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Stress fractures result from repetitive loading and have been regarded as a mechanical fatigue-driven process. However, histopathological data and experimental data from our laboratory suggests that increased remodeling precedes the occurrence of bone microdamage and stress fractures, suggesting a central role for increased intracortical remodeling in the pathogenesis of stress fractures. Thus, we propose that stress fracture occurs through a positive feedback mechanism, in which increased mechanical usage stimulates focal bone turnover, resulting in a locally increased in porosity. Microdamage accumulation and stress fractures result from continued cyclic loading of this transiently osteopenic bone. The proposed experiments test the hypothesis by pharmacologically inhibiting the bone remodeling response, the subsequent accumulation of microdamage and the severity of the stress fracture can be diminished. In the proposed experiments, this hypothesis is being tested experimentally in the rabbit tibial stress fracture model, which was developed in our laboratory. To test the hypothesis that reactive remodeling within the cortex drives the development of stress fractures, the effect of remodeling suppression using a bisphosphonate on the accumulation of bone microdamage and diminishing the severity of stress fracture will be examined. Outcomes of these experiments will be assessed using bone scintigraphy, histomorphometry and biomechanical approaches.

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FOREWORD

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INTRODUCTION

Stress fractures result from repetitive loading and have been regarded as a mechanical fatigue-driven process. However, histopathological data and experimental data from our laboratory suggests that increased remodeling precedes the occurrence of bone microdamage and stress fractures, suggesting a central role for increased intracortical remodeling in the pathogenesis of stress fractures. Thus, we propose that stress fracture occurs through a positive feedback mechanism, in which increased mechanical usage stimulates focal bone turnover, resulting in a locally increased in porosity. Microdamage accumulation and stress fractures result from continued cyclic loading of this transiently osteopenic bone. The proposed experiments test the hypothesis by pharmacologically inhibiting the bone remodeling response; the subsequent accumulation of microdamage and the severity of the stress fracture can be diminished. In the proposed experiments, this hypothesis is being tested experimentally in the rabbit tibial stress fracture model, which was developed in our laboratory. To test the hypothesis that reactive remodeling within the cortex drives the development of stress fractures, the effect of remodeling suppression using a bisphosphonate on the accumulation of bone microdamage and diminishing the severity of stress fracture will be examined. Outcomes of these experiments will be assessed using bone scintigraphy, histomorphometry and biomechanical approaches.

SUMMARY OF RESEARCH

Our objectives in these experiments are to use the rabbit tibial stress fracture model: 1) to determine at the whole bone level whether bisphosphonate inhibition of intracortical remodeling attenuates the increased in focal bone ^{99m}Technetium uptake which characterizes the development of stress fracture, 2) to determine at the tissue level whether bisphosphonate inhibition of intracortical remodeling decreases the accumulation of cortical bone microdamage which occurs at the site of stress fracture, and 3) to determine how stress fracture compromises mechanical properties of long bones and whether pharmacological inhibition of remodeling can offset that functional deficit.

Year 1: Goals:

The goals of the first year of the project were to initiate the first series of loading and pharmacological modulation experiments Mechanically load rabbit hindlimbs (with and without pharmacological inhibition of remodeling) on 32 rabbits (16-3 week duration experiments and 16-6 week duration experiments) for bone scans and histomorphometry.

- Begin non-loaded controls (N=16 animals)
- Perform 64 ^{99m}Tc bone scans on loaded animals

- Harvest tissues from these experiments
- Begin histological processing

KEY RESEARCH ACCOMPLISHMENTS: YEAR 1

The project is proceeding toward the goals originally outlined for Year 1, with all procedures implemented. However, the project is 6 months behind schedule. The start of work on the project was delayed for 6 months because of emergency physical plant problems in our animal care facility, which required a partial shut-down of that facility. Our use of the Technetium radioactive isotope required a dedicated room for our experiments, which could not be provided while our animal housing facility was forced to consolidate animal rooms. As such, our animal experiments could not be initiated at the Henry Ford campus from mid-October 1998, when renovation work was started through April 1999, when the problem was resolved. Since April 1999, work has been progressing, with all processes and procedure implemented as per the original proposal. To date were have completed loading experiments (with and without pharmacological treatment) on 16 animals and 12 controls

REPORTABLE OUTCOMES

None to date. Experiments are ongoing

CONCLUSIONS

None to date. Experiments are ongoing