

Oral Tributyrin Supplementation Attenuates Alzheimer's disease-associated Bone Loss
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Introduction: Dysbiosis of the gut microbiome is associated with various diseases, including Alzheimer's Disease (AD). Alzheimer's Disease is closely associated with several secondary complications, including bone loss. Recent clinical and animal studies indicate that subjects with neurological complications have an elevated risk of developing osteoporosis. A decrease in intestinal butyrate-producing bacteria has been indicated by pre-clinical and clinical studies in AD, therefore, we assessed the effects of long-term oral administration of tributyrin (TB: a butyrate pro-drug) on the development of osteoporosis in a mouse model of Alzheimer's Disease (AD).

Methods: Method: Oral gavage with tributyrin (2 mg/kg) was given twice weekly to female 3xTg mice between 4- and 14-months of age for 4 months. Bones from untreated and or TB treated 8 and 18-month-old mice were formalin-fixed, paraffin-embedded for microscopic analysis of AD-associated bone loss pathology, skeletal phenotype analysis, osteoblastogenesis and osteoclastogenesis.

Results: We examined the skeletal phenotype associated with AD pathophysiology in 3xTg mice, a model of AD, this mutant mouse exhibits plaque and tangle pathology associated with synaptic dysfunction, traits similar to those observed in Alzheimer's disease patients. The 3xTg mice display full-blown neuropathology and neurobehavioral deficits by age 12 months. Using Micro-CT analysis of femurs and vertebrae, we revealed significant reduction of multiple trabecular and cortical bone parameters in 14-month-old female 3xTg mice compared to wildtype (WT) littermates, including BV/TV, bone mineral density, trabecular thickness, and bone stiffness. Bodyweight was not significantly altered in 3xTg vs WT littermates, but DXA scans showed modestly reduced body fat. Osteoblastic differentiation of 3xTg BMSCs was significantly blunted compared to WT BMSCs, with diminished alkaline phosphatase (Alpl) activity, mineralization, and *Alpl* mRNA levels. Osteoclast formation of 3xTg- bone marrow monocytes was significantly enhanced relative to WT- bone marrow monocytes, with increased numbers of TRAP⁺ osteoclasts and increased OPG mRNA levels and decreased RANKL mRNA levels. On the other hand, Tributyrin treatment prevent bone loss in 3xTg mice.

Conclusion: Together, our findings indicate that AD influences bone metabolism and promotes osteoporosis by both inhibiting osteoblast-mediated bone formation and accelerating osteoclast-mediated bone resorption. Our study uncovers previously undefined novel evidence that administering tributyrin improves bone loss in 3xTg-AD mice.

Significance: Our study uncovers previously undefined novel evidence that administering tributyrin improves bone loss in 3xTg-AD mice.

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