

## **Tendinopathy Induced by Serial Low-Dose Collagenase Injections: A Novel Experimental Animal Model in the Achilles Tendon of Rabbits.**

**Cesar Cesar Netto, MD, Cesar Augusto Martins Pereira, Alexandre Godoy-Santos, PhD, Francisco D. Oliveira Lima, Pedro A. Pontin, MD, Talal A. Zahoor, MBBS, Eric J. Dein, BS, Lew C. Schon, MD, Olavo P. Camargo, Tulio Fernandes, PhD**

**Category:** Basic Sciences/Biologics

**Keywords:** Tendinopathy

Achilles Tendon

Animal Models

Achilles Tendinopathy

Induced Achilles Tendinopathy

Collagenase Induced Tendinopathy

Achilles Tendinopathy Animal Model

**Introduction/Purpose:** Numerous studies, as evident in literature, have attempted to develop an induced Achilles tendinopathy animal model. The most common models include collagenase injections and mechanical overload of the tendon, but both are controversial.

The mechanical overload model creates a chronically induced tendinopathy and is time intensive. In addition, once the stimulus is removed the tissue changes often heal. The collagenase injection model is quicker, rarely evolve to healing but frequently results in an early acute tendon reaction.

The primary objective of this study is to compare biomechanical and histological findings between two collagenase induced Achilles tendinopathy protocols.

The hypothesis is that consecutive low-dose collagenase injections will result in progressive and long-lasting tendinopathy findings as compared to the traditional single high-dose injection.

**Methods:** In this IRB approved study, the population was composed of forty-eight (n=48) New Zealand breed rabbits. Forty-two (n=42) rabbits were randomly divided into two groups (n=21). The first group, which served as the control, had both Achilles tendons injected by a single dose (0.3mg) of A1 collagenase (Sigma-Aldrich®), as described in literature. The second experimental group had three low-dose injections (0.10mg) with 2 weeks between each injection. Another six animals (n=6) were also randomized into two groups (n=3) receiving one-dose versus 3 injections of saline solution with 2 weeks between each injection. The animals were euthanized after 10, 12 and 16 weeks. Histological and biomechanic analysis of the Achilles tendons were carried out using a dynamic mechanical testing machine (Electropuls®, model EI0000, Instron®). Mechanical strength and histological scores of tendinopathy (Bonar scoring system) were compared among the groups at each time-point.

**Results:** After 16 weeks, all biomechanical and histological parameters analysed showed consistent differences between the groups ( $p < 0.05$ ), with more pronounced and long-lasting tendinopathy findings in the Achilles tendon of the experimental group (serial collagenase injections), when compared to the control groups (single collagenase dose and single/multiple saline injections). The mean Bonar sum-score of tendons after 16 weeks in the experimental group was greater than the mean histologic score of control tendons ( $8.53 \pm 1.52$  versus  $1.1 \pm 0.83$  in saline group and  $5.2 \pm 1.12$  in single dose group). No statistically significant differences were found between the different collagenase injection groups at weeks 10 and 12.

**Conclusion:** The protocol of three consecutive low-dose collagenase injections has shown biomechanical and histological findings compatible with progressive and long-lasting tendinopathy as compared to single high-dose injection. This protocol represents a feasible and effective animal model of induced Achilles tendinopathy.

---

Foot & Ankle Orthopaedics, 1(1)  
DOI: 10.1177/ 2473011416500095  
©The Author(s) 2016