Effect of exercise and glycemic control on diabetic mouse (db/db) Achilles tendons

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My disclosure is in the Final AOFAS Program Book.
I have no potential conflicts with this presentation.
Specific Aims

- Diabetes causes advanced glycogen end product deposition in tendons leading to increased stiffness and contributing to foot ulcer development.
- To determine if diabetic induced tendon alterations can be ameliorated, we examined metformin and exercise therapy.
- We hypothesize that the histologic, biomechanical and proteinomic properties of mouse Achilles tendons in a diabetic model would improve with exercise and metformin treatment.
Methods

At the completion of 10 week study period, bilateral Achilles tendons were harvested from all mice and used for biomechanic, histologic and proteinomic analysis.

**Proteinomics & Histology:** 8 groups, 5 mice each 10 week study period

**Biomechanics:** 8 groups, 10 mice per group each 10 week study period

**Diabetic (Db/db) mice**

- + Metformin + Exercise
- - Metformin + Exercise

**Control C57BL/6 mice**

- + Metformin - Exercise
- - Metformin - Exercise

**Exercise:** 1h/day on treadmill; 8 meters/minute/7 days per week

**Metformin:** 150mg/kg/day in water

**Proteinomics:** 4 M Guanidine HCl, 0.05 M Sodium Acetate, pH 5.8, and protease cocktail. Spotted on CHCA MALDI matrix.

**Biomechanics:** Instron tensile testing
Results – Glycemic Control

There was a significant elevation of glucose in the db/db mice which was partially ameliorated by exercise but not by metformin treatment. * significantly different from controls p<0.001. # and $ significantly different from db/db p<0.0001
## Results - Histology

<table>
<thead>
<tr>
<th>Mice</th>
<th>Number</th>
<th>Insertional Lesions</th>
<th>Mid-substance Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control+Exercise</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control + Metformin</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control + Exercise &amp; Metformin</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Db/db</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>db/db + Exercise</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>db/db + Metformin</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<td>db/db + Exercise &amp; Metformin</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Sectioning difficulties lead to the loss of a few samples. Histologic testing revealed moderate insertional neutrophil infiltration in 1 db/db mouse without medication or exercise. There were no other pathologic findings in any group.
Histology samples of Achilles tendon Insertions. No pathologic findings for (a) control -exercise(e)/-medication(m) and (b) db/db +exercise-, -medication. Low (c) and high power (d) images of db/db -exercise-, -medication Achilles tendon insertion with moderate neutrophil infiltration.
No significant differences were found between the treated and untreated diabetics or the controls.
Results - Biomechanics

– Testing revealed a decreased maximum load to failure in diabetic mice without metformin/exercise vs. lean control without metformin/exercise (6.09N vs 3.93N, p=0.036). No differences in max stress, strain, modulus of elasticity or stiffness were found.

– No differences in maximum load, stress, stiffness, modulus of elasticity or displacement at maximum load were found between the diabetic control and all treated diabetic groups.
Conclusion

- Infrequent inflammation was seen in db/db mice that was not observed in the exercised and/or metformin treated groups. This is a lower incidence than in ob/ob mouse model.
- Proteininomic analysis failed to identify significant differences in the glycosylation of the tendons. This may be technique related and alternate digestions might reveal additional spikes.
- Biomechanics revealed an decrease in maximum load in db/db mice. Treatment with exercise and/or metformin did not significantly improve the declining maximum load.

Select References: