

Problems Associated With Subcutaneously Implanted Glucose Sensors

The Diabetes Control and Complications Trial Research Group has shown that there is a clear effect of intensive treatment of type 1 diabetes on the development and progression of specific complications like diabetic retinopathy, nephropathy, and neuropathy (1). These observations are supported by the results of the Kumamoto Study, which shows similar effects of intensive insulin therapy in nonobese type 2 diabetic patients (2). Recently, the U.K. Prospective Diabetes Study also showed that an intensive treatment policy affected diabetes-related microvascular complications beneficially in type 2 diabetes (3).

Intensive insulin treatment comprises several blood glucose measurements a day with subsequent adjustment of the insulin dosage. Even with intensive treatment, the number of measurements is still limited and will provide only limited information about the blood glucose pattern during the day. Furthermore, intensive treatment of diabetes increases the risk of severe hypoglycemia. Because there is a significant number of patients suffering from hypoglycemia unawareness, this poses a serious problem. As a consequence, the concept of continuous glucose sensing could result in a more adequate insulin administration. It would also allow the early detection of hypoglycemic events. Ultimately, continuous monitoring could be used as part of an automatic "closed-loop" insulin delivery system or as a hypoglycemia warning system.

In spite of a considerable effort to develop an implantable glucose sensor, to date, there is hardly a clinically applicable concept for continuous glucose monitoring. The subcutaneous tissue is regarded as the most appropriate site for sensor implantation because it is accessible for surgery and the sensor is relatively easy to replace in case of impaired function. Although the occasional sensor continued to function in vivo for weeks to months, most subcutaneously implanted sensors were not capable of reliably monitoring glucose for longer than several hours because of a considerable drift in sensor current (4–8). In

general, this bioinstability was not to be expected from the in vitro performance of the sensors. The fact that the function of explanted sensors was often unaffected indicates that the environment surrounding the sensor played a pivotal role in the behavior of implanted sensors. Wound-healing phenomena, the host response to the implant, and the structure and blood supply of the surrounding tissue are likely to influence sensor performance. Nevertheless, these factors have not been investigated systematically. In this editorial, some of these issues will be addressed.

The article by Updike et al. (9) in this issue evaluates the performance of two different types of glucose sensors in a dog model. The sensors were conventional electrochemical enzyme electrodes based on the detection of hydrogen peroxide provided with multiple membrane layers to improve sensor performance. The sensors, together with a radiotransmitter system, were fully implanted into subcutaneous tissue in polyethylene housing. A Dacron velour polyester flange was used to ensure appropriate subcutaneous anchorage. Altogether, the design of this implant system has been shown to result in superior sensor longevity compared with previously used needle-type sensors (10,11). A novel approach in this investigation has been the addition of an interfacial angiogenesis membrane to the existing design to stimulate the formation of capillaries adjacent to the sensor. Although the concept of improving vascularization around implants is not new (12–16), it has not actually been applied to implantable glucose sensors in an in vivo setting. The application of this membrane was shown to improve sensor lifetime, response time, linearity, and calibration stability. However, some critical remarks have to be made considering the design of the study. The evaluation of both sensor types was performed in two separate experiments with a significant period of time in-between, whereas one experimental setup would have been more appropriate to investigate the actual influence of the

angiogenesis membrane. Furthermore, analysis of both sensor types in the same animal under similar conditions would also have rendered better interpretable results. Finally, only a limited number of newly designed sensors has been evaluated so far.

From a methodological point of view, the study is still interesting for several reasons. The investigators evaluated the accuracy of the implanted sensors through the full clinical range of interest with a well-defined glucose and insulin infusion algorithm. In addition, the drift in sensitivity during the implantation period was addressed by using a moving average of previous calibrations. Although the absolute drift in sensor current was not reported, this method provides a useful tool for comparing calibration stability of different sensors and relating it to the actual performance during implantation. The applicability of this method in sensor research, however, is probably limited because of the usually observed short life span of implanted sensors.

An important outcome of this study was ascertaining that it is possible to monitor glucose in subcutaneous tissue. The drift in sensor output was also significantly lower than reported by other investigators, resulting in a far superior sensor lifetime. These findings were attributed to the formation of a mature fibrous capsule warranting a stable supply of glucose and oxygen to the implanted sensors. The importance of sufficient blood supply for sensor performance was further illustrated by the finding that it was difficult to track glucose in the early stages after implantation. This latter observation puts the results of previous short-term sensor measurements in a different perspective. Perhaps implantation of the relatively large sensor used in the reported study resulted in more extensive damage of the tissue architecture in comparison with the generally smaller needle-type sensors. Application of the angiogenesis membrane was shown to shorten this period of inconsistent monitoring. The investigators reported successful glucose tracking in the first week after implantation. It is, however,

highly unlikely that the stimulatory effect of this membrane on neovascularization occurred this early in the wound-healing process (17). The investigators also stated that this membrane resulted in thinner, more vascularized capsules. Unfortunately, they do not show any histologic results to illustrate this. The general belief is, however, that a fibrous capsule negatively influences sensor performance by increasing the delay in response (18–20). The continuing presence of granulation tissue at the sensor interface after 4 weeks of implantation as observed by the same authors (10,11) in previous investigations might have contributed to the improved sensor performance. The well-vascularized granulation tissue is likely to provide a better diffusion of glucose to the sensor than the relatively avascular fibrous encapsulation that is usually observed around implants. It is important to notice, however, that the presence of granulation tissue at this time point is indicative of a protracted inflammatory reaction (21). Eventually, this ongoing process will affect the lifetime of the implanted device. This seems particularly relevant for a fully implanted system, since replacement of the sensor in case of impaired function requires surgery and is inconvenient for the patient. In this respect, on the other hand, it is important to mention that a fully implantable sensor enables glucose monitoring in a relatively stable environment. The implant design limits manipulation of the sensors during implantation, thereby preventing the origination of small hemorrhages at the implantation site (22–24). Furthermore, reduction of relative movements at the sensor-tissue interface by subcutaneous anchorage of the sensor with a porous flange is likely to cause a reduction in the inflammatory response and fibrous capsule formation (25,26).

Still, a significant number of these devices failed despite selection of the best performing sensors by extensive preimplantation bench top testing and an initial in vivo assessment of sensor responsiveness. As a failure mechanism, the authors mention that the foreign-body capsule occasionally failed to adequately provide oxygen and glucose to the sensor and that this observation was related to the capsule becoming avascular. Unfortunately, the failure modes of individual sensors were not described. We know that the in vitro behavior of a sensor after exposure to a biological environment can often reveal the source of bioinstability (7). In this study, a

postimplantation in vitro evaluation also was performed in an attempt to ascertain the failure mode. Unfortunately, pre- and postimplant data were not compared. This is a problem generally observed in implantation studies. Possible explanations for sensor failure are mentioned but are not investigated. Only with a better understanding of the processes involved in sensor inactivation is it possible to develop adequate strategies to improve long-term in vivo sensor performance. The achievement of this knowledge implies an interdisciplinary approach at a basic scientific level. In vitro experiments can reproduce many elements of the in vivo situation and should be used more often to bridge the gap with implantation studies. In vivo experiments can then be reserved for the more promising approaches. Animal models seem more suitable in this respect than human subjects, since interventions and histological processing are more easily performed. Still, it seems worthwhile also to continue to investigate possibilities of influencing the tissue reaction to implanted devices.

MARTIJN GERRITSEN, MD

From the Department of Biomaterials, University of Nijmegen, Nijmegen, the Netherlands.

Address correspondence to Dr. Martijn Gerritsen, Department of Biomaterials, College of Dental Science, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands. E-mail: m.gerritsen@dent.kun.nl.

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