**Improved Tendon Healing in the Rabbit Achilles Tendon After a Single Injection of CDMP-2**

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**Introduction:** Achilles tendon ruptures in humans are often treated non-operatively, with a healing time similar to operative treatment. However, there is a higher incidence of rerupture. Non-operative treatment might become more efficient with the help of a growth factor. Cartilage Derived Morphogenetic Protein 2 (CDMP-2, human counterpart to GDF-6) is a member of the Bone Morphogenetic Protein (BMP) family. It is closely related to BMP 5, 6 and 7 (Osteogenic Protein 1) and CDMP-1 and 3. Under certain conditions, CDMPs induce tendon or ligament formation rather than cartilage or bone (1). In previous studies we have been able to improve tendon healing by injecting CDMP-2 into an Achilles tendon defect in rats (2). Apart from its small size, this rat model differs from human tendon ruptures in that the paratenon is damaged, so that cells of nontenineous origin can easily enter the repair site. In order to test this principle in a model more similar to a closed human rupture, we now used rabbits in which the paratenon could be sutured.

**Material and Methods:** 40 dwarf long lop-ear rabbits (3132 ± 225 g) of mixed gender were used. The rabbits were split into 3 groups which all underwent the same Achilles tendon operation. The first group (n=20) was used for biomechanical testing after 8 days, and the second (n=12) after 14 days. The third group (n=8) was left for 8 weeks and then the tendons were harvested for radiography and histology. The study was approved by the local ethical board.

The rabbits where operated on under aseptic conditions. A Z-cut was made 1 cm proximal of the ankle. The paratenon was split longitudinally and carefully loosened from the tendon complex. The plantaris tendon was removed. The achilles tendon was transected 2 cm proximal of the calcaneal insertion and a thin polypropylene tube was placed with one end in the defect before the Achilles tendon was transsected 2 cm proximal of the calcaneal insertion and a loosened from the tendon complex. The plantaris tendon was removed. The rabbit was then removed and the rabbits were put back in their cages and allowed free movement.

After 8 or 14 days the tendon with attaching calcaneal bone was taken out. The transverse area of the tendon callus was measured with a digital calliper.

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The tendons where stored at -40°C.

For mechanical testing, the tendon was fixed between two metal clamps and pulled with a constant speed of 1 mm/s until failure (2). Peak force and stiffness were recorded. Data were analysed using Anova and Fisher PLSD.

**Results:** Macroscopically the tendon callus had the shape of a tube, suggesting that it mostly originated from the paratenon surrounding the defect.

Table 1. Results. P-values refer to effect of CDMP-2 treatment in the entire material (2-way Anova)

<table>
<thead>
<tr>
<th>Day</th>
<th>Stress MPa</th>
<th>Stiffness N/mm</th>
<th>Modulus MPa</th>
<th>Energy Nm</th>
<th>Area mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDMP</td>
<td>0.0006</td>
<td>0.06</td>
<td>0.01</td>
<td>0.03</td>
<td>0.0001</td>
</tr>
<tr>
<td>control</td>
<td>0.006</td>
<td>0.01</td>
<td>0.03</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion:** One injection of CDMP-2 increased the proliferation of the early tendon callus, leading to a stronger and stiffer construct at a later stage of repair, when the tendon callus was approaching normal tendon strength. At the early stage (8 days), increased callus mass was associated with inferior material characteristics, although the construct as a whole was slightly stronger. Later, (14 days) the tissue organisation appeared to have caught up with the controls, but the increase in size remained. The absence of radiographic calcifications is about to be verified histologically. The response to CDMPs appears to a great extent to be controled by the mechanical microenvironment, so that tensile loads prevents cartilage and bone differentiation (1 and unpublished data). It needs to be investigated if CDMP-2 injections would have lead to bone formation if the ankle joints had been immobilized.

References:

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