Total Body Irradiation Results in Deficits in Vertebral Bone Structure and Mechanical Properties in Male Rhesus Macaques

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Patients undergoing high-dose radiation therapy (RT) for cancer treatment have an elevated fracture risk, particularly in healthy bones that absorb dose. However, the effects of low-dose total body irradiation (TBI) on skeletally-mature bone are unclear; determining these responses can help develop countermeasures for adult survivors of radiologic events (e.g, “dirty bomb”). This study quantified aging and late effects of TBI on bone microstructure in rhesus macaque (*Macaca mulatta*) non-human primates (NHPs).

Femora and lumbar vertebrae (LV) were obtained post-mortem from 3 groups of skeletally-mature male NHPs: TBI (n=7 femora; n=5 LV, 18.9±2.5yrs of age), age-matched non-irradiated (NR) Controls (n=6 femora; n=4 LV, 18.7±2.0yrs), and NR Young NHPs (n=6 femora; n=6 LV, 9.1±0.1yrs). TBI received an acute dose of 6.0-6.75Gy. Tissues were harvested ~10yrs after TBI. High-resolution computed tomography (CT, Scanco) scans were used to assess trabecular (Tb) microarchitecture of LV and distal femur; cortical (Ct) bone was assessed at femoral mid-diaphysis. Micro-finite element analysis (μFE) of LV was computed using CT scans. Urinary N-terminal telopeptide crosslinks (NTX) were quantified via ELISA at sacrifice. One-way ANOVA and Tukey post-hoc tests assessed group effects. Data presented as mean±SD; percent differences are calculated between group means.

Body mass varied by group, with Young NHPs (18.1±3.3kg) larger than TBI (13.9±2.7kg, p=0.01) and Controls (14.4±4.1kg, p=0.04). TBI resulted in LV Tb deficits: lower bone mineral density (BMD, -20%, p=0.04) and bone volume fraction (BV/TV, -27%, p=0.03) vs Controls (Fig A). LV Tb BMD and BV/TV were similarly lower in TBI vs Young NHPs (-20%, p=0.07; -26%, p=0.04, respectively). μFE stiffness, ultimate force, and apparent modulus were lower in TBI vs Controls (-34%, p=0.11; -30%, p=0.15; -33%, p=0.11) and Young (-37%, p=0.04; -34%, p=0.05; -56%, p=0.048, Fig B). No differences between Control and Young NHPs were detected in LV microarchitecture or μFE measures. By contrast, at the femur, Controls had reduced Tb BMD (-28%, p=0.058) and BV/TV (-32%, p=0.04) vs Young NHPs (Fig C). Yet, TBI had no measurable effect on distal femur Tb bone, Ct bone area (Fig D) and NTX levels across groups.

In the axial skeleton of NHPs, TBI diminished Tb bone microstructure and strength, suggesting TBI exposure could elevate vertebral fracture risk in adult survivors after intentional or accidental radiologic events.

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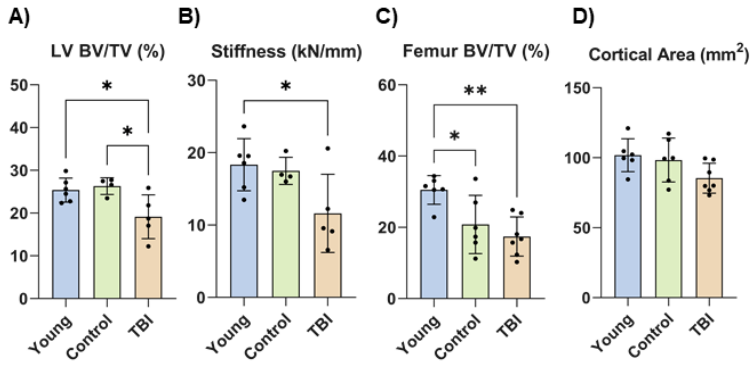

Figure: Bone microarchitectural and finite element stiffness differences associated with aging and total body irradiation (TBI). **A)** Lumbar vertebra (LV) trabecular bone volume fraction (BV/TV), **B)** LV micro-finite element stiffness, **C)** Metaphyseal femoral trabecular bone volume fraction (BV/TV), **D)** Mid-diaphyseal femoral cortical area. Data are presented as mean and standard deviation, with individual data points shown. Statistical significance of Tukey's post-hoc test: * - $p<0.05$, ** - $p<0.01$.