Galactic cosmic radiation and ApoE4 deteriorate lumbar vertebrae trabecular bone microstructure but not strength in male Alzheimer's-like mice

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Irradiation and Alzheimer's are both associated with diminished bone health, though their combined effects are not fully understood. In long-duration space exploration missions, radiation exposure and age-associated comorbidities—such as Alzheimer's—are of great concern. This study aimed to (1) compare murine bone microstructure and strength in Alzheimer's models to wild type and (2) to quantify late-effects of space-like radiation exposure on bone microstructure and strength in the Alzheimer's model.

$APP^{NL-F/NL-F}$ knock-in mice were crossed with human APOE3 or APOE4 floxed targeted replacement mice on a C57BL/6 background. Male APP;E3F (n=9) and APP;E4F (n=9) mice were exposed to 0.75Gy 5-ion mixed field beam irradiation (GCRsim). Sham-treated male APP;E3F (n=9), APP;E4F (n=8), or WT mice (n=6) were used as controls. Mice were sacrificed at 17 months of age. Lumbar vertebral (LV) trabecular (Tb) bone structure was assessed using micro-CT, and mechanical properties via micro-FEA. Pairwise t-tests with Bonferroni correction ($\alpha=p<0.013$) assessed group effects.

APP;E4F-Sham had lower bone mineral density (BMD, $p=0.011$), bone volume fraction (BV/TV, $p=0.006$), Tb.Number ($p=0.005$), and greater Tb.Separation ($p=0.005$) than APP;E3F-Sham, but no difference compared to WT-Sham mice. Compared to APP;E3F-Sham, APP;E3F-GCRsim had lower BMD ($p=0.002$), BV/TV ($p=0.001$), connectivity density ($p=0.010$), Tb.Number ($p=0.003$), Tb.Thickness ($p=0.003$), and greater Tb.Separation ($p=0.001$). Bone microstructure in APP;E4F-GCRsim was not different from APP;E4F-Sham. APP;E4F-GCRsim had lower Tb.Number ($p=0.008$) and greater Tb.Separation ($p=0.009$) than APP;E3F-GCRsim. No changes in LV stiffness, ultimate load, or elastic modulus were detected.

In this Alzheimer's model, APP;E4F induced significant deficits in bone microstructure both with and without GCRsim exposure. Separately, GCRsim also deteriorated LV structure as observed in APP;E3F but not APP;E4F. ApoE4-induced bone deterioration may thus outweigh that of GCRsim exposure. Interestingly, these structural deficits did not correspond to lower strength, warranting further investigation into the effects of structural redundancy in trabecular bone and Alzheimer's in a spaceflight context.