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SYMPOSIUM

Interstitial Fluid Physiology as It Relates to Glucose Monitoring Technologies: Symposium Introduction

Natalie A. Wisniewski, Ph.D.,[1] Ulrike Klueh, Ph.D.,[2] and Julie Stenken, Ph.D.[3]

Abstract

Nearly all commercially available glucose sensors share the subcutaneous interstitial fluid (ISF) compartment as their preferred implantation site. However, ISF physiology as it relates to glucose sensors is not well understood. This special symposium titled "Interstitial Fluid Physiology as It Relates to Glucose Monitoring Technologies" is intended to help to bridge the gap in our understanding. This symposium is intended to foster a greater understanding of biological factors that impact the success of implantable glucose monitors and to inspire additional research in the area of ISF physiology as it relates to glucose sensing. Recognition that sensor designers need to have an intimate understanding of the biological environment in which their sensor will reside is emphasized. The symposium is published in two parts, with part I published in September 2010 and part II published in May 2011. All articles published in this symposium are summarized herein.

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Introduction

Nearly all commercially available glucose sensors share the subcutaneous (SQ) interstitial fluid (ISF) compartment as their preferred implantation site. However, ISF physiology as it relates to glucose sensors is not well understood. This special symposium titled "Interstitial Fluid Physiology as It Relates to Glucose Monitoring Technologies" is intended to help to bridge the gap in our understanding. The symposium is published in two parts; part I was published in the September 2010 issue (http://www.journalofdst.org/September2010/), and part II is published in this May 2011 issue (http://www.journalofdst.org/May2011/).

Many clever attempts have been made to develop long-term, continuous glucose sensors, which can function exceptionally well on the benchtop (i.e., *in vitro*) but often perform unreliably once implanted into the body (i.e., *in vivo*). Approaches to develop better implantable sensors have been largely engineering based, with often minor input from biologists, physiologists, immunologists, pathologists, and other disciplines with biological expertise. However, sensor designers need to have an intimate understanding of the biological environment in which their sensor will reside. Unlike a controlled *in vitro* test environment, the *in vivo* environment immediately at

Author Affiliations: [1]Medical Device Consultancy, San Francisco, California; [2]Center for Molecular Tissue Engineering, School of Medicine, University of Connecticut, Farmington, Connecticut; and [3]Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas

Abbreviations: (FBR) foreign body response, (ISF) interstitial fluid, (SQ) subcutaneous

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Corresponding Author: Natalie Wisniewski, Ph.D., Medical Device Consultancy, 1219 18th St., San Francisco, CA 94107; email address natwis@alumni.duke.edu

the surface of a sensor is in a constant state of change due to short-term influences (activity level, inflammation, diet, temperature swings, sun exposure, and other stressors) and long-term influences [aging, progression of disease states, obesity, the foreign body response (FBR)]. Symposium part I and part II contain articles on the physiology of ISF in the skin that are relevant to the design and use of implantable and percutaneous glucose sensors and other diabetes technologies. These articles are summarized herein.

Histological Characterization of Skin Composition and Transport Modeling: Groenendaal and colleagues[1] quantified the composition of human skin layers through histological characterization. Significant intersubject variability was identified. The authors applied rigorous mathematical modeling to show how variations in skin composition affect glucose dynamics.

Optical and Compositional Heterogeneity in Skin: Alexeeva and Arnold[2] showed the effect of tissue heterogeneity on noninvasive near-infrared glucose measurements in ISF of rat skin. Microspectroscopy allowed exquisite, fine-resolution mapping of optical heterogeneity due to variations of water, fat, keratin, collagen, and other proteins in rat skin.

Concentration Gradients around Continuous Glucose Moniotring: Prichard and associates[3] utilized a novel bioluminescence imaging technique to directly measure for the first time glucose gradients in FBR tissue adjacent to SQ sensors up to 8 weeks in rats. Acute changes in this gradient may be responsible for some of the noise seen in raw sensor data and for loss of sensor calibration. Authors purport that this gradient may be due to inflammation, changing vasculature, and/or consumption by the glucose oxidase that outweighs supply in the FBR tissue that surrounds the sensor.

Time Dependence of Multianalyte Availability in FBR Tissue around Sensors: As a follow-up to prior work comparing SQ tissue transport in rats and humans, Ekberg and coworkers[4] evaluated fluctuations in multiple analytes in wound healing and FBR tissue surrounding SQ microdialysis catheters (used as a simplified model of a glucose sensor) in persons with type 1 and type 2 diabetes. They presented the first known histological evaluation of human biopsies containing implanted glucose monitoring devices.

Cytokine Expression Affects Sensor Function: Klueh and colleagues[5] presented pioneering work that directly links cytokine expression to sensor function. They showed the importance of local interleukin-1 and interleukin-1 receptor antagonist in short-term glucose sensor function *in vivo*. Interleukin-1-receptor-antagonist-deficient mice (knock-out mice) had extensive inflammation and decreased sensor function compared to control and over-expresser mice over 1 week.

Glucose Delay and Offset in ISF and Continuous Glucose Monitoring: The question of delay and sensor offset in the determination of SQ ISF glucose compared with blood glucose was revisited by Rebrin and associates.[6] Numerous models and simulations were presented to illustrate problems related to measurement and correction of ISF glucose delay. A model simulation environment was proposed to facilitate development of new algorithm filtering and calibration strategies.

Biomechanical Considerations in Continuous Glucose Monitoring—Motion and Pressure Effects: In a two-part review, Helton and coworkers[7,8] explored the biomechanics of the sensor–tissue interface as an important aspect of continuous glucose monitoring biocompatibility. Part I provides a theoretical framework of biomechanical factors that affect percutaneous and fully implanted glucose sensors. Part II is an extensive review of the literature, and it contains data that implicates motion and pressure in the FBR and sensor performance. These two reviews highlight the importance of sensor design, motion, specific implant locations, and other biomechanical contributors to long-term sensor performance.

Skin Blood Flow Is Compromised by Diabetic Vascular Endothelial Dysfunction: Petrofsky[9] provided a review of the effect of type 2 diabetes on vascular endothelial dysfunction on skin physiology and activities of daily living. It is critical to understand the effects of vascular endothelial cell damage such as poor skin blood flow, compromised thermoregulation, and altered response to skin pressure in designing diabetes technologies.

Local Tissue Hemorrhage Perturbs Continuous Glucose Monitoring: Klueh and colleagues[10] utilized their mouse model to investigate the effect of local tissue hemorrhage formation at sites of sensor implantation. They concluded that blood clot formation near the sensor could result in a temporarily lowered sensor output reading, which is not reflective of the systemic glucose level. They argue that the lowered sensor output reading is the result of local glucose metabolism by the blood clot.

Monitoring Energy Metabolism after Traumatic Brain Injury to Maintain Homeostasis: Rostami and Bellander[11] used microdialysis sampling to monitor chemical changes in glucose and metabolites in traumatic-brain-injured patients. In efforts to prevent overall hypoglycemia, they monitored glucose in the brain, blood, as well as adipose tissue.

Modulation of the FBR Tissue around Implanted Microdialysis Devices: Mou and associates[12] used the bidirectional nature of microdialysis sampling to locally deliver tissue response modifiers to alter the FBR at the implant site. Internal standards were used to elucidate transport characteristics between different treatments. Interestingly, supply of glucose to the dialysis probe was reduced for both controls and treated animals.

Diabetic Animal Models for Implant Healing: This review by Le and coworkers[13] highlights critical points about differences in the biochemistry of infection and wound healing adjacent to implants in various animal models and persons with and without diabetes. In particular, nitric oxide synthase activity seems to be decreased in diabetic models.

Developers of diabetes technologies, particularly implantable glucose sensors, should be keenly aware of the physiological phenomenon presented in this *Journal of Diabetes Science and Technology* symposium and other forums. However, many unanswered questions still remain about ISF physiology for which further investigations are needed. For example, how does ISF physiology of the wound healing and FBR tissue adjacent to a sensor differ from the physiology of native SQ tissue? How does ISF physiology compare in different compartments of the body (subcutis, dermis, eye, peritoneal)? How does SQ ISF physiology differ in obese versus nonobese people? How does SQ ISF physiology differ in type 1 diabetes versus type 2 diabetes versus nondiabetic persons? What animal models most closely represent human SQ ISF and FBR? How do vascular properties (density of vessels, permeability, flow rate) relate to ISF physiology? How do local cellular metabolism and lymphatics relate to ISF physiology, particularly glucose and other components of interest to glucose sensors (e.g., oxygen and pH)? How heterogeneous is the glucose concentration in the subcutis or dermis at a given point in time (e.g., would a glucose profile map show micrometer-to- micrometer variations in glucose concentration)? What are the effects of anesthesia and various drugs on ISF physiology, particularly glucose and other components of interest to glucose sensors? How will temperatures, pressures, and other applied challenges affect ISF physiology?

We hope that this symposium not only fosters a greater understanding of biological factors that impact the success of implantable glucose monitors, but also inspires additional research in the area of ISF physiology as it relates to glucose sensing. It is only through an expansion of fundamental biological studies, combined with engineering know-how, that we will be able to achieve reliable, accurate, longer lasting *in vivo* sensors for continuous medical monitoring of glucose and other analytes.

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References:

1. Groenendaal W, von Basum G, Schmidt KA, Hilbers PA, van Riel NA. Quantifying the composition of human skin for glucose sensor development. J Diabetes Sci Technol. 2010;4(5):1032–40.
2. Alexeeva NV, Arnold MA. Impact of tissue heterogeneity on noninvasive near-infrared glucose measurements in interstitial fluid of rat skin. J Diabetes Sci Technol. 2010;4(5):1041–54.
3. Prichard HL, Schroeder T, Reichert WM, Klitzman B. Bioluminescence imaging of glucose in tissue surrounding polyurethane and glucose sensor implants. J Diabetes Sci Technol. 2010;4(5):1055–62.
4. Ekberg NR, Brismar K, Malmstedt J, Hedblad MA, Adamson U, Ungerstedt U, Wisniewski N. Analyte flux at a biomaterial-tissue interface over time: implications for sensors for type 1 and 2 diabetes mellitus. J Diabetes Sci Technol. 2010;4(5):1063–72.
5. Klueh U, Liu Z, Feldman B, Kreutzer D. Importance of interleukin-1 and interleukin-1 receptor antagonist in short-term glucose sensor function in vivo. J Diabetes Sci Technol. 2010;4(5):1073–86.
6. Rebrin K, Sheppard NF Jr, Steil GM. Use of subcutaneous interstitial fluid glucose to estimate blood glucose: revisiting delay and sensor offset. J Diabetes Sci Technol. 2010;4(5):1087–98.

7. Helton KL, Ratner BD, Wisniewski NA. Biomechanics of the sensor-tissue interface—effects of motion, pressure, and design on sensor performance and the foreign body response—Part I: theoretical framework. J Diabetes Sci Technol. 2011;5(3):632–46.

8. Helton KL, Ratner BD, Wisniewski NA. Biomechanics of the sensor-tissue interface—effects of motion, pressure, and design on sensor performance and the foreign body response—Part II: examples and applications. J Diabetes Sci Technol. 2011;5(3):647-56.

9. Petrofsky JS. The effect of type-2-diabetes-related vascular endothelial dysfunction on skin physiology and activities of daily living. J Diabetes Sci Technol. 2011;5(3):657–67.

10. Klueh U, Liu Z, Feldman B, Henning TP, Cho B, Ouyang T, Kreutzer D. Metabolic biofouling of glucose sensors *in vivo*: role of tissue microhemorrhages. J Diabetes Sci Technol. 2011;5(3):583–95.

11. Rostami E, Bellander BM. Monitoring of glucose in brain, adipose tissue, and peripheral blood in patients with traumatic brain injury: a microdialysis study. J Diabetes Sci Technol. 2011;5(3):596–604.

12. Mou X, Lennartz MR, Loegering DJ, Stenken JA. Modulation of the foreign body reaction for implants in the subcutaneous space: microdialysis probes as localized drug delivery/sampling devices. J Diabetes Sci Technol. 2011;5(3):619–31.

13. Le NN, Rose MB, Levinson H, Klitzman B. Implant healing in experimental animal models of diabetes. J Diabetes Sci Technol. 2011;5(3):605–18.