Title: Focused ultrasound induced fractionation of tendinopathic tendons

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Focused ultrasound (fUS) can produce a bioeffect within the focal volume through thermal or mechanical mechanisms; however, collagenous tissues, like tendons, have proven resistant to mechanical disruption by fUS. Tendinopathies are characterized by a break in the collagen structures, and so may be more susceptible to mechanical disruption or fractionation by fUS. Here, we evaluated whether fUS can be used to fractionate tendinopathic tendons with single- and dual-frequency fUS exposures. *Ex vivo* bovine tendons were injected with collagenase to induce tendinopathy. Dual-frequency exposures used a 1.07-MHz transducer operating at its fundamental or third harmonic in combination with a 1.5-MHz transducer; 10-ms pulses were repeated every second for 60-s. Single-frequency treatments used 1.07-MHz, 1.5-MHz, or 3.68-MHz at 5-10-ms pulses repeated every 1-5-s for 20-minutes. After treatment, tissues were evaluated grossly and histologically. All 3.68/1.5-MHz dual-frequency exposures resulted in tendon fractionation observed grossly and histologically. Mild or no fractionation was observed for 1.07/1.5-MHz exposures. Single-frequency exposures at 3.68-MHz produced a hole histologically for 5-ms pulse lengths repeated at 2-s; no other parameters resulted in gross or histological tissue fractionation. These results suggest that fractionation is possible in tendinopathic tendons, likely due to the weakened collagen structure. [Work supported by NIH RO1EB032860 and Leighton Reiss Fellowship by Center for Biodevices (Wood, 2022-2023)].