Social Isolation Stress Leads to Bone Loss in Adult Male, but Not Female, C57BL/6J Mice

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Social isolation is a potent form of psychosocial stress and is a growing public health concern, particularly among older adults. Even prior to the onset of the COVID-19 pandemic, which has significantly increased the prevalence of isolation and loneliness, researchers have been concerned about a rising “Epidemic of Loneliness”. Social isolation is associated with increased risk for many health conditions, including mental health disorders, as well as higher overall morbidity and mortality. Previous clinical research has demonstrated that psychosocial stressors, and subsequent mental health disorders, are major risk factors for osteoporosis and fracture, which disproportionally affect older adults. The effects of social isolation on bone, however, have not been thoroughly investigated.

The aim of this study was to test the hypothesis that social isolation would lead to bone loss in male and female C57BL/6J mice. 16-week-old mice were randomized into social isolation (1 mouse/cage) or grouped housing (4 mice/cage) for four weeks (N=16/group). Social isolation significantly decreased trabecular bone parameters, including bone volume fraction (BV/TV) by 26% (Grouped: 21.9 ± 3.6%; Isolated: 16.2 ± 2.1%) ($p < 0.0001$), as well as BMD, Tb. N., and Tb. Th, in the femur of male, but not female, mice. Femoral cortical bone parameters were also significantly decreased in isolated male mice, including a 9% decrease in cortical thickness (Ct.Th.) (Grouped: 0.187 ± 0.011 mm; Isolated: 0.169 ± 0.009 mm) ($p < 0.0001$), as well as Ct.Ar., Ct.Ar./Tt.Ar., and pMOI.

There were no significant differences in cortical measurements in females. Additionally, isolated male mice had signs of reduced bone remodeling represented by reduced osteoblast numbers and osteoblast-related gene expression, and osteoclast-related gene expression. However, isolated females had increased bone resorption-related gene expression, without any change in bone mass. The magnitude of bone loss in isolated males is as high as that seen in previous studies 4 weeks after orchiectomy or ovariectomy.

Overall, our data suggest that social isolation has a dramatic negative effect on bone in males, but may operate through different mechanisms or in a different time frame in females. Future studies will focus on investigating potential mechanisms involving changes in endocrine signaling via glucocorticoid, sympathetic nervous system, and estrogen pathways. These results provide critical insight into the effects of isolation on bone and have key clinical implications as we grapple with the long-term health impacts of the rise in social isolation related to the COVID-19 pandemic.

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