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Award Number: DAMD17-01-1-0817

TITLE: Bone Growth, Mechanical Stimulus and IGF-I

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REPORT DATE: October 2002

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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20030801 034

# REPORT DOCUMENTATION PAGE

Form 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

<b>1. AGENCY USE ONLY (Leave blank)</b>		<b>2. REPORT DATE</b> October 2002	<b>3. REPORT TYPE AND DATES COVERED</b> Annual (10 Sep 01 - 10 Sep 02)	
<b>4. TITLE AND SUBTITLE</b> Bone Growth, Mechanical Stimulus and IGF-I			<b>5. FUNDING NUMBERS</b> DAMD17-01-1-0817	
<b>6. AUTHOR(S) :</b> Vicente Gilsanz, M.D.				
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<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			<b>10. SPONSORING / MONITORING AGENCY REPORT NUMBER</b>	
<b>11. SUPPLEMENTARY NOTES</b>				
<b>12a. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited			<b>12b. DISTRIBUTION CODE</b>	
<b>13. Abstract (Maximum 200 Words) (abstract should contain no proprietary or confidential information)</b>  Available data indicate that the genetic susceptibility for low bone mass is present very early in life. The aim of this project is to establish whether bone acquisition in teenagers who have sustained a fracture and have low bone mass can be enhanced by changing environmental factors, such as mechanical loading. The effects of a twelve-month mechanical intervention on musculoskeletal development will be studied and the results will be compared to matched teenagers undergoing either a classic resistance exercise intervention or no intervention. This study also examines the possible relations between the cross-sectional properties of bone and circulating levels of IGF-I, IGF-binding protein-3, and IGF-I genotypes in teenagers ages 16 to 18 years with sport-related fractures. The possible relations between bone acquisition induced by mechanical stimulus and circulating levels of IGF-I and the IGF-I genotype will be assessed. Recruitment for eligible teenagers for the first phase of this project, the cross-sectional arm in female subjects, began shortly after the approval of the project for human subjects research by the HSRRB and the local IRB on June 14, 2002. As of September 9, 2002, eight subjects have enrolled and completed the cross-sectional study, and seven more have scheduled appointments. Completion of this cross-sectional arm should occur in nine months with the longitudinal arm commencing immediately thereafter.				
<b>14. SUBJECT TERMS</b> mechanical interventions, fractures, IGF-I, teenagers, low bone mass			<b>15. NUMBER OF PAGES</b> 5	
			<b>16. PRICE CODE</b>	
<b>17. SECURITY CLASSIFICATION OF REPORT</b> Unclassified	<b>18. SECURITY CLASSIFICATION OF THIS PAGE</b> Unclassified	<b>19. SECURITY CLASSIFICATION OF ABSTRACT</b> Unclassified	<b>20. LIMITATION OF ABSTRACT</b> Unlimited	

NSN 7540-01-280-5500

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

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## INTRODUCTION

Available data indicate that the genetic susceptibility for low bone mass is present very early in life. The aim of this project is to establish whether bone acquisition in teenagers who have sustained a fracture and have low bone mass can be enhanced by changing environmental factors, such as mechanical loading. The effects of a twelve-month mechanical intervention on musculoskeletal development in teenagers will be longitudinally studied and the results will be compared to matched groups of teenagers undergoing either a classic resistance exercise intervention or no intervention. The mechanical intervention will consist of brief exposure to low level (0.3g; 1g = earth gravitational field) high frequency (30-Hz) mechanical loading for 20 minutes three times per week. The cross-sectional properties of the bone make a substantial contribution to its strength. Data indicate that the cross-sectional dimensions of bone are important determinants of low-energy impact fractures in children, stress fractures in military recruits, and osteoporotic fractures in elderly women. Insulin-like growth factor-I (IGF-I), a major regulator of longitudinal bone growth, has also recently been shown to be an important determinant of cross-sectional bone growth. This study will examine the possible relations between the cross-sectional properties of bone and circulating levels of IGF-I, IGF-binding protein-3, and IGF-I genotypes in teenagers with sport-related fractures. The possible relations between bone acquisition induced by mechanical stimulus and circulating levels of IGF-I and the IGF-I genotype will also be assessed.

## BODY

This research study was initially approved by the local Internal Review Board (IRB), the Committee on Clinical Investigations (CCI), on March 20, 2001. Following the notice of award by the U.S. Army Medical Research and Materiel Command (USAMRMC) on June 25, 2001, we were contacted by the Human Subjects Protection Specialist, Dr. Adrienne King, in the Office of Regulatory Compliance and Quality at the USAMRMC. This office was assigned our proposal for review for compliance with applicable human subjects protection regulations and Dr. King requested copies of the protocol and consents, which were formatted to the U.S. Army specifications and forwarded on August 27, 2001. On September 11, 2001 we received a request for revisions and were notified of the upcoming meeting dates for the Human Subjects Research Review Board (HSRRB). The protocol and consents were revised as requested and resubmitted via federal express on September 21, 2001. On October 19, 2001 a conference call was conducted between the Principal Investigator (Dr. Vicente Gilsanz), COL Zadinsky, and Dr. Adrienne King, resulting in further recommendations for revisions to the documents, which were resubmitted in November for the November 28, 2001 meeting of the HSRRB. Following that meeting, further requirements were made for revisions, which were responded to, and again, in the January 9, 2002 meeting of the HSRRB additional changes were requested, which were also addressed. We received notification on February 26, 2002 that this protocol had been approved for use in human subjects research by the HSRRB.

Thereafter, the approved protocol and consents were forwarded to the CCI at Childrens Hospital Los Angeles for local IRB review and approval. Such approval was issued by the CCI on June 14, 2002.

Due to the constraints indicated above, recruitment efforts for the cross-sectional assessment of females were significantly delayed and commenced just prior to the ending period covered date of this report. As of September 9, 2002, eight females were enrolled and participated in all exams outlined in the Statement of Work for the cross-sectional arm of this project, and seven more were scheduled for appointments. There have been no preliminary findings, no complaints by the participants and no adverse events.

During the next several months, we will enroll a total of 144 female teenagers who have had a fracture in this project. Each participant will have a physical examination, anthropometric measurements, an x-ray of the left hand/wrist, blood will be drawn, and measurements of bone and body composition will be obtained via computed tomography (CT) and dual energy x-ray absorptiometry (DXA). In addition, questionnaires will be completed pertaining to the dietary intake and physical activity of the participants. Thereafter, 72 females with the lowest values for bone mass will be enrolled in the longitudinal study. This work will continue as described in the approved Statement of Work.

To enhance recruitment efforts, we plan to revise the Statement of Work to expand the ages of participants to 15 to 20 years old and to allow recruitment through friends and family members of employees at Childrens Hospital Los Angeles and through local schools, clubs and church groups. These changes will not affect the outcome of this study.

#### **KEY RESEARCH ACCOMPLISHMENTS**

HSRRB and IRB approval. Infrastructure in place to recruit participants. Eight female teenage enrolled and completed cross-sectional arm.

#### **REPORTABLE OUTCOMES**

None

#### **CONCLUSIONS**

None

#### **REFERENCES**

Not applicable

#### **APPENDICES**

None