

## ABSTRACT

### INTESTINAL BARRIER FUNCTION ALTERS BONE DENSITY

By

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1 in 2 women over 50 will experience a fracture due to osteoporosis. Current therapeutics work to prevent further bone loss, however, new therapies which can build bone or prevent bone loss are necessary to identify. The gut-bone axis is a promising target for the prevention of bone loss. Recent studies have shown that the probiotic *Lactobacillus reuteri* prevents bone loss during estrogen deficiency (OVX), type 1 diabetes (T1D) as well as increases bone density in healthy male mice. This finding lead us to examine what changes occur in the intestine following estrogen deficiency. We found that ovariectomy (OVX) leads to decreased intestinal permeability which is prevented by estrogen supplementation. Additionally, OVX was found to decrease epithelial cell turnover as well as mucus production. To determine how treating the intestinal epithelial barrier can affect bone loss, we utilized a high molecular weight polymer, MDY, which is neither metabolized or absorbed to decrease intestinal inflammation and increase mucus in the intestine. MDY treatment in OVX mice prevented estrogen deficiency induced bone loss, highlighting the role of the intestinal barrier in bone density. In addition to characterizing how OVX alters intestine function, T1D was found to alter intestinal motility and permeability, both of which were correlated to bone loss. Treatment of diabetic mice with MDY prevented intestinal inflammation and increased bone density with respect to diabetic controls. Together our studies indicate an important role for the intestinal barrier in the health of bone. Understanding the role of the gut-bone axis can lead to the prevention of bone loss as well as the development of new bone building therapies.