Porous, Dexamethasone-Releasing Coatings Improve the Performance of Indwelling Glucose Sensors in Normal and Diabetic Rats

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Statement of Purpose: Type I diabetes affects millions of patients in the US each year. Due to poor glucose control, patients with diabetes experience impaired wound healing, poor circulation, ketoacidosis, and an increased incidence of blindness. One of the most promising glucose management techniques, is the use of implantable sensors for continuous monitoring.

Unfortunately, the long-term use of such devices has been limited due to the Foreign Body Response (FBR). During the FBR a sensor fails due to migration of inflammatory cells (macrophages)[1], and decreased blood vessel formation in apposition to the sensor surface[2]. In order to improve biocompatibility of glucose sensors, we have developed porous polyurethane coatings that release the anti-inflammatory agent - Dexamethasone (Dex). By combining drug delivery and texturing techniques, we created coatings that can curve inflammation and promote vascularization.

For the present study, we evaluated the effects of porous Dex-releasing coatings on the FBR. We implanted coated Medtronic Minimed glucose sensors in normal and diabetic rats. We then analyzed the FBR in both models over the short (3-7 days) and long-term (21 days).

Methods: Porous Tecoflex® 93A Dex releasing coatings were fabricated using salt-leaching/gas foaming[3]. Glucose sensors with and without porous Dex-releasing coatings were percutaneously implanted in normal and diabetic rat animal models. One month pre-implantation, diabetes was induced in normal rats by delivering streptozotocin for 3 days. Treated and untreated sensors were implanted directly into the dorsum of rats and retrieved 3, 7, and 21 days post-implantation. Sensor functionality was assessed by glucose bolus tests at days 1, 3, 7, 14, 21. Histological evaluation of implants allowed for the study of the FBR. Immune cell infiltration was assessed via H&E and CD68 macrophage marker staining. Collagen deposition was evaluated via Masson's Trichrome stain and angiogenesis was detected via CD31 immunohistochemistry.

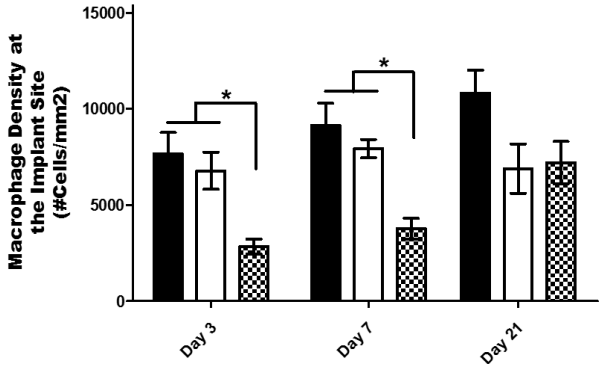

Figure 1. Macrophages surrounding treated and non-treated. Significantly more macrophages were present near Dex-free porous coatings and bare sensors at days 3 and 7 ($p<0.05$). However, there is no difference at day 21.

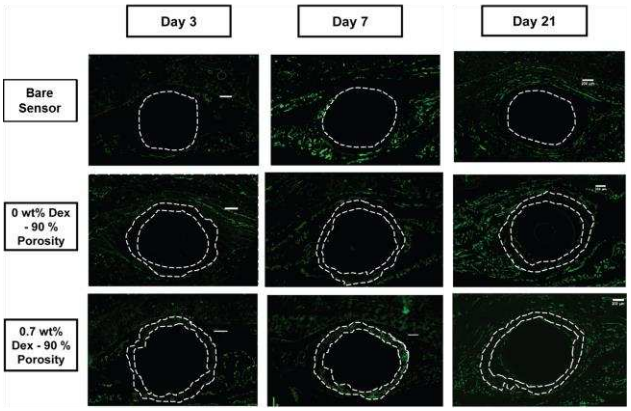

Figure 2. Vascular structures surrounding treated and non-treated glucose sensors. CD31 structures were present near Dex-free porous coatings at day 21. Bare implants showed no signs of neovessel formation at the implant-tissue interface. Enhanced vascularization in Dex-releasing porous coatings is only observed at day 14.

Results: Porous coatings fitted snugly over Medtronic Minimed sensors[3]. In vivo studies of functional glucose sensors showed that porous Dex-releasing coatings were dually capable of decreasing macrophage infiltration while achieving high vascularization on the sensor surface. Porous Dex-releasing coatings effectively decreased the number of macrophages near the sensor within the initial 3 and 7 days in normal and diabetic rats (Figure 1). Macrophage infiltration was curbed in diabetic rats when compared to normal rats. This suggested that diabetic rats mounted a less aggressive immune response to sensor implantation. Porous Dex-releasing coatings had an increased CD31 expression (vascularity) for 21-day implants in both groups. Dex-free porous coatings showed enhanced vascularization at day 21 as well, but did not have an anti-inflammatory action in the earlier time-points. CD31 expression was limited in diabetic rats when compared to normal rats.

Glucose bolus tests showed that the effects of porous Dex-releasing coatings enhanced sensor performance by extending sensor sensitivity in the short-term, decreasing overall lag-time and increasing functional life when compared to bare controls. Dex-free porous coatings also showed enhanced performance at 21 days, but exhibited decreased sensitivity and accuracy at days 3 & 7.

Conclusions: Porous Dexamethasone-Releasing coatings proved to be effective at attenuating inflammation and promoting vascularization around indwelling glucose sensors in normal and diabetic animal models, which translated into improved function of indwelling sensors.

References: [1]Novak, MT, Biomaterials. 2014.
[2]Koschwanez HE, J Biomed Mater Res A. 2008.
[3]Vallejo-Heligon SG, Acta Bio. 2014.