The Effect of Rapamycin and Metformin Treatment on Primary OA Pathology

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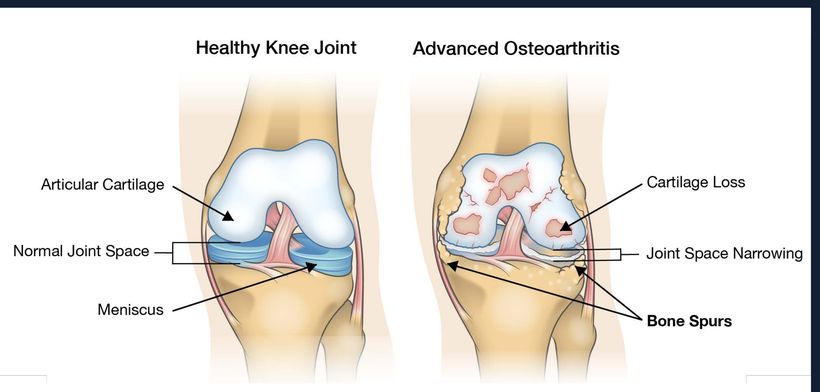
INTRODUCTION

Osteoarthritis (OA), characterized by articular cartilage loss and thickening of subchondral bone, affects 27 million Americans[1] and is a frequent cause of pain and disability among older adults. The metabolic pathway Mammalian Target of Rapamycin (mTOR) is upregulated and AMP-Activated Protein Kinase (AMPK) is downregulated in OA and play a causal role in disease progression[2]. The drug rapamycin can inhibit mTOR and metformin can stimulate AMPK and have been shown to be protective against secondary (injury-induced) OA in young mice[3,4]. However, there are distinct differences in mouse and human joint anatomy that limit limit these findings to aging adults. Therefore there is a need to **determine if rapamycin and/or metformin can delay the onset of primary (age-related) OA, the type of OA most seen in humans.**

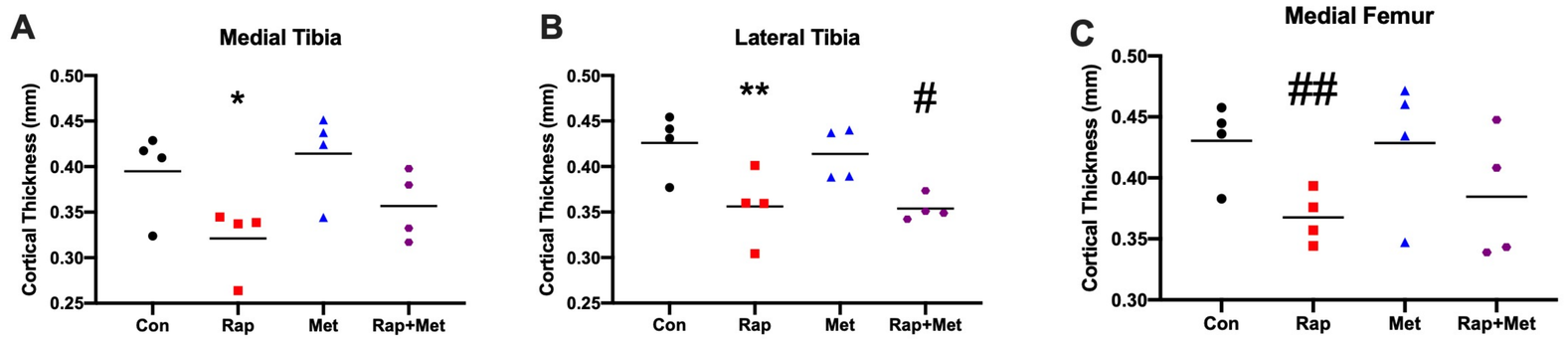


AIM

The goal of our research study was to test if rapamycin and metformin could delay the onset or slow the progression of primary, age-related OA in the Dunkin-Hartley guinea pig.

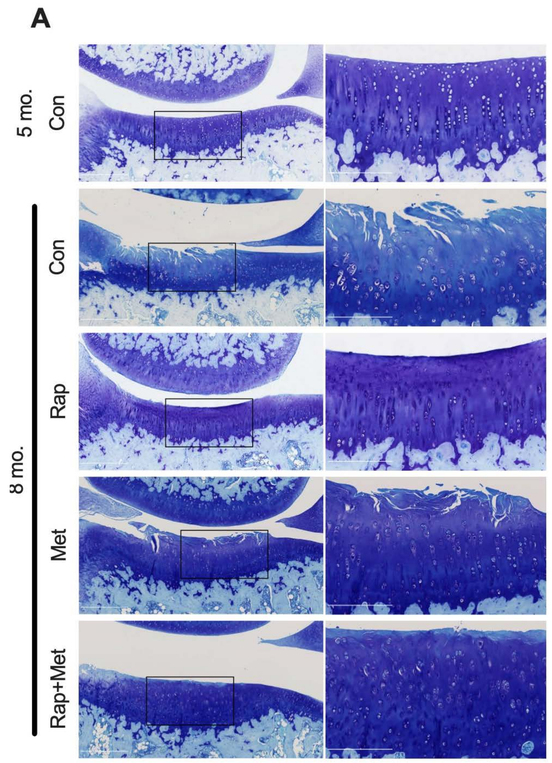
METHODS

Beginning at 5 months of age, guinea pigs were randomized to a control diet or diets enriched with rapamycin (14ppm), metformin (1000ppm), or rapamycin + metformin for 3 months. Upon sacrifice, right hind limbs were collected for analysis and measured for cortical bone thickness as the knee joint and histological samples were given OA scores using the OARSI guideline.

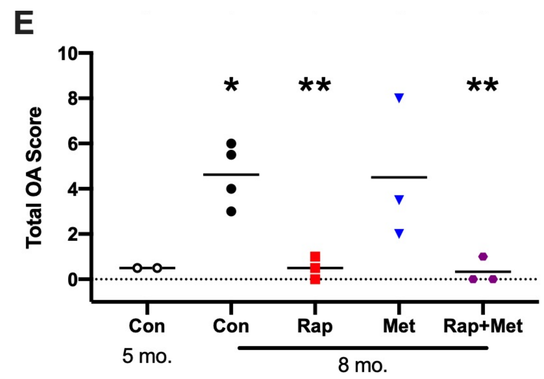


Rapamycin treatment significantly reduced cortical thickness in the tibia and medial femur.

HISTOLOGICAL SAMPLES FOR OA SCORING



OA SCORES



Rapamycin and rapamycin + metformin treatments completely prevent the progression of OA in articular cartilage, shown by the lowest OA scores at the end of treatment.

CONCLUSION

These findings reveal the role of mTOR and AMPK on primary, age-related OA in a model with high potential for clinical translation. These data suggest rapamycin and metformin may be beneficial to treat degenerative cartilage and provide novel insight that rapamycin, or analogs of rapamycin, may be beneficial in humans with age-related osteoarthritis.

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