Conclusions: Our findings show that (a) Wnt/β-catenin signaling acts anti-catabolic in human articular chondrocytes and especially inhibits NF-xB-mediated catabolic events, whereas Wnt/β-catenin signaling in mouse articular chondrocytes stimulates catabolic events, and that (b) AnxA6 via stimulating NF-κB activity and inhibiting Wnt/β-catenin signaling plays a major role in human cartilage degradation during OA pathology. Our findings suggest that targeting AnxA6 function, especially its modulatory function of the NF-κB and Wnt/β-catenin signaling pathways may be a more effective way to control these signaling pathways and their interactions during OA pathology than targeting these individual pathways directly.

428 CONTRAST-BASED MICRO-CT ANALYSIS OF MMP INHIBITOR EFFICACY IN A RAT OSTEOARTHRITIS MODEL
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Purpose: Osteoarthritis (OA) is the most common degenerative joint disease in humans and there are currently no clinically viable disease modifying osteoarthritis drugs (DMOADs). Previous studies have tested matrix metalloproteinase inhibitors (MMPis) in different animal models and demonstrated efficacy. In these studies, histopathology analysis has been used as the traditional method to evaluate efficacy of MMPis. This technique is time consuming, 2D, requires large samples sizes and semi–quantitative. Equilibrium Partitioning of an Ionic Contrast Agent based micro-CT (EPIC-μCT) imaging can be used to nondestructively quantify changes in articular cartilage but has not previously been applied to evaluate the efficacy of DMOADs. Objective: Evaluate the efficacy of a broad spectrum MMPi (ABT-518 from Abbott Laboratories, Abbott Park, IL) in the rat medial meniscal tear (MMT) model using EPIC-μCT based quantitative parameters. Hypothesis: EPIC-μCT provides a sensitive method to detect therapeutic effects of MMP inhibition in a rat OA model.

Methods: Animal model: Weight matched male Lewis rats (275-300g) were separated in three groups: Sham surgery, MMT+MMPi (30 mg/kg orally twice a day for 21 days) and MMT+ vehicle (n=14-15). All surgeries were performed at Abbott Laboratories and approved by the IACUC. μ-CT Imaging: Joints were dissected and scanned following equilibration in Hexabrix contrast agent. Images were evaluated for 3 volumes of interest (VOIs); (1) Only osteophytes (2) Medial 1/3 region of medial tibial plateau cartilage (3) Only focal cartilage lesions (detect > 50% of cartilage thickness) on the medial plateau. Statistics: Data are shown as means ± SEM and analyzed via t-test or one-way ANOVA (GraphPad Prism5 Software)

Results: Osteophyte: Representative coronal grayscale CT images show osteophytes in the vehicle MMT group compared to the MMPi treated and sham group (Fig 1).

Figure 1. Delineation of osteophyte (OP) and representative images from experimental groups. Quantitative EPIC-μCT showed significantly higher total peripheral volume, mineralized peripheral volume, cartilaginous peripheral volume and average 3D peripheral thickness in the vehicle MMT group compared to MMPi treated group (Fig 2). No evidence of osteophytes was observed in the sham animals. Cartilage: Representative images show delineation of the medial 1/3 tibial plateau from the medial tibial plateau and illustration of lesion vs. erosion sites (Fig 3 A, B). Cartilage volume increased at 3 weeks in the vehicle MMT and MMPi treated groups compared to the shams (Fig 3C). Lesion volume was significantly lower in the MMPi group compared to the vehicle MMT group (Fig 3D). The shams showed no lesions on the articular surface.

429 BISPHOSPHONATE USE REDUCES PAIN AND RADIOLOGICAL PROGRESSION IN PATIENTS WITH SYMPTOMATIC AND RADIOGRAPHIC KNEE OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INITIATIVE
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Background: Bisphosphonate use has been studied in patients with OA, with apparent mixed results. Effects on bone have generally been positive: an observational study reported a 90% reduction in odds of having a bone marrow lesion (BML) with the use of alendronate (OR 0.11, p<0.05), whilst risedronate (50mg weekly) prevented an increase in BML size over 24 months although this did not reach statistical significance. Risedronate (15 mg) reduced markers of cartilage
degradation and bone resorption, but did not reduce WOMAC symptoms or joint space narrowing over 2 years. Zoledronic acid reduced knee pain and size of BMI over 6 months. Overall, studies assessed different medications, dosages, endpoints and duration of observation; the longest duration of observation in a clinical trial was 2 years.

**Purpose:** To investigate the effect of bisphosphonate use on symptoms and structural progression of knee OA over four years of observation in participants from the NIH Osteoarthritis Initiative

**Methods:** OAI participants with typical knee OA trial entry criteria (KL2/3, minimum joint space width (mJSW) 2.5-5.0mm and pain >4 on a numerical rating scale [NRS]) were classified as bisphosphonate users (≥3 of the 5 years; n=55) or non-users (no use in the preceding 5 years or during follow-up; n=268). Outcomes were pain (NRS, WOMAC), WOMAC disability and stiffness, joint space narrowing (JSN), proportion reporting radiological and radioclinical progression, and joint replacement. Annual data over 4 years were analysed using linear mixed modelling and generalised estimating equations, after adjustment for age, BMI, and baseline pain where appropriate.

**Results:** Study patients were older women with knee OA, mean age 61±8.4 years (range 45-79), mean BMI 31.4±5.5 (range 18.8 - 48.7). Bisphosphonate users were older, shorter, thinner, less physically active, and more likely to be white than non-users. Bisphosphonate compliance was 85% at year 1, reducing to 76% by year 4. Alendronate was the most common bisphosphonate used (60-70%). NRS pain scores were significantly reduced among bisphosphonate users at years 2 and 3 (Year 3, 0.9 vs -2.2, p=0.004), though not year 4, after adjustment for baseline pain and analgesic use. Differences in WOMAC pain and disability scores did not reach statistical significance at any time point. The trend to less JSN in bisphosphonate users over time (Year 4, 0.51mm vs 0.29mm; p=0.06). Radiological progression (≥0.5 mm) was reduced at year 3 (82% vs 11%, p=0.041). Differences in rates of knee replacement were not significant.

**Conclusions:** We demonstrate reduction in pain intensity (NRS), radiological progression and a trend to less JSN in bisphosphonate users compared to non-users. Significant reduction in NRS pain was observed in the first 3 years; diminution of effects by year 4 may reflect reduced compliance, suggesting beneficial effects may discontinue following medication cessation. Differences in results obtained using NRS and WOMAC may reflect different constructs measured by these tools. The beneficial trend on structural progression should be considered in terms of the sample size.

430 QUANTITATIVE 3D ANALYSIS OF CARTILAGE LESIONS AND OSTEO PHYTES IN A RAT OA MODEL USING CONTRAST BASED MICRO-CT IMAGING IN COMPARISON WITH HISTOPATHOLOGY

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**Purpose:** Development and characterization of small animal models of osteoarthritis (OA) is an important for a better understanding of OA pathogenesis and to evaluate disease modifying OA drugs (DMOADs). A common surgical method of inducing OA involves transecting the medial meniscus (MMT). The traditional method to detect changes in articular cartilage is via histopathology which is a time consuming and semi-quantitative process. Equilibrium Partitioning of an Ionic Contrast Agent based micro-CT (EPIC-μCT) imaging has recently been developed to characterize and quantify changes in the articular cartilage. **Objective:** Quantify articular cartilage changes as a function of time following MMT surgery and compare results with independent histopathology data. **Hypothesis:** EPIC-μCT has the sensitivity to detect and quantify cartilage damage and osteophyte development.

**Methods:** Animal model: Weight-matched male Lewis rats (275-300g) underwent MMT on the right leg (n=18) or sham surgery (n=18) and were imaged at 1, 2 and 3 weeks. μ-CT Imaging: Joints were dissected and scanned using a μCT 40 following equilibration in Hexabrix contrast agent. Images were evaluated for 3 volumes of interest (VOIs): (1) Medial 1/3 of medial tibial plateau (2) Only focal lesions on the medial plateau (3) Only osteophytes (width > 200μm). Cartilage attenuation, a quantitative metric inversely related to proteoglycan content was also established. Focal lesions were defined as: erosions (width > 50% thickness) or lesions (width > 50% of thickness) (Fig 1) (All surgeries were performed at Abbott Laboratories and approved by IACUC).

**Results:** Cartilage attenuation following MMT was significantly higher at week 2 and 3 compared to controls indicating lower proteoglycan content (Fig 2). Similarly, histopathology scoring showed a higher cartilage degradation score at week 2 and 3 compared to day 3 (Fig 2). Lesions were detected and quantified in the MMT animals at week 2 and 3 with the maximum lesion volume being observed in the MMT animals at week 3 (Fig 2). Areas of erosion were evident one week post surgery; however lesions did not begin to develop until week 2. There was a significant increase in the number and volume of lesions between weeks 2 and 3. Osteophyte: Average peripheral thickness increased with time, consistent with 2D histopathology data (Fig 3). Total peripheral volume, mineralized peripheral volume and average 3D peripheral thickness were greater for MMT animals compared to controls at weeks 2 and 3 (Fig 3). Representative images show osteophytes both in histology and micro-CT (Fig 3).

**Conclusions:** This study successfully demonstrates that progression of joint degeneration can be detected by EPIC-μCT over the period of 3 weeks in the MMT model. Additionally, this is the first instance of quantification of osteophyte development and mineralization in the MMT model. Differences in osteophyte thickness and volume were detected as early as 2 weeks via EPIC-μCT which could not be identified via histology. At 3 weeks, EPIC-μCT data replicated 2D histopathology data with the advantage of providing more detailed and quantitative data while requiring fewer animals.