Letters and Comments

Ultrasonic Measurement of Forearm Subcutaneous Adipose Tissue Thickness Suitable for Monitoring of Subcutaneous Glucose Concentration?

The introduction of closed-loop insulin delivery systems for clinical use in diabetic patients is largely dependent on the development of reliable techniques for continuous glucose monitoring. In this respect, nonvascular access for glucose determinations would offer potential advantages, provided the tissue glucose concentration is closely correlated to the circulating glucose level. Recently, the extracellular concentration of glucose in subcutaneous adipose tissue has been investigated with two different techniques, the microdialysis sampling method (1) and the wick technique (2), and was found to be almost identical to that in venous blood. By contrast, Shichiri et al. (3), with a needle-type glucose oxidase sensor in diabetic subjects, reported the subcutaneous tissue glucose concentration to be only ~80% of the blood glucose concentration. In the latter study (3), the sensor (diam 0.8 mm, length not reported) was inserted percutaneously into the forearm and fixed in situ with adhesive bandages for up to 144 h. To explore whether the subcutaneous fat depot at this site is deep enough to allow the implantation of a sensor, we investigated the adipose tissue thickness at different places on the forearm with an ultrasonic technique.

The study included six healthy subjects (3 men, 3 women; aged 24–40 yr) and six insulin-dependent diabetic patients (3 men, 3 women; aged 24–43 yr), all with normal body weight (body mass index: controls 17.1–23.1 kg/m^2, diabetic subjects 20.6–25.6 kg/m^2). The vertical distance between the skin surface and the underlying muscle fascia at the dorsal side of the forearm was measured with a 10-mHz probe (Accuson, New Haven, CT). Determinations were made at three different sites: *1*) 5 cm distal to the external epicondyle of the humerus, *2*) the middle portion of the forearm, and *3*) 2 cm proximal to the ulnar caput, with the forearm placed in a horizontal position and the elbow flexed 90°.

The results (means ± SE) of the ultrasonic measurements at the promixal, middle, and distal sites of the forearm in the control subjects were 4.6 ± 0.4, 5.2 ± 0.3, and 3.5 ± 0.2 mm, respectively. The corresponding values in the diabetic patients were 4.5 ± 0.3, 5.0 ± 0.4, and 3.6 ± 0.2 mm, respectively. Because ultrasonic measurements also included the epidermis and dermis layers, with a known thickness of 1–2 mm, true adipose tissue thickness can be estimated to be 1–4 mm at different sites along the forearm (1–3 mm at the wrist).

Shichiri et al. (3) reported that the subcutaneous glucose concentration is 20% lower than the blood glucose concentration, which seems contradictory to the proposed model of simple diffusion of glucose from the microcirculation to the interstitial fluid (4). Our study shows that the deposition of subcutaneous fat along the forearm, and especially at the wrist, is minute. With our findings in mind, it may be questioned whether the subcutaneous adipose tissue thickness of the forearm is deep enough to allow the subcutaneous implantation of a glucose sensor and to ensure that the device is kept in a fixed position within the tissue for longer periods. Thus, it is open to discussion whether, in the study by Shichiri et al. (3), measurements were made of the true adipose tissue glucose concentration. This may be clarified by demonstration of the exact localization of the

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sensor with ultrasonic (as in our study) or computed tomography techniques (5).

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Reply

We appreciate the letter by Bolinder et al. who questioned whether the subcutaneous adipose tissue of the forearm is thick enough to allow the subcutaneous implantation of a glucose sensor.

We have no human data on the exact localization of the sensor inserted. However, we speculate that a sensor is kept in subcutaneous adipose tissue from experiments with dogs. In these experiments, the needle-type glucose sensor was 0.8 mm in diameter and 20 mm in length. After penetrating the epidermis, a dual-lumen cannula was inserted parallel to the epidermis at a distance of 5 mm. Then, after withdrawal of the inner needle, a half-length of the sensor (10 mm) was inserted through the plastic sleeve left in situ. Therefore, the tip of the sensor might be 2–3 mm beneath the epidermis [= 10 × sine (15)] on the condition that a sensor was inserted at an angle of 10–20° with the epidermis (sine for 15° is 0.25).

We also examined the canine tissue around the sensor-inserted site, after withdrawal of the sensor. These histological examinations showed that the sensor-insertion site was kept in the subcutaneous adipose tissue, and the tip of the sensor did not reach muscle fascia. From these findings, we are convinced that the sensor tip is kept in subcutaneous adipose tissue. However, we agree with the suggestion that the use of ultrasonic or computer tomography techniques are needed to demonstrate the exact localization of the sensor in human subjects.

There still remains the question of whether a sensor inserted in subcutaneous tissue measures glucose concentration precisely in interstitial fluid of the subcutaneous adipose tissue. Recent studies with the microdialysis method or wick technique clearly demonstrated that the extracellular glucose concentration in subcutaneous tissue was almost identical with that in venous blood. Our glucose sensor is designed to measure glucose concentration in the tissue where oxygen tension is low (~30–40 mmHg; 1). Therefore, during implantation of the glucose sensor, tissue reaction to the sensor and protein fixations to the membrane covered on the sensor might affect the availability of oxygen. These mechanisms might be partly responsible for the reduction by 20% of the subcutaneous glucose concentration determined by the sensor and the delayed response to glycemic fluctuation (2,3).

In any case, further studies would be necessary to reach a final conclusion on where the best place for the sensing site is, because sensor output might be dependent on local conditions, such as interstitial fluid circulation and oxygen availability. The histological examinations will also solve these questions.

We are energetically working on the development of a glucose sensor with suitable sensor characteristics in vivo for long-term implantation.

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Novopen—A Useful Aid Also for Blind Diabetic Patients

In Norway, insulin pens, especially NovoPen (Squibb-Novo, Princeton, NJ), have become widely used (1–3). Approximately 30% of Norwegian insulin-dependent diabetic (IDDM) patients use insulin pens in multi-injection regimens. In the literature there are no reports on the usefulness of insulin pens for blind diabetic pa-

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