

IMPACT OF A RAGE ANTAGONIST ON TENDON BIOMECHANICAL PROPERTIES IN A MOUSE MODEL OF TYPE 2 DIABETES

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INTRODUCTION: Disruption of tendon extracellular matrix homeostasis and altered biomechanical properties pose significant clinical challenges for millions of people with diabetes. Adding to the problem, controlling blood glucose levels does not restore tendon properties in those with diabetes. Advanced glycation end-products (AGEs) accumulate in the serum of people with diabetes through hyperglycemia, consumption of AGE-rich foods, and decreased kidney clearance of AGEs. In cell culture, we have demonstrated that AGEs alter pathways associated with extracellular matrix regulation, cell survival, and connective growth and adaptation. We hypothesize that serum AGEs and RAGE activation are mechanisms underlying impaired tendon properties in diabetes. We determined the effect of RAGE inhibition on tendon biomechanical properties in a translational mouse model of type 2 diabetes.

METHODS: The Purdue University Animal Care and Use Committee approved this study (Protocol #: 1905001903). Thirty-four db/db mice, a mouse model of type 2 diabetes with naturally elevated serum AGEs and impaired tendon function, were treated daily with a RAGE antagonist [Azelniragon (AZ), n=9 male, n=5 female] at 4mg/kg body weight or vehicle [DMSO (n=15 male, 5 female)] for three weeks. Upon completion of the experiment, mice were euthanized after inhaling CO₂. The patellar tendon of one limb was extracted and tested for biomechanical properties. Structural and material properties were calculated from the ramp-to-failure. Stiffness and modulus were calculated from the linear portion of the load-displacement and stress-strain curves, respectively. A one-way ANOVA was utilized to compare groups. A multiple comparison assessment was utilized to assess differences between treatments and sex. An alpha value of 0.05 was selected to determine statistical significance, while Sidak's method was utilized to adjust p-values for pairwise comparisons. Biomechanical testing was completed at the Penn Center for Musculoskeletal Disorders Biomechanics Core under the supervision of Dr. Dymant.

RESULTS: All data are expressed as mean ± SE. Patellar tendon stiffness and modulus were greater (p<0.05) in male mice receiving AZ (stiffness: 14.2±1.3 N/mm, modulus: 163.9±23.1 MPa) compared to vehicle (stiffness: 8.7±1.2 N/mm, modulus: 99.6±13.2 MPa). Patellar tendon max load was not different in male mice receiving AZ (6.2±0.6 N) compared to vehicle (5.4±0.4 N). Patellar tendon stiffness and modulus were not different in female mice receiving AZ (stiffness: 11.9±2.2 N/mm, modulus: 124.6±24.5MPa) compared to vehicle (stiffness: 13.9±1.4 N/mm, modulus: 191.1±13.17). Patellar tendon max load was lower (P<0.05) in female mice receiving AZ (4.8±1.3 N) compared to vehicle (7.8±0.7 N).

DISCUSSION: This study demonstrated that RAGE antagonism increased tendon stiffness and modulus in male mice, while no significant effects were observed in females. Interestingly, RAGE antagonism led to a reduction in maximum load in female mice, an effect not seen in their male counterparts. Our results suggest sex-based differences exist that limit the impact of RAGE antagonism. Our findings also suggest that RAGE at least partially mediates the impact of diabetes on tendon functional outcomes in a state of diabetes. RAGE is a multi-ligand receptor; thus, further work is needed to delineate how RAGE is activated in mice with diabetes. Our preliminary results provide a foundation for detailed mechanistic investigations and the development of therapeutic strategies to prevent tendon complications in people with diabetes through RAGE inhibition.

SIGNIFICANCE/CLINICAL RELEVANCE: These preclinical findings indicate that inhibiting RAGE may offer a promising therapeutic strategy to enhance tendon properties in individuals with diabetes. Although further research is necessary to clarify RAGE's role in tendon regulation, our initial results lay the groundwork for in-depth mechanistic studies and support the development of targeted therapies aimed at preventing tendon-related complications for individuals with diabetes.

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