2-2-2003

Combination of Volitional Exercise and Bisphosphonate Treatment is Able to Restore Bone Loss Induced by Hindlimb Suspension

Timothy L. Norman
Cedarville University, tnorman@cedarville.edu

N. Mukherjee

C. Cutlip

O. Wirth

N. Clovis

Follow this and additional works at: http://digitalcommons.cedarville.edu/engineering_and_computer_science_presentations

Part of the Biomedical Engineering and Bioengineering Commons

Recommended Citation
Norman, Timothy L.; Mukherjee, N.; Cutlip, C.; Wirth, O.; and Clovis, N., "Combination of Volitional Exercise and Bisphosphonate Treatment is Able to Restore Bone Loss Induced by Hindlimb Suspension" (2003). Engineering and Computer Science Faculty Presentations. 110.
http://digitalcommons.cedarville.edu/engineering_and_computer_science_presentations/110
Introduction: It has been previously established in numerous radiodensitometric and biochemical studies of human bone and animal models that paralysis, immobilization and weightlessness result in loss of bone mass or disuse osteoporosis. Loss of bone due to microgravity has raised considerable concern about the increased fracture risk of astronauts, especially post-menopausal females. Despite the serious implications of bone loss and fracture fragility of the human skeleton, no countermeasure has been clearly established that would maintain bone mass during periods of weightlessness. Data from many laboratories suggest that exercise and pharmacological agents are capable of reversing bone mass/quality loss due to a variety of conditions like aging, menopause/ovariectomy and skeletal unloading/disuse. The objective of this research was to determine the efficacy of combined interventions of volitional resistance (weightlifting) and anti-resorptive pharmaceutical therapy in conserving bone mass in a rat hindlimb suspension model.

Methods: Male Sprague Dawley rats were obtained from Hilltop (Scottsdale, PA) at 22 weeks of age. During a training and acclimatization period of four weeks, the rats were reduced to their proper weight (80% of ad libitum feeding weight) and trained to exercise on a previously validated volitional resistance-training model. At approximately 26 weeks of age, the rats were assigned randomly to test groups of hindlimb suspended (HS) and hindlimb suspended with exercise and Risedronate (HSRisEx). After rats were trained, they were hindlimb suspended using a harness made of a polyester mesh fabric (Harvard Biosciences). The exercised rats were released from the suspension system and the lift response exercise began and lasted daily for 60 minutes or 80 full lifts, whichever came first. The exercise protocol was maintained 5 days per week. The hindlimb suspension protocol was continued for 21 days. Twice per week, Residronate was injected subcutaneously at a dosage of 5 mg/kg. Six days prior to sacrifice, Calcitonin (5 mg/kg) and thirteen days prior to sacrifice Democlocycline (15 mg/kg) was administered to label bones. The animals were sacrificed by AMVA approved methods.

Essential Results: Mechanical testing for strength of the femoral neck revealed significant differences between groups. The ground bearing (GB) and ground bearing exercise (GBE) control group had ultimate load of 125 N (SD=21.26 N) and 114.55 N (SD=24.28 N), respectively. The hindlimb suspended (HS) group had an ultimate load of 82.76 N and the combined treatment of exercise and bisphosphonates (HSRisEx) was able to bring the ultimate load up to 148.89 N (SD=4.26 N). Histomorphometric analysis indicated that TBV was significantly less (p<0.05) in HS than in all other groups, which was restored by a combination treatment of Exercise and Risedronate (HRisEx). Mean TBV of HSRisEx was slightly greater than in GB and GBE groups but the difference was not significant (Figure 1a). A analysis of the fluorescent images (Figures 1b, c,d) indicated significantly (p<0.0008) greater new bone formation in the HSRisEx group than the HS group.

Discussion: Few studies have looked at the effects of combining different therapies. As far as we are aware, only one such study exists for rats where exercise and bisphosphonates are combined. Tamaki et al. examined the effects of treadmill training (TR) following treatment with the bisphosphonate etidronate (E) in rats with and without ovariectomy (ovx). Results indicated that the bone mineral density of the femur and the femur bone area of the tibia was significantly greater in E and/or Tr compared to ovariectomized groups. They concluded that the etidronate treatment for two weeks beforehand influenced the effects of subsequent exercise training on maintaining BMD in the proximal femur and the trabecular bone area of the femur. In another study investigating the combined effect of exercise and bisphosphonates in humans, Grigoriev et al. tested nine bedrest subjects using the exercise protocol using calcium with four of the subjects receiving the bisphosphonate ethane-1-hydroxy-1-disphosphate. The bisphosphonates combined with exercise reduced negative calcium balance over the entire 360-day test period. Exercise alone had no effect until the second 120 days. Our results seem to support these studies that show that bisphosphonates can be effectively used together with exercise to reduce calcium loss. This pilot study indicated that combination of therapies appears to be feasible to reverse bone loss due to disuse/microgravity.

References:
1. Dempster and Lindsay, Lancet 341:797-801, 1993
8. Schulthesis et al., 45th Annual Meeting ORS, p. 784, 1999a
9. Schulthesis et al., 45th Annual Meeting ORS, p. 569, 1999b
10. Schulthesis et al., 46th Annual ORS, p. 724, 2000