Total body irradiation results in long-term deficits in vertebral but not femoral bone structure in male rhesus macaques

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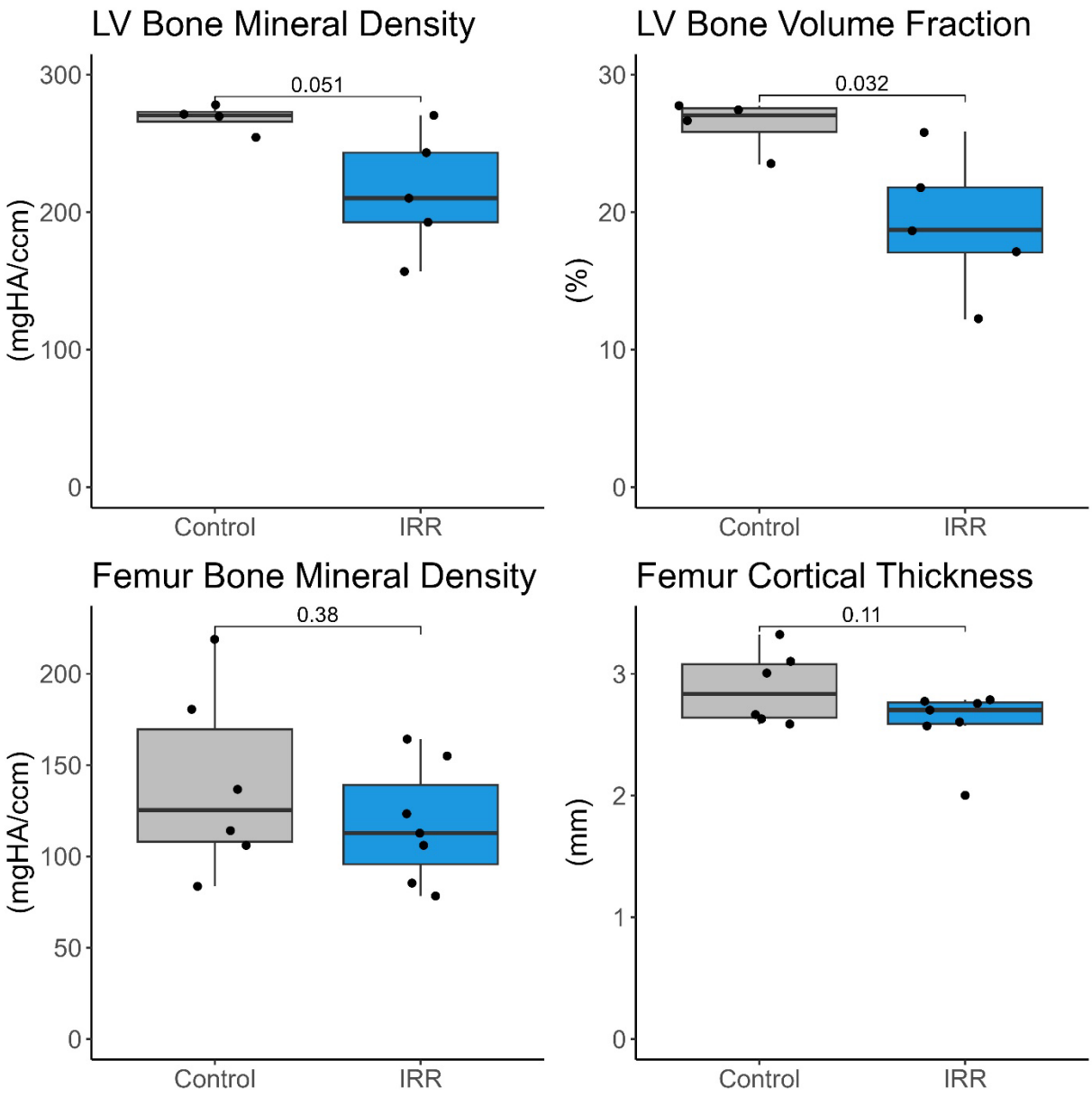
Skeletal fractures are a late effect of high-dose clinical radiation therapy (RT) for cancer treatment, particularly in normal bone that absorbs dose during the course of RT. However, relatively little is known about the effects of lower-dose, survivable total body irradiation (TBI) on skeletally-mature bone. The objective of this study was to quantify late effects of TBI on vertebral and femoral bone microstructure from rhesus macaque (*Macaca mulatta*) non-human primates (NHPs).

Femora (n=7) and lumbar vertebrae (LV; n=5) were obtained post-mortem from irradiated (IRR) male NHPs as part of the Wake Forest Radiation Late Effects Survivor Cohort; LV (n=5) and femora (n=6) from age- and sex-matched non-irradiated controls were also obtained. Skeletally-mature NHPs received an acute 6.0-6.75 Gy dose of TBI (mean=6.5 Gy) and tissues harvested an average of 10 years after TBI. High-resolution computed tomography scans were used to assess trabecular (Tb) bone structure of the LV and distal femur; femoral cortical bone was assessed mid-diaphysis. Urinary N-terminal telopeptide crosslinks (NTX), a marker of osteoclastic resorption of bone, was quantified at sacrifice. T-test assessed group effects; data reported as mean [95% CI]; α $p<0.05$.

Mean age (19 ± 2.2 yrs) and body weight (14 ± 3.3 kg) were similar in IRR and controls ($p>0.5$ for both). In the LV, IRR NHPs had 27% lower Tb bone volume fraction (19.1% [13, 25] vs. 26.3% [23, 29]; $p=0.032$) and number (1.6mm^{-1} [1.1, 2.1] vs. 2.2mm^{-1} [1.7, 2.7]; p=0.042) vs. control. LV BMD was also lower in IRR vs. control (-20%; $p=0.051$). In contrast, femoral trabecular and cortical bone outcomes in IRR were similar to control. NTX levels did not differ between groups (IRR: 994 mMBCE [647, 1342]; control: 1142 mM BCE [323, 1962]; p=0.71).

TBI resulted in long-term Tb bone loss in the axial skeleton of adult NHPs when comparing age- and sex-matched non-irradiated controls. This Tb bone loss would weaken the LV, likely leading to increased risk of vertebral fracture. NTX was similar between groups, suggesting bone turnover rate was similar and therefore bone deficits from TBI persisted from earlier atrophy of bone. These results indicate that survivable TBI from a radiologic event could result in chronic weakening of vertebrae and predispose fracture among adult survivors. [U01AI150578, T32AG023480]


LV Bone Mineral Density
0.051
300
200
100
0
(mgHA/ccm)
Control
IRR
LV Bone Volume Fraction
0.032
30
20
10
0
(%)
Control
IRR
Femur Bone Mineral Density
0.38
200
150
100
50
0
(mgHA/ccm)
Control
IRR
Femur Cortical Thickness
0.11
3
2
1
0
(mm)
Control
IRR