The Pathological Interaction Between Alzheimer's Disease and Osteoporosis in 5xFAD Model

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Abstract

Alzheimer's Disease (AD) and Osteoporosis are common degenerative diseases of aging. AD has been considered a risk for osteoporosis and previous studies have shown that patients with AD have an increased risk for hip fractures which are the result of osteoporosis, suggesting a link between reduced bone mass and AD. This experiment studied the 5xFAD mouse model which recapitulates many AD-related phenotypes. The objective was to compare the bone mass of 5xFAD mice with AD-like phenotypes to mice without AD. The results demonstrate that 5xFAD mice have a progressive loss of bone mass as they age. Although previous papers have denoted similar results in another AD mouse model, Tg2576, this is the first time these results were shown in the 5xFAD mouse model. As each mouse model of AD recapitulates a different aspect of the disease, these findings can help narrow down what connects osteoporosis and AD. The findings confirm that AD mice have significantly reduced bone mass, consistent with the development of osteoporosis. The substantial change in bone mass over time between the 5xFAD mice and Wild-Type mice suggests that the disease's effects are age-dependent.

Introduction

- Alzheimer's Disease (AD) and Osteoporosis are common degenerative diseases of aging. Previous research has found that AD and osteoporosis may overlap [4].
- Observational studies demonstrate a correlation between the osteoporosis and AD that suggest, rather than one condition causing the other, both conditions are related by a common underlying mechanism [4].
- Previous studies have investigated bone mass in mouse models that recapitulate the pathology of AD [4].
- This study focuses on the 5xFAD mouse model, another AD mouse model that exhibits a more aggressive form of AD. Thus, the 5xFAD mouse model rapidly recapitulates major features of AD amyloid pathway: rapidly accumulating Aβ42 in the brain, early amyloid deposition and gliosis, robust intraneuronal Aβ labeling, neurodegeneration and neuron loss.
- The goal of this study was to investigate the skeleton of the 5xFAD mice and compare its bone density to age-matched healthy control mice.

Methodology

5xFAD and Wild-Type (Control) Mice Tissues
The 5xFAD mouse model is a validated model of familial Alzheimer's disease.

Micro-Computed Tomography (μCT)
The right femur of the wild-type (control) mice and 5xFAD mice were scanned and analyzed using *μCT*. Trabecular bone architecture was measured in a proximal region. Primary trabecular parameters included bone volume per total volume (BV/TV). Cortical geometry was measured in a 100 slice region at the midshaft at 50% of the total length of the femur. Primary cortical parameter includes cortical area (mm^2).

Bone Histological Analysis:
After μCT scanning, the bones were prepared for histological investigation by dehydration and decalcification of the femoral tissues. After all the calcium from bones were removed, samples were embedded in paraffin, cut into sections and mounted for tartrate-resistant acid phosphatase (TRAP) and Sudan Black B staining.

Results and Discussion

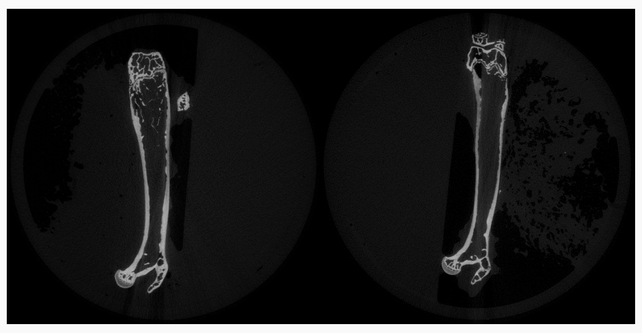

Figure 1: X-ray scan of the Femurs. The left image displays an X-ray of a Wild-Type mice femur. The right image displays an X-ray of a 5xFAD transgenic mice femur.

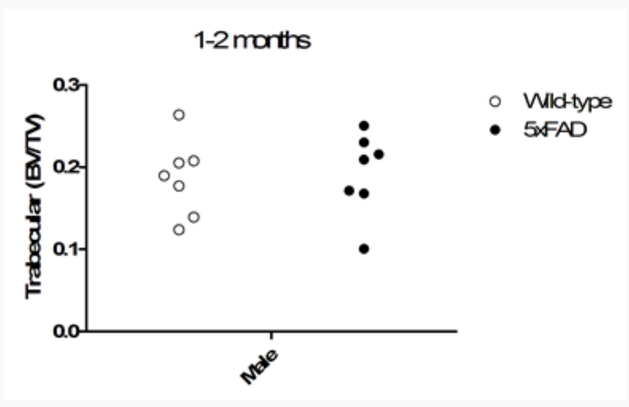

Figure 3: Trabecular Bone Volume per Total Volume (BV/TV) Comparison.

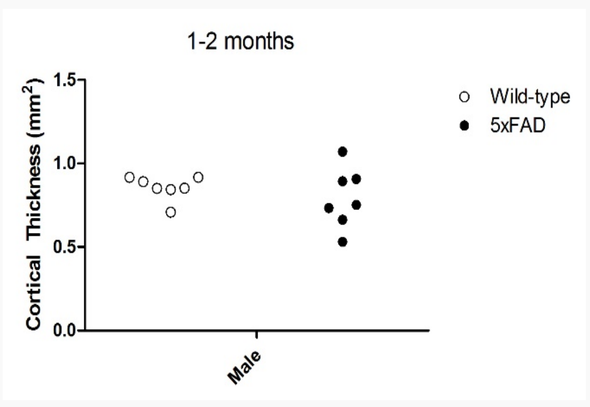

Figure 5: Cortical Area of Femur Bone

Findings

- The data suggest that 5xFAD mouse model recapitulates the low bone mass characteristics of osteoporosis
- The change in bone density over time observed in the 5xFAD mice suggest that the bone mass loss is progressive
- The data and images collected from the study provide evidence to suggest that the combination of mutations in the diseased 5xFAD mice have an effect on the bone resorption of the trabecular bone in the 5xFAD mice in comparison to the WT mice (Figure 1,4).
- Male 5xFAD mice do not experience cortical bone resorption to the same extent observed in female mice (Figure 5, 6).

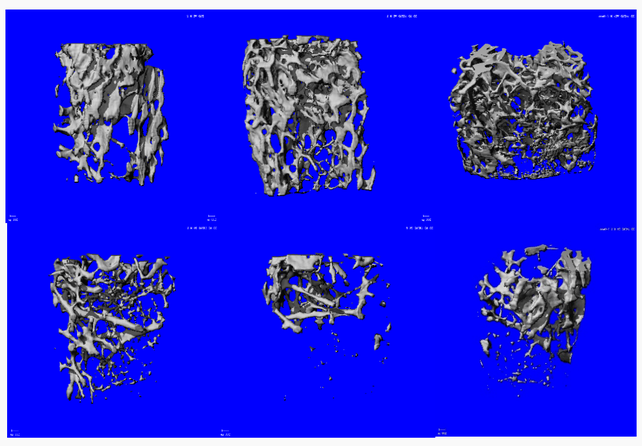

Figure 2: 3D Reconstruction of μCT Scanned Trabecular Bone.

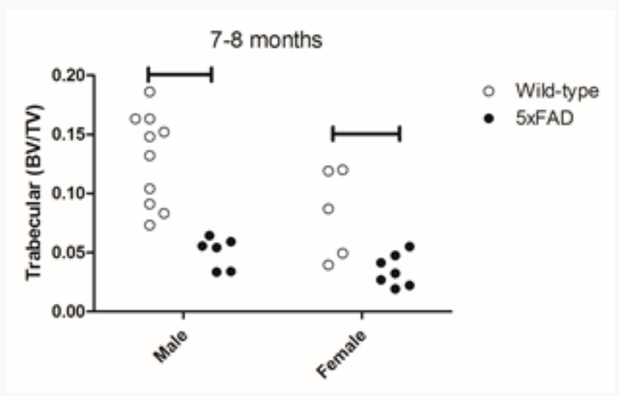

Figure 4 Trabecular Bone Volume per Total Volume (BV/TV) Comparison.

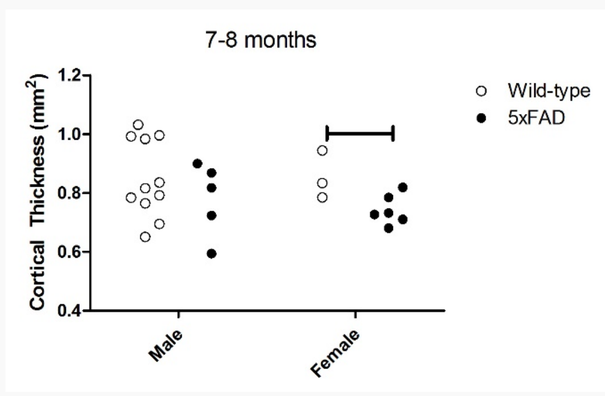

Figure 6: Cortical Area of Femur Bone

Trabecular Bone

Male 5xFAD mice exhibit a decrease in trabecular bone density over time in contrast to Wild-Type (WT) mice (Figure 3). Older female 5xFAD mice exhibit a lower trabecular bone density than the WT mice.

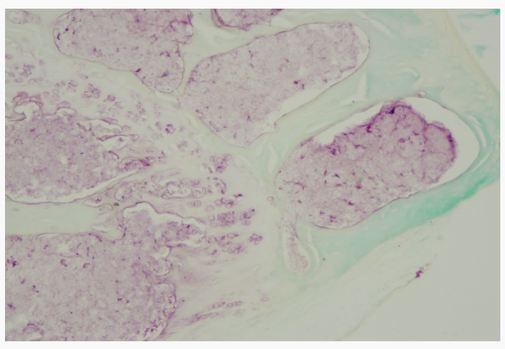

Figure 7: Tartrate Resistant Acid Phosphatase (TRAP) Staining for Osteoclasts.

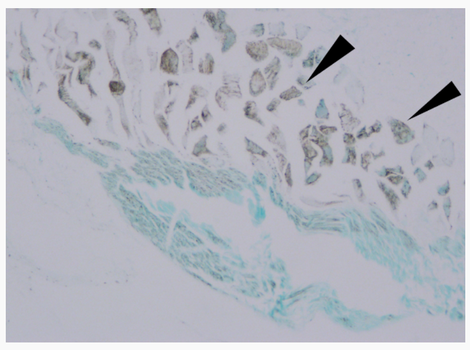

Figure 8: Sudan Black B (SBB) senescence Staining.

Cortical Bone

μCT analyses show that over time male 5xFAD mice do not have a decreased cortical bone are in comparison with WT mice. Older female mice exhibit a lower cortical bone area than WT mice.

Conclusions and Future Work

- We are currently performing TRAP staining, which is a method to identify active osteoclasts.
- Considering other mouse models that recapitulate AD exhibit similar effects in trabecular and cortical bone, our current model could share the same mechanisms and pathologies that are driving the effects seen in those mouse models. Future work is necessary to identify the role of Aβ and RANKL Pathway in the 5xFAD model.
- We are also performing Sudan Black staining to investigate senescence, a process known to occur in the brains of AD patients, to understand whether the bone resorption is due to cellular aging.
- Bone loss has not been studied nor published before in the 5xFAD model. Although AD and osteoporosis are not commonly considered linked diseases, past research presents compelling information that they are interconnected. Continuing to investigate the AD mouse models to is crucial to further our understanding of these two devastating diseases of aging.

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