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Moderate deformation of cartilage micropellets in a fluidic custom-made device enhances the expression of chondrocyte markers

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Introduction

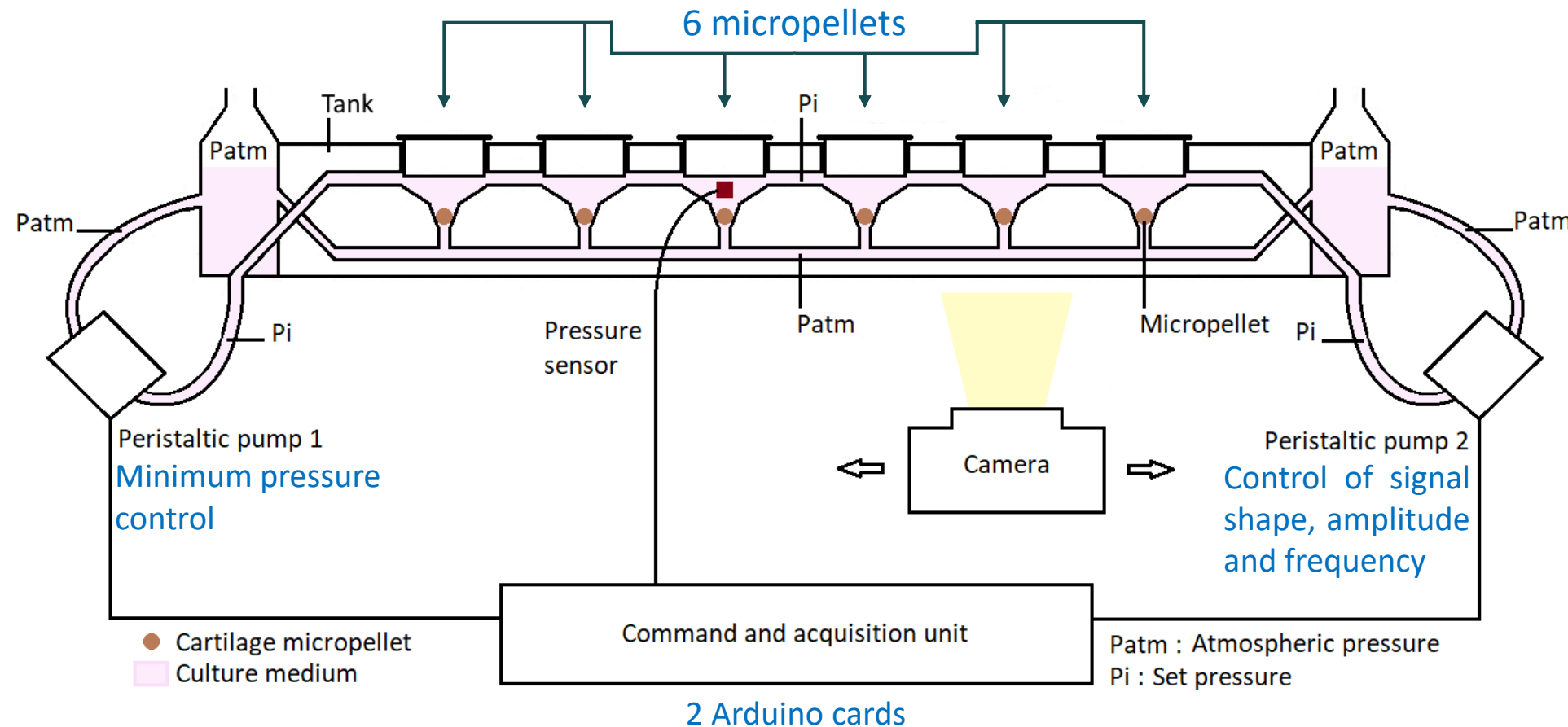
Cartilage engineering approaches are being developed for evaluating the repair of articular cartilage lesions but few of them have reached the clinics. One limitation of current approaches is the lack of mechanical stimulus. Cartilage micropellet is a well-known model of cartilage growth but no study has evaluated the impact of mechanical stimulation on their development by analyzing both their biochemical and biomechanical properties.

Objectives

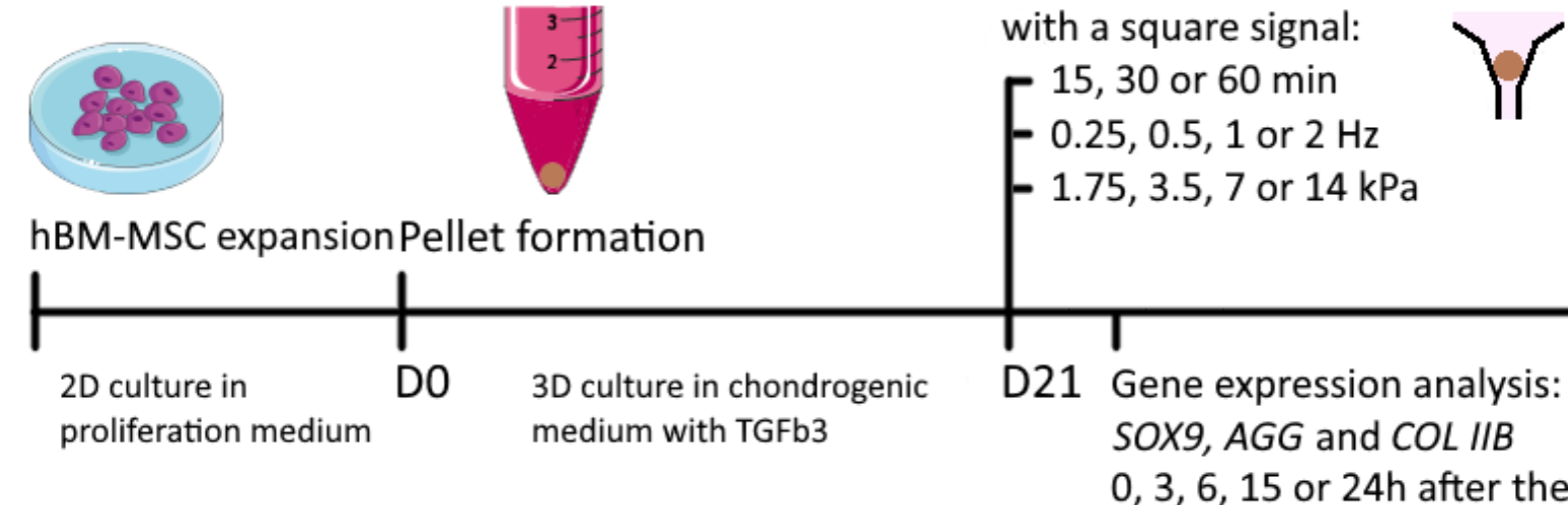
We relied on the use of a **fluidic custom-made device** for **biomechanical stimulation and characterization** of mesenchymal stromal cells (MSCs)-derived **cartilage micropellets**.

Methods

- The fluidic custom-made device:



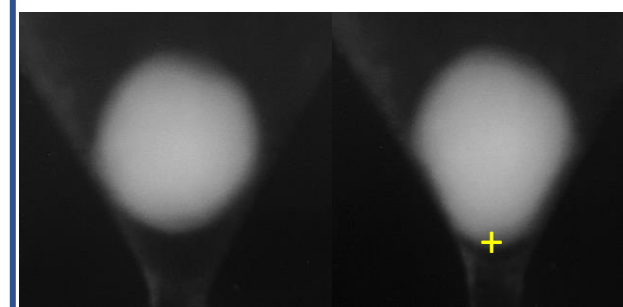
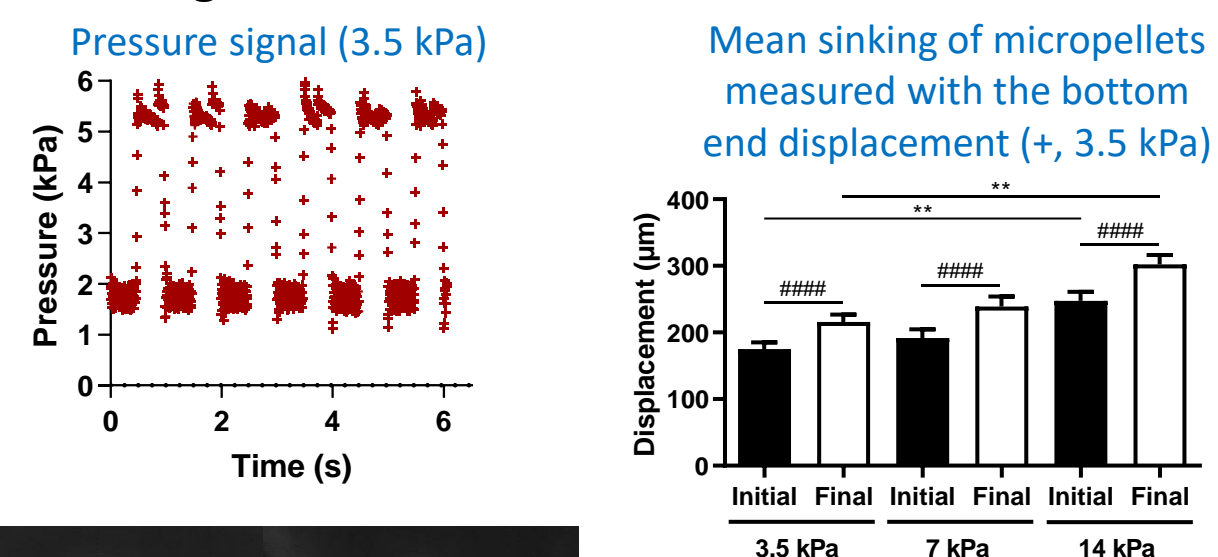
- Biomechanical stimulation:



Results

1/ Moderate and non destructive deformation of cartilage micropellets under biomechanical stimulation

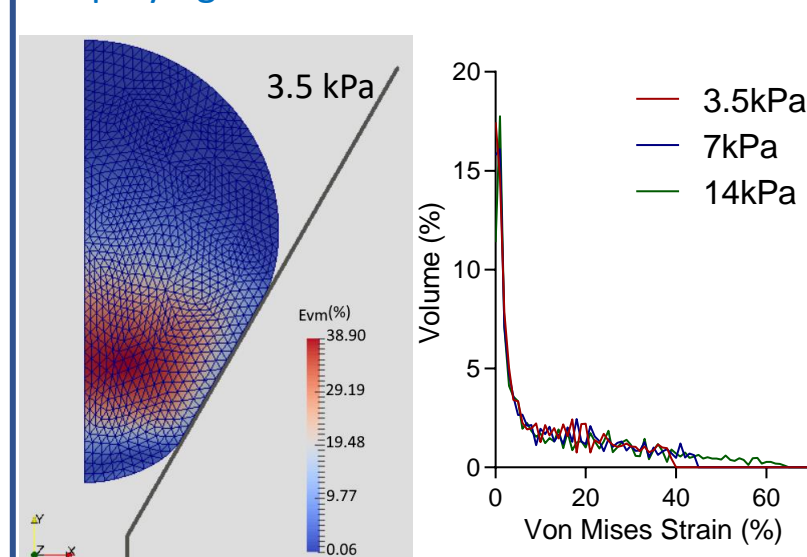
- Sinking of micropellets in their conical wells during biomechanical stimulation:



Micropellet sinking increases with the amplitude of pressure and stimulation time

- Deformation of micropellets in their conical wells during biomechanical stimulation:

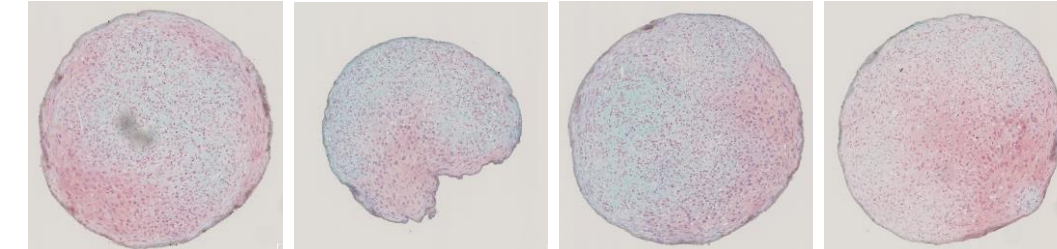
Distribution of Von Mises strain evaluated with a finite element model employing a neo-Hookean law



Von Mises strain can reach 38.90% at 3.5 kPa amplitude of pressure but 80% of the micropellet have strains < 20%

- Micropellet microstructure:

Safranin O staining of proteoglycans after biomechanical stimulation

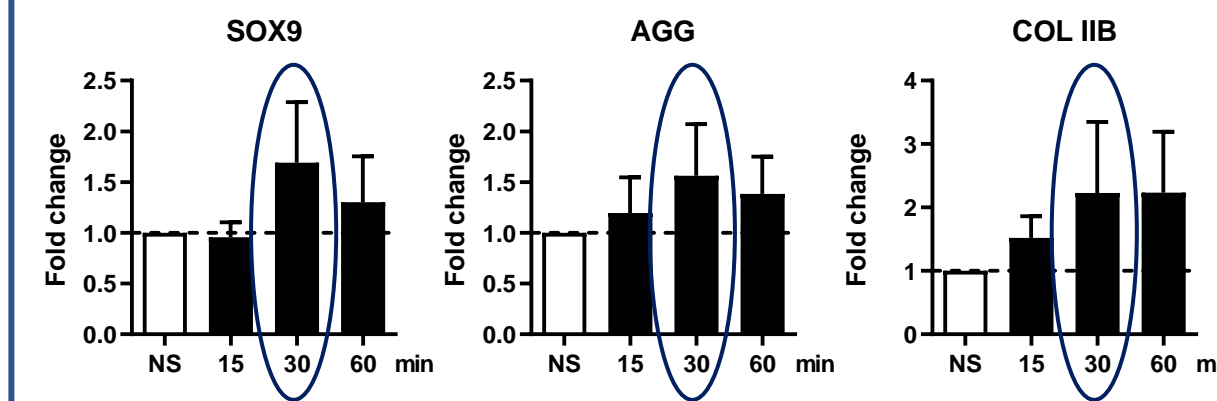


The microstructure of micropellets is not altered

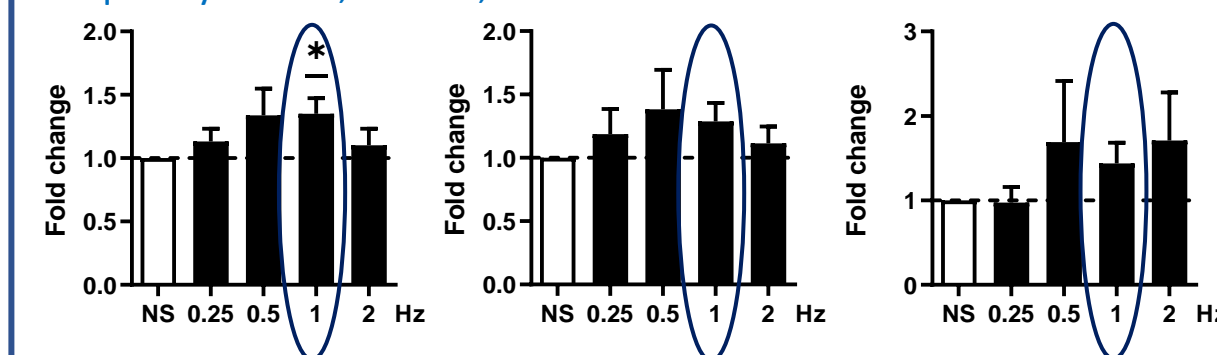
2/ Regulation of chondrocyte gene expression by biomechanical stimulation

- Chondrocyte gene expression 24h after biomechanical stimulation:

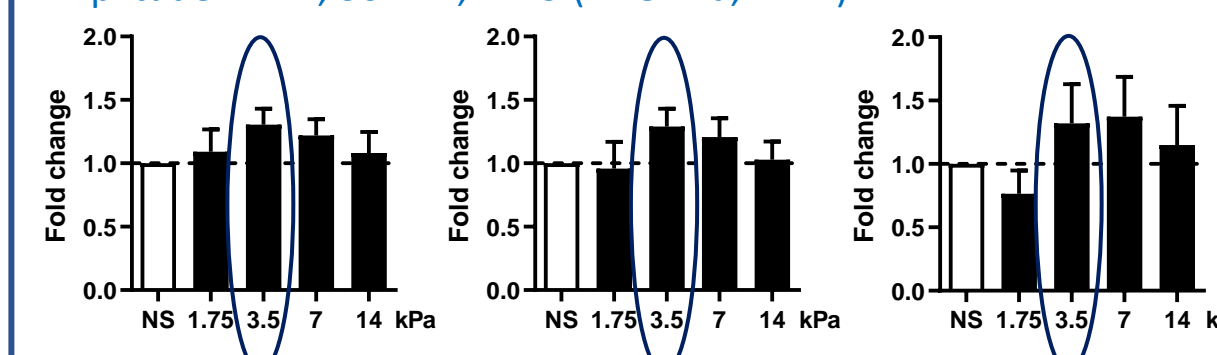
Duration : 7 kPa, 1 Hz, n = 5



Frequency : 7 kPa, 30 min, n = 7

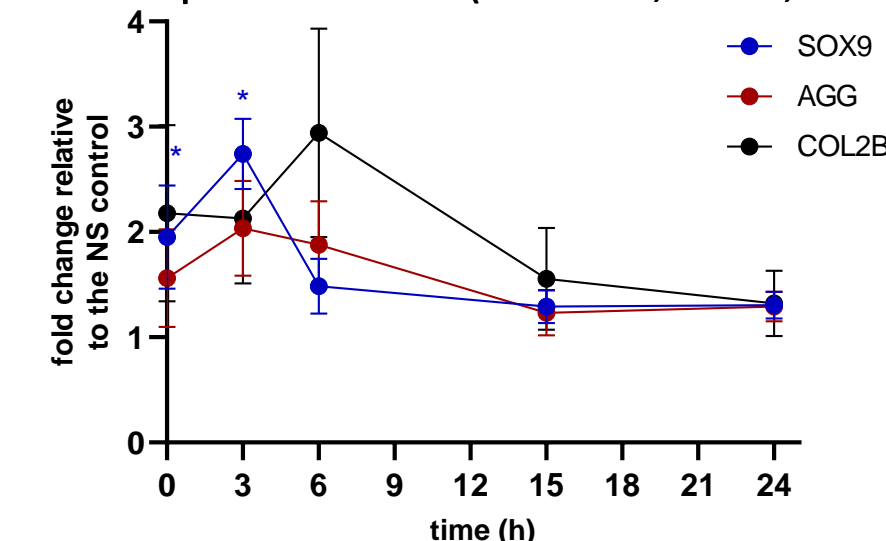


Amplitude : 1 Hz, 30 min, n = 9 (1.75 kPa, n = 4)



Higher expression of SOX9, AGG and COL IIB was measured at 3.5 kPa, 1 Hz, 30 min

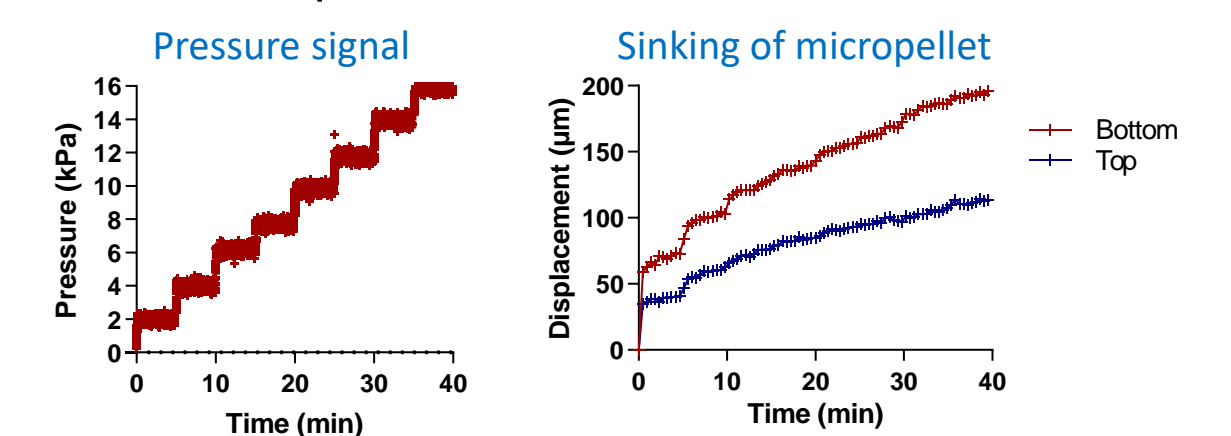
- Time-dependent analysis of gene expression for constant parameters (3.5 kPa, 1 Hz, 30 min):



Gene expression is upregulated at early time points (3h seems the best)

3/ Mechanical characterization of micropellets with the fluidic device

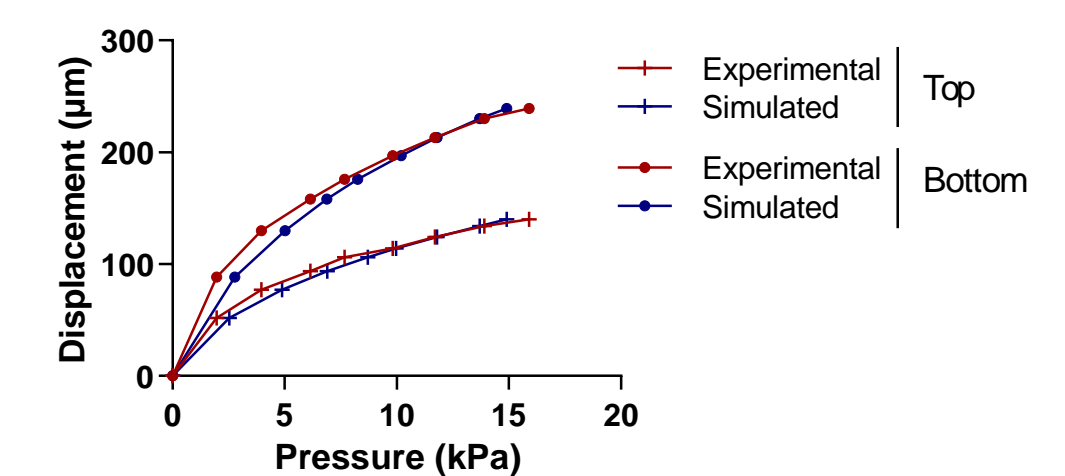
- Multi-creep test at D21:



- Determination of the mechanical properties at equilibrium by inverse analysis:

Experimental curves: Last point of each pressure step and normalization of the displacement with the radius of micropellets

Simulated curves: Estimated pressure from experimental displacements



A Young's modulus of 47.6 ± 26.2 kPa and a Poisson ratio of 0.46 ± 0.02 were obtained at the equilibrium

Conclusions

- The micropellets can be biomechanically stimulated in the fluidic device without being microstructurally altered
- The biomechanical stimulation enhances the expression of chondrocyte genes
- The mechanical properties of cartilage micropellets can be assessed in the device