Realistically, we anticipate that we might offer a maximum of 6 additional sessions to our subjects during these recesses, or a total of 600 across the entire group. We would hope that, on average, the entire sample would elect to take part in half of these sessions. This would result in us staffing 300 additional training sessions. To acknowledge subjects' willingness to participate, I would provide each with an additional stipend of $5 per extra session. We also will need to staff these extra sessions, for which I propose to pay staff an additional similar amount ($5 per subject training session). Since we have scaled back the number of subjects to be enrolled (now, we are proposing 100 rather than 120), this will make $3,200 available to cover the expenses I have outlined here. Thus, at a cost of $10 per added training session, we could offer up to 320 additional sessions with these funds.*
4) **Strategies to Encourage Subject Adherence and Retention.** *The proposal that accompanies this memorandum outlines our strategies. We wish to assure the IRB and the USAMRAA Human Subjects Research Review Board that these procedures will be managed in a fashion that is fully respectful of subjects' rights. Subjects who do not maintain high attendance will be encouraged by staff to adhere to their training program, as prescribed by our protocol. However, all subjects will be treated appropriately with regard to their decisions to take part in or decline participation in any of our proposed "adherence promotion activities." Furthermore, in this college student population, I firmly believe that the economic value of these particular awards are not sufficient to coerce the subjects to continue in the study, should they wish to drop out. All project staff understand the continuing importance and expectation that all study participants are to be treated with respect and concern.*

Thank you for the opportunity to present this request. I trust that Mr. Lapse or Ms. Pascal will share these communications with Ms. Elayne Seiler (301-619-7358) at an appropriate time, as I understand that she is USAMRAA fiscal officer who oversees our grant budget. I will be indebted for your early response, as your decisions will have an immediate influence on how we proceed.

Please call on me, if I may be of assistance.

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Appendix D

Approval of Protocol Modifications from Local IRB (Virginia Tech)

October 2000

Virginia Tech
VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

Institutional Review Board

Dr. David M. Moore
IRB (Human Subjects) Chair
Assistant Vice Provost for Research Compliance
CVM Phase II - Duckpond Dr., Blacksburg, VA 24061-0442
Office: 540/231-4991; FAX: 540/231-6033
e-mail: moored@vt.edu

9 October 2000

MEMORANDUM

TO: William G. Herbert
Human Nutrition, Foods, and Exercise (0430)

FROM: David M. Moore

SUBJECT: MODIFICATIONS TO AN IRB EXPEDITED APPROVAL – "Effect of Isokinetic Strength Training and Deconditioning on Bone Stiffness, Bone Mineral Density, and Bone Turnover in Militarily Aged Women" – IRB #00-188

This memo is regarding the above referenced protocol which was previously granted expedited approval by the Virginia Tech IRB on 5/5/00. Pursuant to your request of October 6, 2000, to review and approve modifications to your approved protocol, I, as Chair of the Virginia Tech Institutional Review Board, have granted approval for the modifications as detailed in your memorandum of 10/9/00 to Mr. Danny Laspe and Ms. Louise Pascal of USAMRAA.

cc: Sharon Nickols-Richardson

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Appendix E

Approved Adherence Strategies

October 2000

Proposed Strategies & Procedures
To Encourage Subject Adherence and Retention

October 6, 2000

USAMRAA Protocol DAMD17-00-1-0114:

Effects of Isotonic Strength Training and Deconditioning on Bone Stiffness, Bone Mineral Density, and Bone Turnover in Military-aged Women

Promoting adherence of subjects in physical training research protocols is notoriously difficult, particularly in studies that involve interventions lasting more than a few months. Strategies to conserve demands on subjects' time must be developed. Investigators also must strive to assure a positive experience for subjects by scheduling experimental activities to accommodate their schedules, provide a pleasant and convenient facility, and demonstrate genuine concern for the quality of each subject's participation. Those steps are essential to project success and we have developed these in our study. Despite the best efforts, attrition rates of 50% or more often are found in published literature where physical training protocols are involved. Thus, it is necessary for us to implement special strategies to promote subject adherence and prevent dropout. Our original research proposal called for offering of two special courses on health issues for women, one each for the fall and spring semesters of the 2000-2001 academic year. Prospective subjects showed little interest in these courses for either term, so offerings were cancelled. We have documented that the 2-3 volunteers, who did register, were not inconvenienced by the cancellation of the fall course. We cannot justify offering the spring 2001 special course, as we are convinced that interest will be low again and the resources originally budgeted for this purpose, i.e. $ 4,800.00, may be much more effectively used to promote adherence by the methods described in this proposal.

So, we now seek approval from the Virginia Tech IRB and the USAMRAA Human Subjects' Research Review Board (HSRRB) to allow us to provide our subjects with a three-level program of conveniences and incentives to promote adherence. We assure the IRB and the HSRRB that information about these awards will not be disclosed any of the previously approved news media advertisements and/or announcements or in any communications by project staff during screening interviews. Instead, we will disclose the information about these awards only to those that already have been cleared medically for entry in the study and are ready to begin training. The information about the awards, therefore, would not be added to the informed consent. None of the proposed rewards has a particularly high financial value, but by conventional standards a few do have "moderate" value. Thus, we suggest withholding disclosure to subjects until they have met all other requirements. These approach guards against both the reality and appearance that the volunteers are coerced into a decision to participate for rewards that are nontrivial.

Level One: Conveniences in the Training Facility (~$1,000)

We will purchase a small refrigerator ($200: ~3 ft X 2.5 ft X 2 ft), stock it with fruit juices, and provide healthy snacks ($750: cookies, celery, carrots, etc.) which subjects may accept after each training session. Background music will be provided in the facility during exercise, with an existing compact disk player. Some CD's will be purchased, as well as the refrigerator, paper cups, etc. ($50).

Level Two: Nominal Value Incentives (~$2,600)
We will develop a large number of small value awards that subjects may win by achieving a targeted participation level. For example, the attendance level might be set at 90% of the subjects' available training sessions for one of three periods: October 16-November 16, 2000; January 15-March 2, 2001; or March 12-April 4, 2001. Subjects would be notified of the opportunity at the outset of each period. Awards might include such items as movie theater tickets, sports event tickets, performing arts theater tickets, coupons for restaurants, coupons for beauty shop services, etc., none to exceed $ 10-20 in value. We would anticipate that most subjects would qualify for these awards. If the IRB/HSRRB has no objection, we will encourage local businesses to contribute to these awards by matching our investment (e.g. $10 each from study funds and from local business; not to include any awards that could be spent on alcoholic beverages). If 80 subjects qualified for each of the three training intervals, the cost for this level would be $2,600.

Level Three: Moderate Value Adherence Awards (~$1,200)
For this level, we will develop a few awards with values in the range of $100 to $400. Eligibility will be based upon the subjects achieving a pre-determined participation level that is moderately high (~80%), but lower than that we will set for the level two awards. Those eligible will be entered into one or two drawings, one held in the fall 2000 semester and the other in the spring 2001 semester. The awards for this level would be airline tickets or coupons that might be used toward purchase of airline tickets. We envision four of these awards at the $100 level and two at the $400 level. One for each level would be given in each drawing. As with the level two component, we would like to increase the number of awards by inviting local travel agencies or the airlines to participate by matching what we invest through our project budget.

Appendix F

Professional Meeting Abstracts

Professional Meeting: Experimental Biology, April 2001

Bone mineral density (BMD) of the lower legs and tibias in young-adult females with low and high total body BMD. M. W. Zack[a], S. M. Nickols-Richardson[a], J. M. Beiseigel[a], D. F. Wootten[a], L. E. Miller[a], L. H. Cross[b], W. K. Ramp[c], and W. G. Herbert[a]. [a]Department of Human Nutrition, Foods and Exercise, [b]Department of Statistics, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 24061-0430, and [c]Health Research Group, Blacksburg, Virginia, 24060.

The purpose of this study was to explore differences in bone mineral density (BMD) of the left and right lower legs (LL) and tibias in groups of young-adult females with low (n = 20) or high (n = 20) total body (TB) BMD (mean ± SEM = 1.063 ± 0.008 vs. 1.160 ± 0.009 g/cm^2, respectively, $p < 0.0001$). TB and left and right LL BMDs were measured by dual energy X-ray absorptiometry. Mean daily dietary energy and calcium intakes were estimated from four-day dietary records. Group differences in mean values (by *t*-tests) were not found for age (20.4 ± 0.3 vs. 20.2 ± 0.3 y), height (164.2 ± 1.4 vs. 164.3 ± 1.2 cm), weight (57.5 ± 1.7 vs. 59.0 ± 1.4 kg), body mass index (21.3 ± 0.5 vs. 21.9 ± 0.5), fat mass (16.5 ± 1.0 vs. 16.2 ± 0.8 kg), fat-free soft tissue mass (39.5 ± 1.0 vs. 41.2 ± 0.9 kg), percent body fat (28.1 ± 1.0 vs. 27.0 ± 1.0 %), energy (1730 ± 95 vs. 1926 ± 110 kcal/d) or calcium intakes (741 ± 75 vs. 850 ± 78 mg/d) between low and high TB BMD groups, respectively. However, differences were measured between groups for the mean left LL (0.878 ± 0.016 vs. 0.956 ± 0.017 g/cm^2, $p < 0.01$), right LL (0.893 ± 0.015 vs. 0.952 ± 0.017 g/cm^2, $p < 0.02$), left tibial (0.970 ± 0.022 vs. 1.066 ± 0.024 g/cm^2, $p < 0.01$), and right tibial (0.985 ± 0.021 vs. 1.056 ± 0.024 g/cm^2, $p < 0.03$) BMDs. TB BMD measures may be useful in identifying females with low or high LL and tibial BMDs. (Supported by USAMRMC grant #DAMD17-00-1-0114).

Professional Meeting: Experimental Biology, April 2001

Fat-free soft tissue mass predicts tibial bone mineral density in a group of young-adult females. S. M. Nickols-Richardson[a], J. M. Beiseigel[a], M. W. Zack[a], D. F. Wootten[a], L. E. Miller[a], L. H. Cross[b], W. K. Ramp[c], and W. G. Herbert[a]. [a]Department of Human Nutrition, Foods and Exercise, [b]Department of Statistics, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 24061-0430, and [c]Health Research Group, Blacksburg, Virginia, 24060.

Tibial stress fractures are problematic for female military personnel. The purpose of this study was to identify variables associated with BMD of the tibias in females of military recruitment age ($n = 89$). BMDs of the left and right tibias were measured by dual energy X-ray absorptiometry (DXA). Fat (FM) and fat-free soft tissue (FFST) masses were measured by total body (TB) DXA scans. Four-day dietary records were analyzed to estimate mean daily dietary energy and calcium intakes. TB BMD ($r = 0.35$, $p < 0.001$) and FFST mass ($r = 0.35$, $p < 0.001$) had positive while energy ($r = -0.30$, $p < 0.01$) and calcium ($r = -0.29$, $p < 0.01$) intakes had negative associations with the left total tibial BMD. Body weight ($r = 0.35$, $p < 0.001$), body mass index ($r = 0.27$, $p < 0.02$), TB BMD ($r = 0.44$, $p < 0.0001$), and FFST mass ($r = 0.43$, $p < 0.0001$) had positive while energy ($r = -0.33$, $p < 0.01$) and calcium ($r = -0.33$, $p < 0.01$) intakes had negative associations with the left ultra-distal tibial BMD. The same patterns of relationships were found for the right total and ultra-distal tibial BMDs. Stepwise regression analyses indicated that FFST mass and energy intake predicted left total tibial BMD ($p < 0.0001$, $R^2 = 0.21$), left ultra-distal tibial BMD ($p < 0.0001$, $R^2 = 0.31$), and right total tibial BMD ($p < 0.0001$, $R^2 = 0.19$). The right ultra-distal tibial BMD was predicted by FFST mass and calcium intake ($p < 0.0001$, $R^2 = 0.23$). Simple body composition and dietary intake variables may be useful in identifying young-adult females with low tibial BMDs. (Supported by USAMRMC grant #DAMD17-00-1-0114).

Professional Meeting: American Dietetic Association, October 2001

TITLE: TIBIAL BONE MINERAL DENSITY IS PREDICTED BY LEAN BODY MASS AND ENERGY NEEDS IN A GROUP OF YOUNG-ADULT FEMALES

AUTHOR(S): S.M. Nickols-Richardson, PhD, RD, J.M. Beiseigel, M.K. Zack, D.F. Wootten, L.E. Miller, W.G. Herbert, PhD, Department of Human Nutrition, Foods & Exercise, and L.H. Cross, PhD, Department of Statistics, Virginia Tech, Blacksburg, VA; W.K. Ramp, PhD, Health Research Group, Blacksburg, VA.

LEARNING OUTCOME: To identify body composition and dietary factors that are associated with and predict tibial bone mineral density in young-adult females.

ABSTRACT TEXT: Stress fractures of the tibia are problematic for female military personnel who engage in intense training regimens and often consume inadequate dietary intakes of macro- and micro-nutrients. The purpose of this study was to identify variables associated with bone mineral density (BMD) of the right and left tibias in females of military recruitment age ($n = 40$; age = 20.3 ± 0.2 years, height = 164.3 ± 0.9 cm, weight = 58.2 ± 1.1 kg; mean ± SEM). Tibial BMD was measured by dual energy X-ray absorptiometry (DXA). Fat (FM) and lean body (LBM) masses were measured by total body (TB) DXA scans. Four-day dietary records were analyzed to estimate mean daily dietary energy and calcium intakes. Energy needs were estimated from each woman's height, weight, age, and self-reported physical activity level. Correlational analyses indicated that the left total tibial BMD had positive associations with LBM ($r = 0.44$, $p < 0.01$), TB BMD ($r = 0.69$, $p < 0.0001$), energy needs ($r = 0.35$, $p < 0.05$), body weight ($r = 0.33$, $p < 0.05$), and body mass index (BMI; $r = 0.33$, $p < 0.05$). LBM ($r = 0.42$, $p < 0.01$), TB BMD ($r = 0.63$, $p < 0.0001$), energy needs ($r = 0.41$, $p < 0.01$), body weight ($r = 0.38$, $p < 0.05$), and BMI ($r = 0.39$, $p < 0.01$) had positive associations with the left ultra-distal tibial BMD. A similar pattern of relationships was found for the right total and ultra-distal tibial BMD. Stepwise regression analyses indicated that LBM predicted left total tibial BMD (F-value = 9.18, $p < 0.01$, $R^2 = 0.19$), left ultra-distal tibial BMD (F-value = 8.06, $p < 0.01$, $R^2 = 0.18$), and right total tibial BMD (F-value = 6.04, $p < 0.05$, $R^2 = 0.14$). The right ultra-distal tibial BMD was predicted by energy needs (F-value = 6.94, $p < 0.05$, $R^2 = 0.15$). Estimation of LBM and energy needs may assist dietitians in identifying young-adult females with low tibial BMD. (Funded by USAMRMC grant #DAMD17-00-1-0114.)

Professional Meeting: American Society for Bone and Mineral Research, October 2001

Modeling Contributors to Bending Stiffness of Human Long Bones *in vivo*: Differentiating Factors in Weight Bearing (Tibia) vs. Non-weight Bearing (Ulna) Bones L. E. Miller,[1] D. F. Wootten,[1] M. K. Zack,*[1] J. M. Beiseigel,*[1] S. M. Nickols-Richardson,[1] L. H. Cross,*[1] W. K. Ramp,[2] C. R. Steele,*[3] W. G. Herbert.[1] [1]Virginia Polytechnic Institute and State University, Blacksburg, VA, USA, [2]Health Research Group, Blacksburg, VA, USA, [3]Stanford University, Stanford, CA, USA.

Dual energy x-ray absorptiometry (DXA) is widely used to evaluate bone quality at specific anatomical sites for research and clinical purposes. However, bone mineral density (BMD) and bone mineral content (BMC) have limitations for determining bone mechanical strength and fracture risk. Mechanical response tissue analysis (MRTA) is a non-invasive procedure that assesses bone stiffness using low frequency vibrations. The measured variable, EI, which is the product of Young's modulus of elasticity (E) and the cross-sectional moment of inertia (I), is a measure of the bending stiffness in long bones. Mechanical failure limits of monkey tibiae have shown that EI, in comparison to BMD, is a stronger predictor of maximum bone strength (Roberts et al., J Biomech 29: 91-98, 1996). Although McCabe et al. (J Bone Miner Res 6: 53-59, 1991) have quantified the relationship of EI vs. BMC ($r = 0.59$) for the ulna in young women, these relationships have not been described for the human tibia *in vivo*. Twenty-nine females (mean±SD: 20.0±1.7 yr, height 164.1±6.3 cm, weight 59.7±7.5 kg) underwent DXA, ulnar and tibial MRTA, and isokinetic strength tests. Ulnar width demonstrated a positive relationship ($r = 0.46$) with ulnar stiffness. Neither BMC, BMD, nor upper arm isokinetic strength were related to ulnar EI. For the tibia, the sum of fat-free leg mass and leg BMC was positively correlated ($r = 0.61$) with EI. In addition, tibial EI was positively correlated with tibia width, tibial BMC, total body BMC, and eccentric knee extension strength. However, using multiple regression, the sum of fat-free leg mass and leg BMC was the only predictor of tibial EI. Finally, bone stiffness values were divided into tertiles for the ulna and tibia, with comparisons made between high and low EI groups. No significant differences were noted in any variable means between ulnar EI groups when controlling for height, weight, and body fat percentage. However, when groups were separated into tertiles on the basis of tibial EI, and controlled for the same variables, significant differences were observed in fat-free leg mass (adjusted mean±SE: 7.5±0.2 vs. 6.5±0.2 kg, $p<.03$) and the sum of fat-free leg mass and leg BMC (7.9±0.2 vs. 6.8±0.3 kg, $p<.02$). These results suggest that weight-bearing bones have a dependence on regional muscle mass and BMC, whereas nonweight-bearing bones are influenced primarily by bone width. (Supported by USAMRMC grant #DAMD17-00-1-0114).

Appendix G

Request for 12-month No Cost Extension

Virginia Tech

Research Office for T.i.B.I.A.L. Trial at Virginia Tech

VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

Laboratory for Health & Exercise Science
213 War Memorial Hall
Blacksburg, Virginia 24061-0351
Office phones: 540-231-8209 and -231-6565: fax 540-231-8476
E-mails: wgherb@vt.edu or dwootten@vt.edu

MEMORANDUM

TO: Ms. Wendy Cockerman, USAMRAA Contract Office
CC: Ms. Louise Pascal, USAMRMC Office for Human Subjects Board
David M. Moore, Ph.D., Chair, Virginia Tech IRB
Ms. Pat Hobbs, Contracts and Grants Administrator, Virginia Tech

FROM: William G. Herbert, Ph.D., Professor, Lab for Health & Exercise Science
Principal Investigator, USAMRAA Protocol DAMD17-00-1-0114
DATE: 20 June 2001
SUBJECT: Request for One-Year No Cost Extension

I hereby ask your approval for one-time extension for our above-captioned research project, which would result in a performance completion date 12 months later than originally approved, i.e. 06/30/2003. In accordance with the provisions of our assistance agreement with USMRAA for support of this project, I am not requesting any additional funds or modifications of the approved budget. The additional time needed to complete this project will allow us to double the number of subjects in our study by replicating the research protocol during the period 2001-2003. We expect to achieve a total sample size (N > 100) for purposes of data analysis and enable our research group to more effectively address the main study objectives.

Our research group was unable to initiate research activities on March 1, 2000, as outlined in the original approved Statement of Work, due to post-award requirements of the USAMRMC Human Subject Research Review Board (HSRRB) to amplify human subjects' precautions. Final approval for the protocol was received on 04/28/2000 and the contract was approved for start date of 06/01/2000. The pages appended to this letter show a revised Statement of Work, which will fit the new time frame related to this requested extension.

I am grateful for your consideration and look forward to a decision that will allow us to extend this project.

Revised Statement of Work

2000

Jun1 – Aug 15	Recruit and screen 150 female volunteers; purchase/install Biodex® isokinetic training units and Pentium desktop computer for database in War Memorial Hall training/lab facility.
Mar 20-Aug 15	Employ and train Graduate Research Assistants.
May 22-July 30	Document measurement protocols; complete final precision studies for MRTA, DXA, and Biodex®.
Jun 15	Submit quarterly financial report to USAMRMC.
Aug 14 -Sept 1	Baseline testing for isokinetic power; MRTA; biomarker assays; DXA; Biodex®; general health and physical activity history assessments; dietary records/nutrition analysis, counseling as needed; randomize NBD subjects to CON and ECC training groups; randomize LBD subjects to training; prescribe individual training regimens.
Sept 4	Initiate supervised training for CON and ECC groups; promote adherence.
Sept 1-15	Analyze baseline data for muscular power, physical, and biochemical variables.
Sept 15	Submit quarterly financial report to USAMRMC.
Nov 27-Dec 6	Complete testing for mid-training interval (16 weeks); same measures as baseline, but no DXA scans; interview subjects to promote adherence and subjective responses to training; implement strategies to optimize subject adherence to study requirements and retention; analyze and store data.
Dec 15	Submit quarterly financial report to USAMRMC.

2001

Mar 15	Submit financial report to USAMRMC, with summary of scientific issues and accomplishments; submit quarterly financial report to USAMRMC.
Apr 13-May 3	Conclude isokinetic training for first group of subjects (n = ~ 50); complete testing for immediate post-training interval (32 weeks) for first group of subjects (n = ~50); same measures as baseline; begin 36 week deconditioning period
Mar 30-May 3	Recruit and screen 60-80 female volunteers to begin training in Sept. 2001 for second group of subjects. Complete physical exams for subjects that have not had a physical within one year.

May 3-Aug 15	Analyze measurement variables to include MRTA, biochemical variables, and muscular strength variables. Maintain contact with subjects that will begin training in September, via e-mail and phone.
Jun 15	Submit quarterly financial report to USAMRMC.
Aug 20 -Sept 1	Baseline testing for isokinetic power; MRTA; biomarker assays; DXA for second group of subjects; Biodex®; general health and physical activity history assessments; dietary records/nutrition analysis, counseling as needed; randomize NBD subjects to CON and ECC training groups; randomize LBD subjects to training; prescribe individual training regimens.
Sept 4	Initiate supervised training for CON and ECC groups; promote adherence.
Sept 1-15	Analyze baseline data for muscular variables.
Sept 15	Submit quarterly financial report to USAMRMC.
Nov 27-Dec 6	Complete testing for mid-training interval (16 weeks); same measures as baseline, but no DXA scans; interview subjects to promote adherence and subjective responses to training; implement strategies to optimize subject adherence to study requirements and retention.
Dec 15	Submit quarterly financial report to USAMRMC.

2002

Jan 21-Feb 1	Complete testing for post-deconditioning interval for subjects who completed training in May 2001 (36 weeks after cessation of training); same measures as baseline; administer survey instruments to establish subjects' physical activity patterns over deconditioning interval; analyze test results; store data.
Apr 13-May 3	Conclude isokinetic training for first group of subjects (n = ~ 60); complete testing for immediate post-training interval (32 weeks) for first group of subjects (n = ~60); same measures as baseline; begin 36 week deconditioning period
May 7-Aug 12	Analyze data; Investigator meetings at 4 week intervals to review data.
Jun 15	Submit quarterly financial report to USAMRMC.
Sept 15	Submit quarterly financial report to USAMRMC and an interim scientific report on findings from the training phase of the study.
Dec 15	Submit quarterly financial report to USAMRMC.

2003

Jan 21-Feb 1	Complete testing for post-deconditioning interval for subjects who completed training in May 2002 (n= ~60) (36 weeks after cessation of training); same

measures as baseline; administer survey instruments to establish subjects' physical activity patterns over deconditioning interval; analyze test results; store data.

Feb 4-Mar 15 Perform batch assays for biomarkers of bone cell turnover; this will involve purchase of assay kits and control procedures to maximize quality assurance in the analyses. Blood samples will have been stored throughout the experimental period so that assays will be performed on all study samples at the same time.

Mar 10 - May 10 Investigators meet to review findings, including deconditioning test results and complete final scientific reports for USAMRMC.

May 31 Submit final scientific and financial reports to USAMRMC; prepare two-three manuscripts for publication in scientific journals, to be submitted by August.

Appendix H

Request for HRSSB Review and Approval of Addendum

to Protocol DAMD17-00-1-0114

Virginia Tech

Research Office for T.i.B.I.A.L. Trial at Virginia Tech

VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

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E-mails: wgherb@vt.edu or dwootten@vt.edu

TO: Louise M. Pascal, RN, MS and Human Subjects Protection Specialist
USAMRMC Office of Regulatory Compliance and Quality

FROM: William G. Herbert, Ph.D., Professor
Principal Investigator, USAMRAA Protocol DAMD17-00-1-0114

CC: Mr. Danny L. Laspe, USAMRAA Contract Office
David M. Moore, Virginia Tech IRB Chair
Assistant Vice Provost for Research Compliance

DATE: 6/21/2001

SUBJECT: Review and Approval for Addendum to Research Project
USAMRAA Protocol DAMD17-00-1-0114

This memorandum is submitted to introduce three requests for HSRRB review and approval. The first seeks confirmation that we may proceed with extending the study for purposes of replicating the protocol with a second set of subjects during the period fall 2001-spring 2003. We will conduct the research activities and treat the human subjects in exactly the manner currently authorized by HSRRB. The local IRB at Virginia Tech has recently conducted a re-review and approved a 12-month extension to continue our protocol, based on a detailed report of our first 12-month experience and explanation of the reasons for continuing the study (see enclosures). That report gave evidence that the actual risk of harm to subjects in this protocol, based on our experience, appears to be far less than anticipated by the safety precautions currently required. Nonetheless, in replicating the protocol with an additional group of ~80 subjects, we will utilize the same precautions and monitoring techniques as currently applied with the first cycle of subjects.

The second request relates to a HSRRB review of a protocol addendum. We seek approval to add a study involving a subset of ≤ 30 subjects in a protocol with ½ the treatment duration used with subjects in the standard protocol. Exactly the same experimental procedures as those already approved will be used for subjects in this addendum, except that the training and deconditioning periods will be shortened to ~16 weeks each and no mid-training physical testing will be performed. The circumstances that led to this proposed addendum have been documented and presented to USAMRAA. A teleconference between the investigators and representatives of USAMRAA was held on 2/20/01 to discuss human subjects, scientific, and fiscal aspects of plans to resolve management of a small, late starter group of subjects (N = 11) who had undergone baseline testing in late fall 2000 and couldn't be entered into the study early enough to complete their full 32 weeks of exercise training before leaving their University residences for summer 2001 recess. The local IRB, as part of its 12-month re-review, was asked to review this protocol addendum including an addendum to the informed consent addendum that would be used with these late starter subjects who entered the protocol last year and would be expected to return for their post-deconditioning physical testing in September 2001. In May 2001, when these 11 late-starter subjects completed their post-training physical tests, each was given an explanation of this minor protocol change that might be offered to them, i.e. return for their post-deconditioning tests in September 2001 rather than January 2002. All indicated that this would be fully

2002. All indicated that this would be fully acceptable to them and consistent with an experience as a participant that is not different in any important way from that offered to someone who completes the standard protocol. Hence, should the HSRRB approve this addendum, these subjects will be contacted in August and asked to return for their final testing this coming September. In order to derive acceptable scientific value from the data of these late-starters, I further ask the HSRRB to give approval for us to replicate this protocol addendum with another similar-sized group of late-starter subjects over the period fall 2001-fall 2002. An exercise intervention of ~16 weeks was not included in our original proposal; however our research team now has an unique opportunity to further the scientific merit of this research project. The addition of this experimental group will provide valuable information related to temporal skeletal adaptations resultant from exposure to isokinetic muscular training of varying duration. An adequate sample of subjects will allow our research team to evaluate skeletal adaptations resulting from exercise intervention of ~32 weeks in duration compared to that of ~16 weeks in duration.

The third request I submit to the HSRRB for consideration is for approval to reduce the stipend paid to subjects who participate in the replication of the full protocol in 2001-2003 and in the protocol addendum in 2001-2002. For the first cycle of subjects in this study, i.e. all those who entered in fall 2000, the informed consent specifies that subjects are paid $40 each time they complete a scheduled physical test. This total to be paid to those completing the standard protocol is $160 (baseline plus mid-training, post-training, and post-deconditioning tests) and $120 for those to complete the proposed addendum protocol (no mid-training test). On querying many of the subjects who completed their testing last May, none indication that $40 vs. some smaller amount would have altered their decision to complete the study or detracted from the quality of their experience. Instead, typical comments related that having access to health-related information about themselves (DXA, screening blood measures, etc.) was beneficial, experiencing research as a subject *per se*, establishing new social relationships with other subjects, or having the chance to win some prizes of modest value (approved incentive program) were more important. Consequently, we are asking HSRRB to approval a lower stipend of $25 for all subjects who enter the protocol in the next cycle (those beginning fall 2001). The funds saved by this stipend reduction will be applied to covering costs of increased subject enrollment in the study.

Upon approval of these three requests by the HSRRB, relevant changes in dates, duration of treatments (addendum protocol), and stipends will be made in the informed consent forms and these changes will be applied to all new subjects who enter the study beginning fall 2001. Should you wish to receive copies of these revised informed consents, we can forward copies for your records.

These proposed changes have no discernible implications for risk or subjective effects on the subjects' experiences in the protocol and will only enhance scientific aspects of the research. Therefore, I am hopeful that the HSRRB can give expedited approval for these changes in the near future. In any event, I will be pleased to answer any questions that may assist your review and processing of these requests.

Best wishes.

Addendum to Protocol DAMD17-00-1-0114
Subjects Undergoing an Abbreviated Experimental Treatment

The duration of the treatment intervention and the duration of the deconditioning period will differ between the subjects undergoing the abbreviated exercise intervention and the subjects undergoing the full exercise intervention. Due to the duration of the abbreviated treatment intervention, no meaningful changes in any of the variables of interest are expected at the mid-point of training (8 weeks), therefore the subjects assigned to the abbreviated exercise intervention will not undergo a mid-training testing series. There are no other differences in the subjects assigned to the abbreviated training program, and those assigned to the full training program.

The following methods section was extracted from the original proposal, and where appropriate, new text included to descibe changes associated with the abbreviated training subjects. Sub-sections that do not differ between the full training subjects and the abbreviated training subjects are indicated by "NO CHANGE FROM ORIGINAL PROPOSAL". Only the design of the main project and subjects recruitment sub-sections differ for the abbreviated training subjects. Otherwise, the handling of the abbreviated training subjects will be identical to that of the full training subjects except for the training duration, deconditioning duration, and the elimination of one testing series.

Methods

Design of Main Project.

This study will include 30 female volunteers from the Blacksburg, VA, Virginia Tech, and surrounding communities. Many subjects are expected to be recruited from the Sophomore and Junior undergraduate classes at Virginia Tech. Subject recruitment, informed consent, and collection of preliminary data on basic health and demographic variables will be completed during the fall, 2001. In conjunction with the recruitment plan, subjects satisfying initial inclusion/exclusion criterion will be administered a health history form, which provides information regarding basic health, and demographic variables. David Wootten will administer the health history form through paper and pencil self-report, and interview.

Prospective subjects will undergo final screening and review for presence/absence of exclusion criteria (see Methods section - *Subjects*) between late summer and very early fall semester, 2001. All who qualify (n = 30) will then perform baseline assessments for all variables including right and left ulnar and tibial stiffness (IE_{MRTA}), DXA scans, blood samples for assays of bone cell biomarkers, and isokinetic maximal elbow and knee flexion/extension power with all four limbs. Based on baseline DXA measurements, BMD normative data, and researcher criteria, subjects will be categorized into normal (NBD) and osteopenic (LBD) groups based on total body BMD (targets for NBD and LBD groups are n = 15 each). Subsequently, NBD subjects will be randomized to one of two groups for 16 weeks of isokinetic training. Both groups will perform knee and elbow flexion/extension-training exercises *only* with their non-dominant limbs using an angular velocity controlled by the Biodex® at 60 degrees/sec^{-1}. Non-dominant limbs will be determined by asking each subject to identify her writing hand (dominant body side). One

subgroup will perform these exercises only in the concentric mode (CON: n = 15), and the other will perform only in the eccentric mode (ECC: n = 15). The other group, LBD, will be similarly randomized to the same training subgroups (CON and ECC). At the end of training (16 weeks), all baseline measures will again be repeated. Following completion of training, subjects will be encouraged to return to their normal, routine lifestyles with regard to physical activity, but will maintain weekly logs of physical activities over the course of the subsequent 18 weeks (detraining period). Investigators will provide subjects with standardized physical activity questionnaires with which to log this information. During this deconditioning phase, subjects will return questionnaires in person or by mail at 1-month intervals. Telephone and mail follow-up will be used to maintain adherence to this requirement and promote retention of subjects. At the end of the deconditioning phase, all subjects will complete final measures (i.e., the same measures as conducted at baseline.

Subjects (NO CHANGE FROM ORIGINAL PROPOSAL)

Subject Recruitment
Subjects will be recruited during the fall semester 2001, through the same methods outlined in the original proposal. Subjects will complete baseline testing in the late fall, and begin the exercise training program at the beginning of the spring semester 2002, thereby following the same training and testing timeline as the eleven "late starter" subjects from the previous year.

Informed Consent Administration (NO CHANGE FROM ORIGINAL PROPOSAL)

Retrieval of Medical Records (NO CHANGE FROM ORIGINAL PROPOSAL)

Unilateral Isokinetic Resistance Training: (NO CHANGE FROM ORIGINAL PROPOSAL)

Monitoring for Nutrition, Menstrual Status, and Physical Activity Habits (NO CHANGE FROM ORIGINAL PROPOSAL)

Measurement of Dependent Variables:

Measurement of Bone Stiffness of the Tibia and Ulna. (NO CHANGE FROM ORIGINAL PROPOSAL)

Bone Mineral Density and Content. (NO CHANGE FROM ORIGINAL PROPOSAL)

Biomarkers of Bone Turnover. (NO CHANGE FROM ORIGINAL PROPOSAL)

Isokinetic Muscular Power Testing. (NO CHANGE FROM ORIGINAL PROPOSAL)

Appendix I

Documentation of Local IRB Re-review of Protocol,
and Authorizations to Continue Standard Protocol
and Implement Protocol Addendum

Virginia Tech

Research Office for T.i.B.I.A.L. Trial at Virginia Tech

VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

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MEMORANDUM

TO: David M. Moore, IRB Chair
Assistant Vice Provost for Research Compliance

FROM: William G. Herbert, Ph.D., Professor
Lab for Health & Exercise Science
Principal Investigator, USAMRAA Protocol DAMD17-00-1-0114
Departmental IRB Reviewer, HNFE Department

DATE: 05/03/2001

SUBJECT: Re-review and Approval for Continuation of Research Project,
USAMRAA Protocol DAMD17-00-1-0114

This memorandum requests your approval to extend the above-captioned research project – for an additional 12 months, until the date of May 5, 2002.

1. Original signed IRB approvals. The Virginia Tech IRB approved this project on May 5, 2000, as indicated on the memorandum of approval from Mr. Tom Hurd (attached). This approval was secured, following adoption in our protocol of several added human subject safeguards that had been requested by the Surgeon General's Human Subject Review Board at the offices of the USAMRMC. The project is funded for the two-year period, beginning June 1, 2000. On October 9, 2000 a number of protocol modifications were discussed with the sponsor, these dealing mainly with subject retention strategies and how to handle scientifically the data from a small subset of subjects who were recruited into the protocol during fall 2000 and thus could not be entered into the study until January 2001. These proposed modifications were documented in the memorandum to Mr. Danny Laspe of October 6, 2000 (memo attached) and approved by the Virginia Tech IRB Chair (see memo attached, October 10, 2000).

2. Brief progress report. Subject recruitment in the late summer and fall of 2000 yielded 114 female college students, out of 478 respondents, who were able to satisfy the selection criteria. After informed consent and a physical examination, 77 completed a battery of baseline tests for muscular strength, bone mineral density (BMD) and content, lateral bending stiffness of the tibia and ulna, and bone turnover activity. These subjects were randomized to treatments and began one of two experimental exercise/training interventions that involved 32 weeks of thrice weekly training of one arm and one leg; the untrained arm and leg were control limbs. Using isokinetic training, one group exercised their arm and leg concentrically (muscles undergo shortening while contracting) and the other eccentrically (muscles undergo lengthen while contracting). Since training began, 23 subjects have dropped out and the reasons for discontinuing were recorded for use in minimizing future attrition. There have been no serious adverse events. Fifty-four subjects are presently undergoing post-training testing and, after a subsequent 32-week period in which the training has been

discontinued, these subjects will be reassessed. Thus far, results of this study have shown that tibial BMD is positively related to body composition, calcium intake, and energy needs, and that total body BMD may be useful in evaluating lower leg BMD. Further validation of the technique for determining tibial and ulnar lateral bending stiffness with mechanical response tissue analysis (MRTA) has demonstrated that the strength of weight-bearing bone is depend on the extent of local muscle mass. This finding supports the use of MRTA for measuring bone strength.

3. Planned changes in the protocol that impact and/or alter level of risk to the human subjects. As indicated under item one of this memo, we continued to enroll new subjects in our study through the late fall, 2000 in order to increase our sample size. Therefore, ~25 subjects began the exercise training in January 2001 (late-starters), rather than September 2000. The duration of the exercise treatment for these late-starters necessarily is brief compared to the early starters (~16 weeks rather than 32 weeks) because they will leave the community for summer recess when spring academic term ends in May 2001. Presently, 13 of the 25 late starters have remained in the study, and are completing the end-of-training testing series. Due to their abbreviated training intervention, there was no scientific value in re-measuring them at the midpoint of their training (8 weeks), as we expected no meaningful changes in any important parameters over a period so brief. Therefore, we did not complete a mid-point testing series for this group, as is the standard protocol for those who are in the 32-week training intervention. Additionally, these late starters will have an abbreviated de-training period (16 weeks de-training) compared to subjects who began in the early fall (36 weeks de-training). The only consequence of these time changes for the small late-starter group of 13 is that the interval between their final post-training and post-detraining tests will be reduced from 36 to 18 weeks. This change is not associated with any foreseeable increase in risk to these subjects. We propose that the attached addendum be used to supplement the original informed consent for the late-starter subjects, when they report to our laboratory in fall 2000 to complete their final detraining evaluations.

4. Re-analysis of risks/benefits in light of experience in the project to date. In the original proposal, several elaborate precautions were included at the request of the Surgeon General's HSRB to monitor for the signs and symptoms of potential muscle damage that might arise from the muscular strength and resistance training. To date, we have conducted well over 200 strength tests and 1000 training sessions, with no signs or symptoms suggestive of muscle damage occurring in any subject. Therefore, the level of risk for muscle damage resulting from the strength tests, and resistance-training sessions appears to be far lower than initially anticipated. Despite these findings, we will apply exactly the same procedures and subject safeguards, when we recruit and complete a second large group of ~80 women subjects during the 2001-2002 academic year.

5. Estimate of the time required for completion of the study. In the next 30 days, we will be requesting of the USAMRAA that they approve a 12-month no-cost extension – to May 31, 2003. The extension will enable us to complete a total of ~120 subjects in the protocol, as originally proposed, including those who enter in fall 2001 and not be ready for their final detraining evaluations until January 2003. The USAMRAA business office has stated that they will support the request for this extension. We expect to submit a written request to them within the next 30 days. A revised statement of work indicating the 12-month extension is attached.

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
ADDENDUM

The research coordinator will provide you with the original informed consent that you read and signed when you agreed to participate in this research project. You are required to re-read the original informed consent prior to signing this addendum

Informed Consent for Participants of Investigative Project

Title of Study:
Effect of Isokinetic Strength Training and Deconditioning on Bone Stiffness, Bone Mineral Density, and Bone Turnover in Military-aged Women.

Location of Study:
228 War Memorial Hall, Virginia Polytechnic and State University, Blacksburg, VA

Investigators:
William G. Herbert, Ph.D., Sharon M. Nickols-Richardson, Ph.D.,
David F. Wootten, Ph.D, Warren K. Ramp, Ph.D., and Lawrence H. Cross, Ph.D.

You understand that following the resistance training exercise program, your de-training period will be 18 weeks, and not 36 weeks as indicated in the original informed consent which you read and signed, when you agreed to be a participant in this research project. You also understand that you will only undergo three testing series throughout this project. The mid-training testing series was eliminated for you because there was very little possibility for the investigators to detect meaningful skeletal changes over such a brief period (8 weeks).

You have had the opportunity to ask questions. Any questions that you have asked have been answered to your complete satisfaction. You hereby acknowledge the above and give your voluntary consent for participation in this study.

Questions/Responses:_____
_____
_____
_____

Print Name Signature Date

Permanent Address City State Zip

Print Name: Witness Signature: Witness Date

Should you have any questions about this research or its conduct, you will contact:

David Wootten, Ph.D. (540) 231-8299
Research Associate, Virginia Tech

William Herbert, Ph.D. (540) 231-6565
Principal Investigator, Virginia Tech

Warren Ramp, Ph.D. (704) 355-5658
Biomedical Consulting and Editing

Sharon Nickols-Richardson, Ph.D., R.D. (540) 231-5104
Co-Investigator, Virginia Tech

Lawrence Cross, Ph.D. (540) 552-6019
Co-Investigator, Virginia Tech

David Moore, Ph.D. (540) 231-4991
Chair, University IRB, Virginia Tech

Virginia Tech
VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

Institutional Review Board

Dr. David M. Moore
IRB (Human Subjects) Chair
Assistant Vice Provost for Research Compliance
CVM Phase II - Duckpond Dr., Blacksburg, VA 24061-0442
Office: 540/231-4991; FAX: 540/231-6033
e-mail: moored@vt.edu

4 May, 2001

MEMORANDUM

TO: William Herbert
HNFE 0430

FROM: David M. Moore

SUBJECT: IRB EXPEDITED APPROVAL "Effect of Isokinetic Strength Training and Deconditioning on Bone Stiffness, Bone Mineral Density, and Bone Turnover in Military Aged Women" – IRB #01-256 ref 00-188

This memo is regarding the above referenced protocol which was previously granted expedited approval by the IRB on May 5, 2000. The proposed research is eligible for expedited review according to the specifications authorized by 45 CFR 46.110 and 21 CFR 56.110. Pursuant to your request of May 3, 2001, as Chair of the Virginia Tech Institutional Review Board, I have granted approval for extension the study for a period of (12) months, effective as of today's date.

Approval of your research by the IRB provides the appropriate review as required by federal and state laws regarding human subject research. It is your responsibility to report to the IRB any adverse reactions that can be attributed to this study.

To continue the project past the 12-month approval period, a continuing review application must be submitted (30) days prior to the anniversary of the original approval date and a summary of the project to date must be provided. Our office will send you a reminder of this (60) days prior to the anniversary date.

cc: file

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