

## Application of Amniotic Membrane Improves Repair in a Diabetic Animal Model for Delayed Tendon Healing

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**Introduction/Purpose:** Tendon injuries often heal with significant scar formation and compromised biomechanical function. For diabetics, these injuries are further complicated by changes in the extracellular matrix of the tendon, leading to higher incidences of injury and slower healing. Defective or delayed healing is a result of several factors including an impaired ability to form a collagen matrix, compromised angiogenesis, and inadequate production of growth factors. Consequently, complications and re-rupture rates are higher in diabetic patients. Amnion-derived cells resulted in improved tendon healing in an otherwise healthy animal model, in part due to their ability to provide numerous regenerative cytokines to the repair site. The purpose of this study was to evaluate the effect of amniotic tissues on tendon healing in a diabetic model with impaired healing.

**Methods:** For this study BBZDR/WOR animals, an insulin dependent Type II diabetic rodent model, were used. After appropriate anesthesia, a full thickness injury was made through the Achilles tendon; immediately following injury, the tendon was repaired using the modified Kessler method. Repaired tendons were wrapped with a 0.5 x 0.5 cm section of either a fresh hypothermally stored human amniotic membrane (HSAM), a dehydrated human amnion chorion membrane (dHACM), or left unwrapped as a control. Contralateral tendons were used as sham controls, which were exposed then immediately closed. Tendons were retrieved at 14 or 28 days and evaluated using histology, immunohistochemistry, and qPCR. At 28 days, both experimental tendons and contralateral controls from five rats per group were harvested and tested to failure and peak force, stiffness, energy uptake, and displacement at rupture were then determined.

**Results:** At day 14, histological evaluation found significant increases in cellular recruitment at the site of injury in both dHACM and HSAM treated animals ( $p=0.0001$ ). qPCR and immunofluorescence results confirmed several biomarkers implicated in tendon repair were highly expressed in the treatment groups, but not in untreated controls. In dHACM treated animals, TNF- $\alpha$ , TGF $\beta$ -1, IL6, FLAP, Tenascin-C, and Scleraxis expression was elevated at 14 days. Control animals with only primary repair resulted in a tendon repair failure rate of 20%; whereas animals treated with HSAM or dHACM had a 6% and 0% failure rate, respectively. dHACM treated tendons also had significant improvements in biomechanical properties compared to controls including increases in the max force, stiffness and strain ( $47\pm 21\%$ ,  $146\pm 90\%$ , and  $59\pm 35\%$  respectively).

**Conclusion:** Augmentation of tendon repair with placental-derived membranes may improve diabetic tendon repair and reduce re-rupture rates. This study presents compelling data suggesting chorion-containing dHACM is more efficacious than the amnion-only HSAM for tendon repair. The cause for this difference is unclear, we hypothesize that cytokine content, important for tendon healing, within the chorion may be responsible. Components of placental tissue contribute different cytokines, ECM and cell populations—this study highlights that differences in components-delivered and processing techniques may impact outcomes and results may vary for different clinical applications. This study highlights a promising treatment option for a clinically challenging population.

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