mechanics beyond what can be detected with KAM variables. This observation was further confirmed by the absence of correlation between muscle and KAM changes. In general, LH and VL activities decreased with LW, suggesting lesser constraints on knee tissues and a possible protective effect of LW against OA. Consequently, these results did not support the hypothesis that LW systematically induce counterproductive muscle changes. However the individual responses to the LW, highlighted by the absence of correlation between muscle and KAM variables, suggested that LW could be appropriated for some patients (positive KAM and muscle responders) and not for others. This inference particularly agrees with the experiment as one outlier subject reported similar KAM reduction to the other participants, but much stronger muscle adaptations. This concept of individual kinetics and muscle response to the LW could actually contribute to explain the absence of consistent improvements reported in prior LW clinical trials, even when KAM changes were taken into account in the analyses. Further research with OA patients and longer follow-up is necessary to understand the overall muscle, kinetic and kinematic changes induced by LW and possibly identify particular patient profiles that could benefit from this simple intervention.

Table 1. Relative differences for the LW condition compared to the neutral footwear condition alone (reported as: median [interquartile range]), and correlations between relative EMG and KAM differences (*: p< 0.05 and **: p< 0.01).

		Relative differences, %	Correlation coefficient
Muscle	VL	**-19.3 [30.2]** *	-0.54
	RF	5.0 [57.3]	0.71
	VM	-14.6 [40.8]	-0.07
	LH	**-19.8 [14.4]** *	-0.32
	MH	-8.5 [9.7]	-0.36
	LG	-16.5 [40.7]	-0.04
	MG	-12.9 [9.7]	-0.14
Kinetics	KAM	**-7.6 [5.6]** **	n/a

144

EFFECT OF AGGRECANASE AND COLLAGENASE RESISTANT KNOCK-IN, AGE AND JOINT-OVERUSE ON MURINE CARTILAGE

M. Azadi †, H.T. Nia ‡, S.J. Gauci §, F. Rogerson §, C. Ortiz †, A.J. Fosang §, A.J. Grodzinsky †. † *MIT, Cambridge, MA, USA;* ‡ *Harvard Univ., Cambridge, MA, USA;* § *Univ. of Melbourne, Melborne, Australia*

Purpose: Aggrecan loss, collagen fatigue and proteolytic degradation in cartilage precede clinical symptoms of osteoarthritis (OA). Detection at the early stages of degeneration associated with age or joint overuse (excessive running) is import for understanding the molecular mechanisms of disease progression and potential therapeutic interventions. This study utilized murine models and aimed to detect and quantify the effects of age and running on the frequency-dependent rheological properties of knee cartilage. Genetically modified (GM) mice having mutations of substrate cleavage sites of aggrecan and collagen II resulting in aggrecanase resistant (Jaffa) and collagenase resistant (Baily-Het) were used. The effects of animal age and joint overuse on cartilage morphology, low and high frequency stiffness and energy dissipation were measured in knee cartilage of knock in and wild-type control mice.

Methods: 84 knee joints (20 GM mice and 16 Wildtype mice) were harvested at 3 age groups: 100, 160 or 220 days old. Half the mice were put on running wheels daily from 6 weeks of age when they were skeletally mature. As a result, the population used in this study was relatively young, and those who ran on wheels ran long distances (up to 2,000 km). Mice not subjected to running wheels were used as controls for statistical analysis in detecting the effect of exercise, and wildtype mice were the control for GM mice at the three ages tested. Three in-vitro assessment methods were used: 1-Histological scoring on right knee, 2-Micromechanics (on left femoral condyles) using force-displacement atomic force microscopy (AFM), and 3-Nanodynamics (on left femoral condyles) using our novel high-bandwidth AFM rheology system. This newly-developed AFM protocol is described by the authors in a recent report published in the Journal of Biomechanics. General linear mixed effect models with post-hoc tests were used to test statistical significance ($p < 0.05$).

Results: Effects of wildtype age on biomechanical properties: Micromechanical and the nanodynamical measurements on non-running wildtypes detected softening with increasing age; nanodynamical methods also detected loss of tissue self-stiffening with age (i.e., the ratio of high-to-low frequency modulus, Fig 2a) pertinent to running and impact-injury. Effects of running on same genotype mice: No statistical differences were observed between non-running (all three GM mice) and their corresponding non-running wildtype controls. Running did not result in any significant changes in the micromechanical or nanodynamical properties of 100-day wildtype Bailey-Het within each age group. However, excessive running caused significant softening at high loading rates (decreased high frequency stiffness) of 160-day Jaffa (Fig 2b) and Baily-Het mice. Effects of running (wildtype as control): No significant differences in any measurements were detected between non-running Bailey-Het mice compared to their corresponding wildtypes. However, knee cartilages of Jaffa running mice were significantly stiffer than wildtypes at higher loading rates (~1kHz) and had correspondingly lower hydraulic permeability (Fig 2c). Thus, Jaffa showed better protection against high loading rate activities. Histological scoring did not show any significant changes in these knee cartilages.

Conclusions: When GM joints were not loaded excessively by running, their assessment outcomes were similar to those of wildtype controls. When loaded by running, however, protection against degradation caused by high loading rates was found only for the older Bailey-Het and Jaffa mice. As degradation of Collagen II generally softens the tissue at low rates and loss of aggrecan causes cartilage softening, particularly at high frequency loading, these results suggest that the AFM nanodynamical assessment can reveal early changes in cartilage mechanical properties associated with long-term joint use (age and over-use) and the effects changes in ECM due to genetic modification on joint function.

These results suggest that excessive running can cause substantial changes in fluid-solid interactions and even the possibility of aggrecan loss even in aggrecanase-resistant mice. Thus, age as well as the intensity of running appears to have a profound influence on the ECM even on relatively young mice.

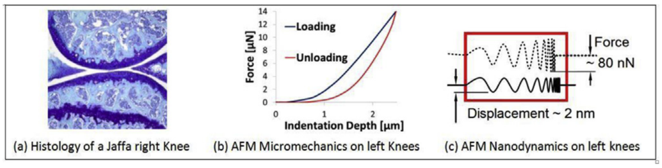

Figure 1. (a) Representative histological image of aggrecanase resistant (Jaffa) joint morphology; (b) AFM micro-indentation measurement utilizing 2-3 μm approach-retract displacements (force-displacement tests) analyzed via the Hertz model; (c) AFM-based wide bandwidth nanodynamic assessment utilizing 2nm displacement amplitudes applied in the 1Hz to 10 kHz frequency range, to measure the equilibrium and high frequency stiffness, energy dissipation, and to compute hydraulic permeability.

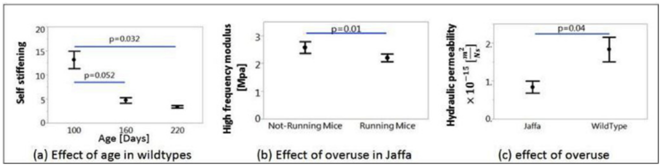

Figure 2. Data are mean ± SE n>3; indentation applied to >5 location on each joint surface.

145

IMPROVED GAIT IN PERSONS WITH KNEE RELATED MOBILITY LIMITATIONS BY A ROSEHIP FOOD SUPPLEMENT (GOOD STUDY): A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

E. Ginnerup-Nielsen, R. Christensen, H. Bliddal, G. Zangger, L. Hansen, M. Henriksen. *The Parker Inst., Copenhagen, Denmark*

Purpose: Knee-related mobility limitation affects a large part of the elderly population and has a profound impact on the affected