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Optimization of Insulin Delivery through a CSII Catheter

Analysis of the Inflammatory Response to Insulin Infusion Systems

In collaboration with: Medical University of Graz

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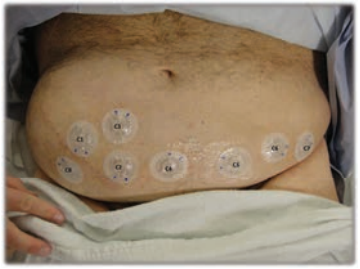
Background and Aims:

Approximately one-half million people in the world manage their diabetes with an insulin pump and a continuous subcutaneous insulin infusion (CSII) catheter. Patients are required to insert a new CSII catheter every two to three days in order to ensure safe and effective blood glucose control. After 3 days of wear-time, the absorption of insulin from the subcutaneous tissue into the circulation becomes variable and unreliable which can lead to hypo- and hyperglycemia and other clinical complications such as ketoacidosis. Currently, a pilot study is being performed in ambulatory humans scheduled for a surgical abdominoplasty to compare tissue histology and cytokine gene expression profiles of the tissue surrounding Teflon CSII catheters inserted 4 days, 3 days, 2 days and 2 hours prior to surgery. The results will help formulate a hypothesis, why insulin absorption into the circulation becomes more variable two to four days after catheter insertion.



Methods:

Two CSII catheters (Quick-set®, 9 mm) were inserted into the subcutaneous abdominal tissue of 3 ambulatory humans 4 days, 3 days, 2 days, and 2 hours prior to elective plastic surgery to remove excess skin and subcutaneous tissue. During this period of time no insulin was infused. Tissue surrounding CSII catheters was removed and stained with H&E, Reticulin, and Trichrome to determine morphological changes and inflammatory cells in the tissue. RNA was isolated from the second CSII catheter-tissue specimen from each time period and quantitative real-time PCR (qPCR) carried out to measure fold-changes in gene expression of pro- and anti-inflammatory cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-a, TGF-b) and the macrophage marker CD68. Data are shown as mean fold-change ± SEM compared to the constantly expressed reference genes beta actin and glyceraldehyde 3-phosphate dehydrogenase.

Results:

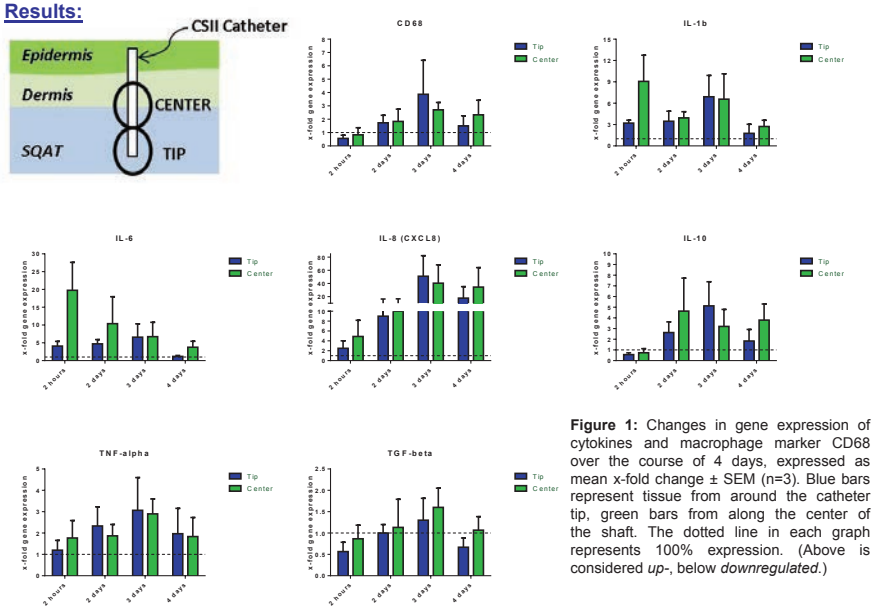


Figure 1: Changes in gene expression of cytokines and macrophage marker CD68 over the course of 4 days, expressed as mean x-fold change ± SEM (n=3). Blue bars represent tissue from around the catheter tip, green bars from along the center of the shaft. The dotted line in each graph represents 100% expression. (Above is considered *up*-, below *downregulated*.)

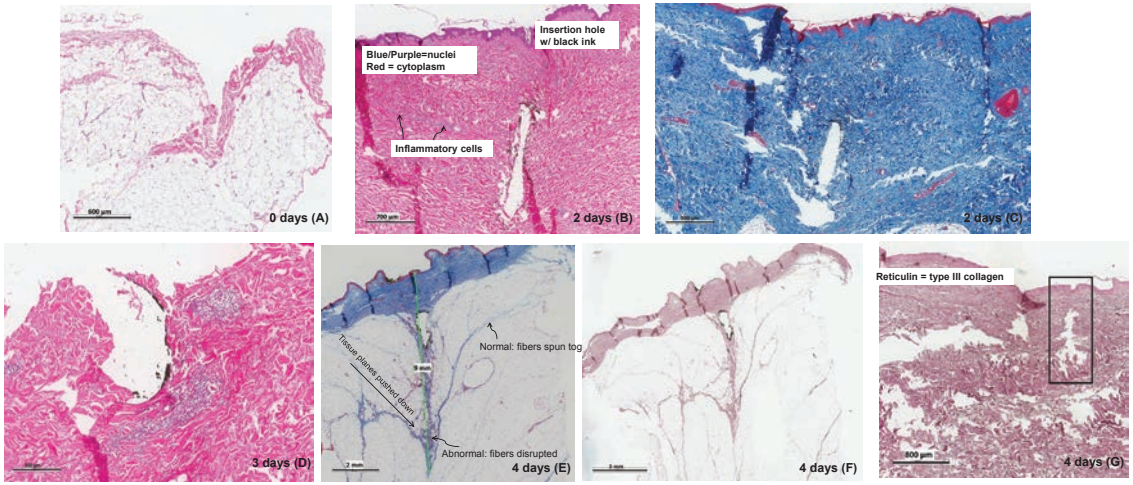
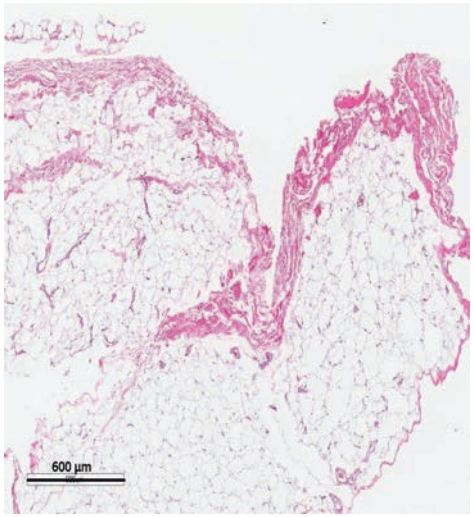


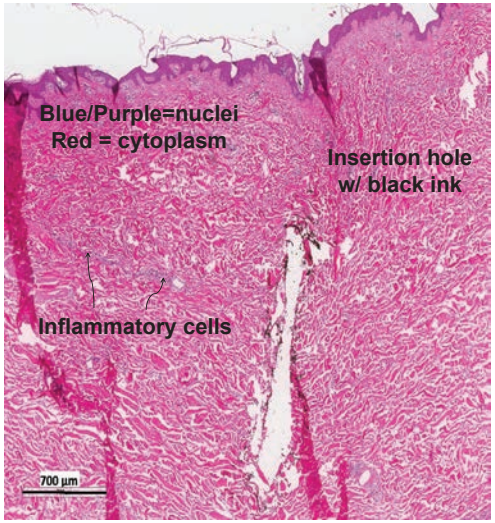
Figure 2: Visualization of the insertion channel by means of histological staining. (A) Catheter tip; tissue dragged down by catheter force. (B) Insertion hole on skin surface with slight re-epithelization; inflammatory cells migrating towards channel. (C) Insertion hole in the dermis; tissue disruption; no bleeding. (D) Inflammatory cells (mostly neutrophils) at the catheter tip. (E) Full length of insertion channel; disruption of collagen fibers and tissue morphology. (F) & (G) Reticulin fiber disruption.

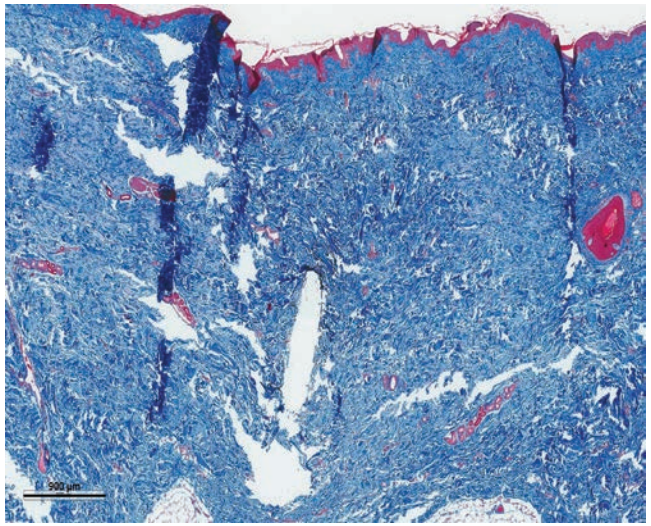
Discussion:

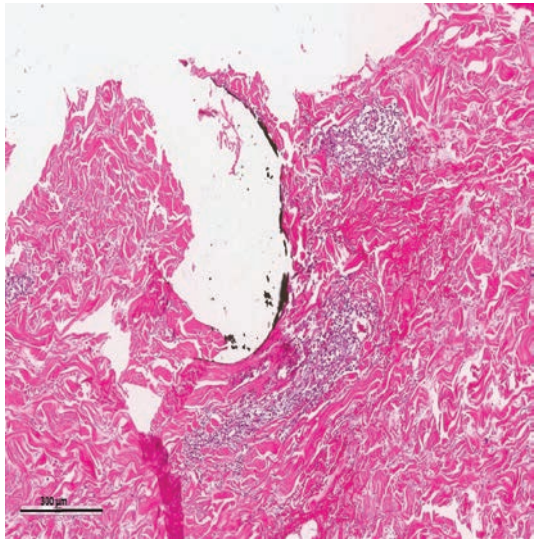
CSII catheter insertion damaged adipose and connective tissue, and triggered the foreign body response immediately after insertion, leading to an upregulation of cytokine gene expression. Acute phase proteins such as IL-6 are secreted immediately after insertion while the anti-inflammatory IL-10 and chemotaxin IL-8 play a later role (48-72 hours post-insertion). Histology showed rapid ingrowth of epithelial cells down the insertion hole (Figure 2B) but no severe bleeding or thrombus formation around the catheter tip. Connective tissue is substantially disrupted after 4 days of catheter wear-time. Immunohistochemical staining of CD68 (data not shown) did not show a great increase in number of macrophages but gene expression of CD68 increased 4-6 times by day 3. The combination of histology and quantitative real-time PCR is a potent tool to understand tissue inflammation surrounding a CSII catheter and to determine possible biomarkers for impaired insulin absorption into the circulation. For this study, we will recruit 3 more patients and further studies in humans are planned.

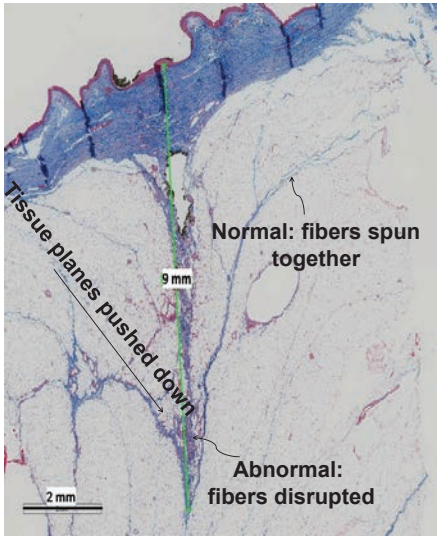
Support: This study is funded by the Frederick Banting Foundation

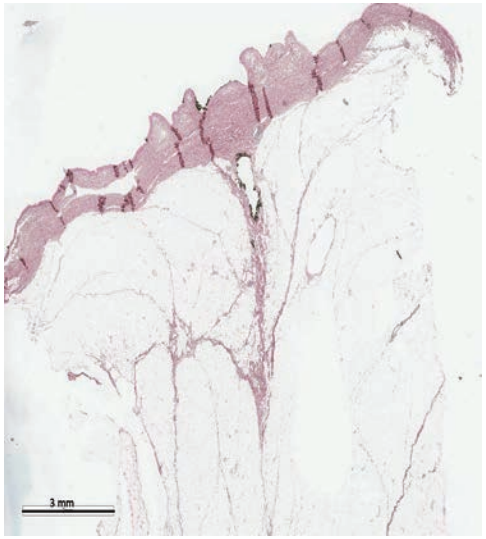

600 µm

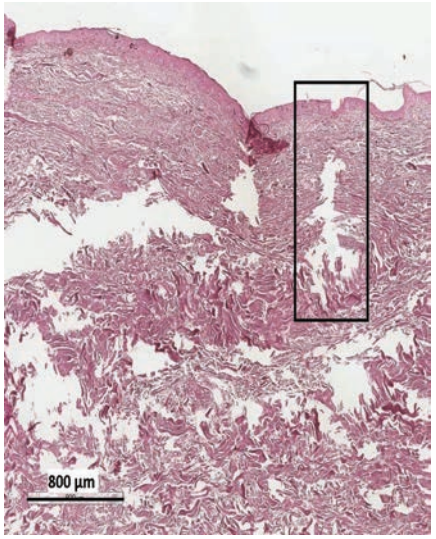

Blue/Purple=nuclei
Red = cytoplasm
Insertion hole
w/ black ink
Inflammatory cells
700 µm




300 µm


Tissue planes pushed down
Normal: fibers spun
together
9 mm
Abnormal:
fibers disrupted
2 mm


3 mm


800 µm