Tissue histology surrounding each CSII cannula was visualized using H&E and Trichrome stains. A pilot swine study was performed to better understand the mechanisms that cause insulin absorption variability. Tissue histology and high resolution Micro-CT imaging were used to evaluate the distribution pattern of an insulin x-ray contrast bolus infused through commercial CSII catheters implanted in swine for 7 days, 5 days, 3 days, 8 hours and 10 minutes.

Methods

CSII catheters with a 6 mm Teflon cannula (Inset, Unomedi cal a/s, Osted, Denmark) were implanted within the soft abdominal tissue of two ambulatory swine for 7 days, 5 days, 3 days, 8 hours and 10 minutes.

CSII catheters with a 6 mm Teflon cannula (Inset, Unomedi cal a/s, Osted, Denmark) were implanted within the soft abdominal tissue of two ambulatory swine for 7 days (n=2), 5 days (n=2), 3 days (n=2), 8 hours (n=2), and 10 minutes (n=2).

Insulin lispro (U-10) was used to evaluate the distribution pattern of an insulin x-ray contrast agent bolus infused through commercial CSII catheters implanted in swine for 7 days, 5 days, 3 days, 8 hours and 10 minutes.

Figure 1. CSII catheter insertion in female swine abdomen.

Figure 2. Representative histology (top) and Micro-CT 3D reconstruction (bottom) images of the insulin/contrast agent bolus for Teflon catheters indwelling for 0 hours, 8 hours, 3 days, 5 days, and 7 days (left to right).

Discussion

1. Insulin movement onto the skin surface.
2. Insulin degradation within the inflammatory tissue by proteases.
3. Variable distance to functioning capillary vessels.
4. Variable local capillary blood flow.
5. Variable insulin absorption across capillary endothelial cells.
6. Variable distance to functioning lymph vessels.
7. Variable absorption into local lymph vessels.
8. Insulin degradation within lymph nodes by proteases.
9. Variable rate of insulin diffusion through inflammatory tissue.
10. Variable rate of insulin diffusion through subcutaneous tissue.

Table 1. Descriptive statistics of insulin/contrast agent bolus surface area and volume.

<table>
<thead>
<tr>
<th>Micro-CT Analysis</th>
<th>Surface Area (mm²)</th>
<th>Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td>Min</td>
<td>112</td>
<td>273</td>
</tr>
<tr>
<td>1st Quartile</td>
<td>194</td>
<td>310</td>
</tr>
<tr>
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<tr>
<td>Std Error</td>
<td>28</td>
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The layer of inflammatory tissue may function as a mechanical barrier, slowing or inhibiting the movement of insulin into adjacent subcutaneous tissue containing capillary and lymph vessels. The bolus of insulin/contrast moved through the inflammatory tissue and subcutaneous tissue along the path of least resistance due to damaged cells, connective tissue, and extracellular matrix. CSII cannula movement while indwelling caused additional tissue damage.

The resistance to flow into adjacent vascular tissue was variable due to the heterogeneous anatomy of adipose tissue and the variable density, thickness, and continuity of the surrounding layer of inflammatory tissue.

Results

Figure 3. Representative histology images for Teflon catheters indwelling for 0 hours, 8 hours, 3 days, 5 days, and 7 days (left to right).

1. Variable rate of insulin diffusion through inflammatory tissue.
2. Variable rate of insulin diffusion through subcutaneous tissue.
3. Variable distance to functioning capillary vessels.
4. Variable local capillary blood flow.
5. Variable insulin absorption across capillary endothelial cells.
6. Variable distance to functioning lymph vessels.
7. Variable absorption into local lymph vessels.
8. Insulin degradation within lymph nodes by proteases.
9. Variable rate of insulin diffusion through inflammatory tissue and subcutaneous tissue.
10. Variable rate of insulin diffusion through subcutaneous tissue.

DISCUSSION

INTRODUCTION

Patients managing their type 1 diabetes with an insulin pump are required to insert a new continuous subcutaneous insulin infusion (CSII) catheter every 2-3 days to minimize the risk for hyperglycemia, hypoglycemia and diabetic ketoacidosis. CSII catheters with a 6 mm Teflon cannula (Inset, Unomedi cal a/s, Osted, Denmark) were implanted within the soft abdominal tissue of two ambulatory swine for 7 days, 5 days, 3 days, 8 hours and 10 minutes.

RESULTS

Five minutes after each bolus, the CSII catheter and capillary/lymph vessels localized to the region of cannula insertion. The region had minimal thrombus and no inflammatory cells.

Histology 8 hours after insertion revealed mild infiltration of the surrounding tissue with neutrophils, macrophages and fibroblasts.

Histology 3.5, and 7 days after insertion revealed a progressively larger region of damaged tissue, thrombus, and inflammatory cells.

The layer of inflammatory tissue surrounding the CSII cannula became thicker, denser and more continuous over time.

The 70 µL bolus of insulin lispro (U-100) and x-ray contrast agent traveled from the cannula’s orifice (distant tip) into adjacent inflammatory tissue and connective tissue septa along the path of least resistance.

The insulin/contrast bolus distended the connective tissue fibers to form a spherical distribution with a few “finger-like” projections.

Surface area and volume were variable among insulin/contrast agent boluses.

Tissue histology immediately after CSII cannula insertion (0-10 min) revealed damaged adipose cells, connective tissue, and capillary/lymph vessels localized to the region of cannula insertion. The region had minimal thrombus and no inflammatory cells.

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The resistance to flow into adjacent vascular tissue was variable due to damaged cells, connective tissue, and extracellular matrix. CSII cannula movement while indwelling caused additional tissue damage.

A layer of inflammatory tissue formed around the cannula consisting of thrombus, neutrophils, macrophages, fibroblasts, and cellular debris. The layer became thicker, denser and more continuous over time.