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NIDDM, non-insulin-dependent diabetes mellitus.

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Response to Giugliano

Dr. Giugliano's work is an interesting contribution to the literature on combination therapy, a combination withdrawal study. As we noted in our review, some patients in almost all of the studies respond much better than the average patient to combination therapy. The problem is finding identifying characteristics for prediction of that response. The current work suggests that a parallel group is present who deteriorate to a greater degree when sulfonylurea is withdrawn.

We disagree with Dr. Giugliano about what is scientifically known regarding the best therapy for NIDDM. Although we hope the ongoing United Kingdom Study will help in this regard, human experiments have not made clear whether low dose insulin is preferable to sulfonylurea or whether combination therapy is preferable to high dose insulin (>1 U $\cdot$ kg^{-1} $\cdot$ day^{-1} as defined by Dr. Giugliano) in prevention of complications if the same degree of glycemic control is achieved. We do agree that combination therapy is worth a try in individual patients on large doses of insulin with poor glycemic control. If minimal response is seen, the sulfonylurea can be withdrawn.

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NIDDM, non-insulin-dependent diabetes mellitus.

Measurement of Subcutaneous Glucose Concentration

Influence of the method on the result

In 1992, Schmidt et al. (1) used a microdialysis-based enzyme sensor, calibrated in vitro, for the estimation of the subcutaneous glucose concentration and recently extended their investigations using the same sensor technique and two additional methods: subcutaneous filtrate collection and an equilibration method using ultrafiltration (2). The subcutaneous glucose concentration appeared to be 44–46% of the corresponding blood glucose.

We have some concerns about the methods used for estimating subcutaneous glucose concentration. From microdialysis studies in the brain, it is known that the recovery of the microdialysis (=dialysate concentration of a substance/concentration in the undisturbed surrounding) is considerably lower in vivo than in vitro (3), because the mass transport of substances in the tissue differs from the situation in aqueous solutions. According to Bungay et al. (4), the recovery in vivo is considerably lower because of local drainage of the analyte leading to a concentration gradient in the surrounding of the microdialysis probe. The theoretical predictions have been verified in practice (3,5). Similar results were obtained by Benveniste et al. (6)—theoretically and practically—using a different mathematical approach.

Considering the theory of microdialysis, the subcutaneous glucose concentration might be underestimated when measured by a microdialysis-based glucose sensor, calibrated in vitro. The ultrafiltration technique removes glucose from the subcutaneous space, and thereby local drainage occurs, leading to underestimation of the subcutaneous glucose concentration. This view is supported, because the volume of the ultrafiltrate decreased and reached a constant level of 40 μl after 6 h (1).

The divergent results of Schmidt et al. (7) compared with the wick technique cannot be attributed to contamination of the wicks with blood, because wicks stained with blood were not used to measure the glucose concentration. On the other hand, implanting the wicks

at 20-min intervals could increase the local blood flow and change the capillary barrier. Thus, the subcutaneous glucose concentration is overestimated by the wick technique. For this reason we used another technique to estimate the subcutaneous glucose concentration: A microdialysis probe (outside diameter 500 μm; membrane length 10 mm) was implanted subcutaneously for 300 min in healthy volunteer subjects (n = 10). Buffer was recirculated 44 times in the fasting state, reaching 72 ± 6% of the corresponding blood glucose, and 36 times during a hyperglycemic clamp, reaching 78 ± 6% of the corresponding blood glucose (8,9).

These results are in contrast to the results of Schmidt et al. who observed a decline of the glucose concentration to 46% of the blood glucose in the hourly collected equilibration fluids of hollow fibers that were implanted subcutaneously in 9 healthy volunteer subjects. In 5 cases, 100 μl saline without glucose was filled into the hollow fibers. By removing the equilibrate and refilling with a glucose-free solution every hour, drainage of the surrounding tissue occurred, which explains the decrease of the glucose content in the equilibrate. In 4 cases, the hollow fibers were filled with 5 mM glucose, and the glucose concentration of the equilibrate decreased to 50 ± 13% of the corresponding blood glucose (Schmidt et al., 1). The high SD implies that the variation is considerable. It seems questionable, if these 4 highly variable cases allow further conclusions.

We agree with the authors that there are local glucose concentration differences in the subcutaneous space and consider a microdialysis-based glucose sensor feasible for healthy volunteer subjects (10) and diabetic patients (11,12). However we feel that the three methods of the authors influence the subcutaneous glucose concentration, leading to underestimation of the subcutaneous glucose concentration. The recirculation technique gives further insight into the measurement of subcutaneous glucose concentration.

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Measurement of the Subcutaneous Glucose Concentration

Determination of the glucose concentration in the subcutaneous extracellular space still proves to be a point of contention. Several methods were used by different research groups, all leading to different hypotheses. For several years, the wick technique was believed to be most suitable, but discussion on this item tends to continue.

Our group managed to apply three different methods leading to the same result, subcutaneous glucose concentration being about half of the concomitant blood glucose value. The onset for this study was the good correlation between in vivo and in vitro calibration factors obtained with our microdialysis based glucose sensor. The sensor constantly measured 45 ± 9% of the blood glucose value.