anterior part of the cartilage, the percentage of MMP-13-positive cells in the posterior part of the cartilage was significantly higher for the ACL-T/Ex group than for the CAJM/Ex group (p=0.02) (Fig. 3C).

Conclusions: Previous studies reported that exercise alone could delay the progress of OA. However, our present Results indicate that the internal environment of the joint strongly modulates the effect of exercise, sometimes completely canceling the benefit. In other words, when prescribing exercise, we need to consider the internal environment of the knee joint.In the clinical setting, these findings may translate in the need to consider an intervention to correct abnormal joint movement before prescribing physical exercise in the treatment of OA.

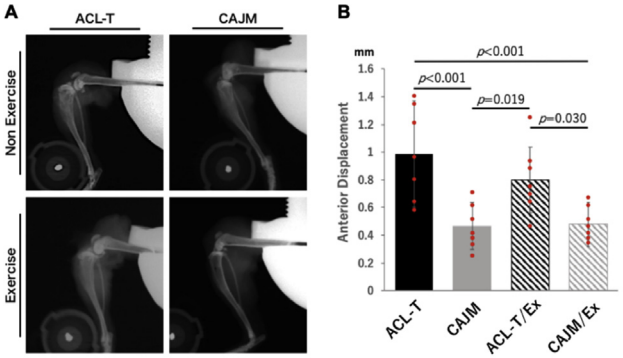

Figure 1. (**A**) Representative soft X-ray radiograph taken during the anterior drawer test on the right knee joint of a mouse that had undergone surgical induction of knee OA followed by exercise intervention. (**B**) Tibial anterior displacement on the anterior drawer test. tibial anterior displacement was significantly smaller in the CAJM and CAJM/Ex groups than in the ACL-T and ACL-T/Ex groups.

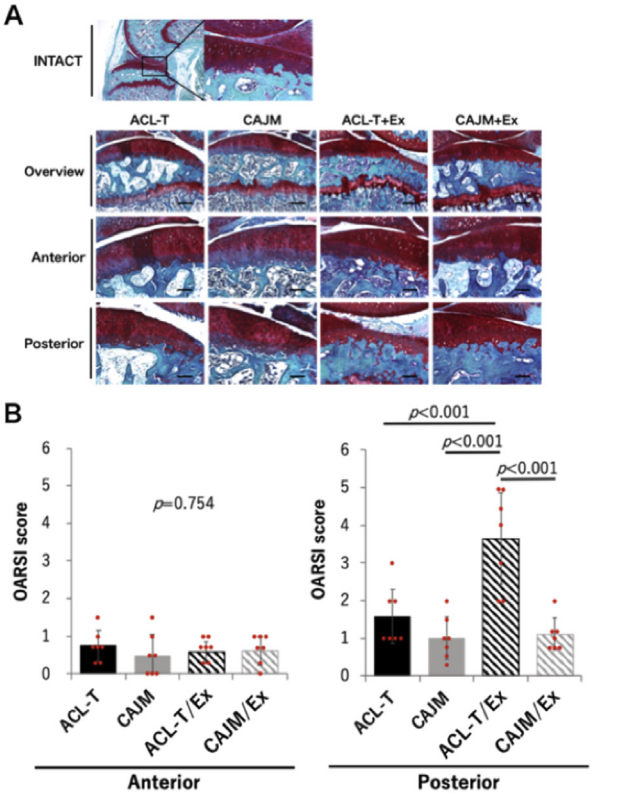

Figure 2. (**A**) Results of safranin-O/fast green staining. (**B**) OARSI scores. There was no difference among the four groups regarding the OARSI scores in the anterior part of the joint. The OARSI scores in the posterior part were significantly higher for the ACL-T/Ex group.

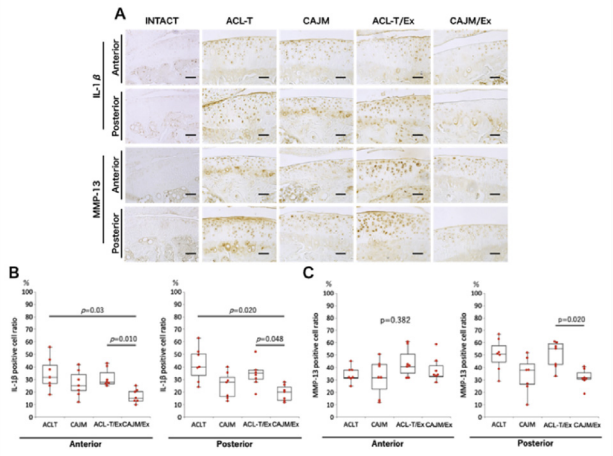

Figure 3. (**A**) Representative immunohistochemical stains for il-1β and MMP-13. (**B**) Percentage of il-1β-positive cells. The percentage of il-1β- positive cells was lower in the CAJM/Ex group than in the ACL-T and ACL-T/Ex groups. (C) Percentage of MMP-13-positive cells. The percentage of positive cells in the posterior part of the joint was lower in the CAJM/ex group than in the ACL-T/Ex group.

706
AN OLEUROPEIN-BASED DIETARY SUPPLEMENT IMPROVES JOINT FUNCTIONALITY IN OLDER PEOPLE WITH HIGH KNEE JOINT PAIN

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Purpose: The aim of this study was to investigate the effects of a 6-month intervention with an Olive Leaf Extract (OLE) standardized for oleuropein content on knee functionality and biomarkers of bone/cartilage metabolism and inflammation.

Methods: The study was a randomized, double-blind, placebo-controlled, multi-centric trial of 124 subjects with mild knee pain or mobility issues. Subjects were randomized equally to receive twice a day one capsule of either maltodextrin (control treatment, CT) or 125-mg OLE (Bonolive^{TM}, an Olive Leaf Extract containing 50 mg of Oleuropein) for 6 months. The co-primary endpoints were Knee injury and Osteoarthritis Outcome Score (KOOS) using a self-administered questionnaire and serum Coll2-1NO2 specific biomarker of cartilage degradation. The secondary endpoints were each of the five sub-scales of the KOOS questionnaire, Knee pain VAS score at rest and at walking, OARSI core set of performance-based tests and serum biomarkers (Coll2-1, MPO, CTX1, osteocalcin, PGE_2 and Vplex cytokines assay in serum) and concentration of Oleuropein's metabolites in urine.

Results: Primary (global KOOS score, biomarker Coll2-1 NO2) and secondary endpoints (the five subscales of the KOOS score) improved time dependently in both groups. OLE treatment showed significantly elevated urinary oleuropein metabolites (oleuropein aglycone, hydroxytyrosol, homovanillyl alcohol and isomer of homovanillyl alcohol), and was well tolerated without significant differences in number of subjects with adverse events. At 6 months, OLE group showed a higher global KOOS score compared to placebo (treatment difference = 3.73; 95% CI = [-4.08;11.54]; p = 0.34), without significant changes of inflammatory and cartilage remodeling biomarkers. Subgroup analyses demonstrated a large and significant treatment effect of OLE in subjects with high walking pain at baseline (14.4; 95% CI = [1.19;27.63], p=0.03). This was observed at 6 months for the global KOOS score and each different subscale and for pain at walking (-23.07;95% CI = [-41.8; -4.2]; p=0.02). These treatment effects at 6 months were significant for KOOS score as well as for the subscales Pain and QoL and the pain at walking.

Conclusions: OLE was not effective on joint discomfort in people with low to moderate pain at baseline but significantly benefited subjects with high pain at treatment initiation. As oleuropein is well-tolerated, OLE can be used to relieve knee joint pain and enhance mobility in subjects with articular pain the most painful subjects.