Fatigue loading induces osteocyte apoptosis in long bones in rats [1]. It has been suggested that bisphosphonates can prevent osteocyte apoptosis [2]. The purpose of this study is to determine the effect of nitrogen-containing bisphosphonates on osteocyte apoptosis by using a cyclic loading model known to cause osteocyte apoptosis in response to microdamage [1, 3]. We hypothesize that risedronate or alendronate treatment prevents or delays osteocyte apoptosis in a dose response fashion in a cyclic fatigue loaded animal model.

Rats were used because they are an established model for producing bone microdamage with known amounts of loading; and they do not normally undergo intracortical remodeling, so there will be greater potential to detect and evaluate regions of increased bone metabolism without the overlying confounding effects of cortical bone turnover. Dose levels were determined based on previous data in rats where a 5 μg/kg/day risedronate dose produced optimal bone anti- resorptive activity.

Methods: Forty nine female 6 month old Sprague Dawley rats were divided into seven groups, treated daily during 17 days with vehicle or one of three doses of risedronate or alendronate, and loaded by cyclic compression of the right ulna one time for 1 hour to induce microdamage (Figure 1).

Beginning 7 days before loading, animals were given a daily subcutaneous injection either of saline vehicle (CNT, n=7) or were treated daily with a subcutaneous injection of Risedronate (Ris) at a dose of 0.05 μg/kg per day (Ris-low n=7), 0.5 μg/kg (Ris-med, n=7) or 5.0 μg/kg (Ris-high, n=7); or Alendronate (Aln) at a dose of 0.1 μg/kg per day (Aln-low n=7), 1.0 μg/kg (Aln-med, n=7) or 10.0 μg/kg (Aln-high, n=7). After 7 days, the rats were loaded to a 10% stiffness loss. Bisphosphonate administration was continued for 10 days following loading, at which time the rats were sacrificed.

Results: There was no difference between the number of apoptotic osteocytes in the CNT group compared to the Non-Mdx area (Figure 4). At lower doses, bisphosphonates were less effective at preventing apoptosis: there were significantly more apoptotic osteocytes in the damaged cortex than in the non-damaged cortex.