Low-Magnitude High-Frequency Vibration Induces Catabolic Changes In Human Intervertebral Disc Independently Of Piezo1

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Disclosures: None.

INTRODUCTION: Intervertebral disc (IVD) degeneration is a leading cause of chronic back pain, affecting millions of people worldwide. The related socioeconomic impact highlights the need to better understand the underlying mechanisms and its potential modulation. Low-magnitude high-frequency vibration (LMHFV) is commonly used in exercise and rehabilitation. However, it has shown conflicting effects on IVD health, ranging from protective effects[1] to catabolic changes.[2–4] This study aimed to investigate the role of LMHFV on human IVD cells and tissues, focusing on the mechanosensitive ion channel Piezo1 as a potential mediator for IVD degeneration.

METHODS: Human IVD cells (1 female/3 male donors, mean age = 43.3 years) and tissues (3 female/1 male donors, mean age = 26 years) were treated with LMHFV, Yoda1 (a selective Piezo1 activator), or both. Gene expression was analyzed after 2 days in cell cultures, targeting markers of senescence (*CDKN1A*, *CDKN2A*), inflammation (*PTGS2*, *IL6*, *IL8*), and matrix remodeling (*MMP3*, *MMP13*, *COL1A1*, *COL2A1*). IVD tissues were cultured for 21 days and analyzed for functional and structural changes. Annulus fibrosus (AF) and endplate (EP) stiffness were measured via spatial indentation testing, while AF tensile modulus was assessed by pull-to-failure tests. Collagen and glycosaminoglycan (GAG) content were evaluated by histology and biochemical assays. Statistical analysis: Kruskal-Wallis test.

RESULTS SECTION: LMHFV and Yoda1, whether applied separately or together, significantly increased *CDKN1A* expression compared to controls ($p<0.05$), while *CDKN2A* remained unchanged. Yoda1 did not affect inflammatory markers (*PTGS2*, *IL6*, *IL8*) but downregulated *MMP3*, *COL1A1*, and *COL2A1* ($p<0.05$, Fig. 1), and increased AF stiffness ($p<0.05$, Fig. 2A). LMHFV significantly upregulated inflammatory markers ($p<0.05$, Fig. 1A). It showed similar trends for matrix-degrading enzymes and collagen genes (Fig. 1B–C) and reduced EP stiffness ($p<0.05$, Fig. 2A). Combined LMHFV+Yoda1 treatment decreased EP stiffness compared to Yoda1 alone ($p<0.05$, Fig. 2A). No significant differences were observed in AF tensile modulus or in collagen and GAG content across groups (Fig. 2B–D).

DISCUSSION: LMHFV induced catabolic effects in human IVD tissues, including increased inflammation, matrix remodeling, and mechanical weakening, which are hallmarks of IVD degeneration. Piezo1 activation through Yoda1 treatment contributed to senescence and matrix regulation but did not reproduce the full degenerative effects of LMHFV. The combined treatment of LMHFV + Yoda1 upregulated *IL6* expression, indicating that LMHFV and Piezo1 activation with Yoda1 may have a cumulative degenerative effect. Overall, the results align with recent reports identifying Piezo1 as a stress-responsive channel in IVD degeneration.[5,6] Although the data support a catabolic role of LMHFV in IVD degeneration, the findings demonstrated that its effect occur, at least in part, independently of Piezo1 activation, while further suggesting that additional mechanotransduction pathways are involved. This highlights the importance of understanding mechanosensitive signaling in the improving targeted IVD therapy.

CLINICAL RELEVANCE: The presented findings indicate that targeting Piezo1 alone may be insufficient for treating IVD degeneration, further highlighting the need to identify additional mechanotransduction pathways for multi-targeted therapies.

REFERENCES: 1. Holguin et al., 2009; 2. McCann et al., 2015; 3. McCann et al., 2017; 4. Widmayer et al., 2023; 5. Wu et al., 2022; 6. Liu et al., 2023.

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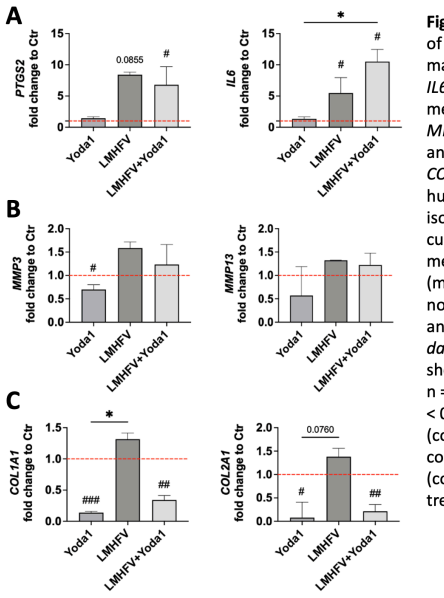

Fig. 1: Gene expression of **(A)** inflammatory markers *PTGS2* and *IL6*, **(B)** matrix metalloproteinases *MMP3* and *MMP13*, and **(C)** collagens *COL1A1* and *COL2A1* in human IVD cells. RNA isolated after 2 days of culture. Levels of messenger RNA (mRNA) were normalized to *GAPDH* and to the control (= 1, *dashed line*) and are shown as $2^{-\Delta\Delta CT}$. n = 3–4. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ (comparison to control); * $p < 0.05$ (comparison between treatment groups).

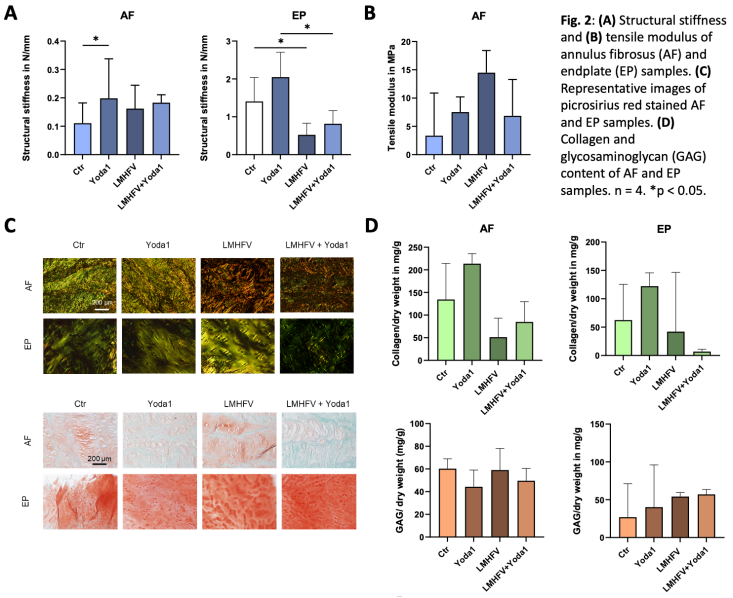

Fig. 2: **(A)** Structural stiffness and **(B)** tensile modulus of annulus fibrosus (AF) and endplate (EP) samples. **(C)** Representative images of picrosirius red stained AF and EP samples. **(D)** Collagen and glycosaminoglycan (GAG) content of AF and EP samples. n = 4. *p < 0.05.