Review Article

Can Glucose Be Monitored Accurately at the Site of Subcutaneous Insulin Delivery?

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Abstract

Because insulin promotes glucose uptake into adipocytes, it has been assumed that during measurement of glucose at the site of insulin delivery, the local glucose level would be much lower than systemic glucose. However, recent investigations challenge this notion. What explanations could account for a reduced local effect of insulin in the subcutaneous space? One explanation is that, in humans, the effect of insulin on adipocytes appears to be small. Another is that insulin monomers and dimers (from hexamer disassociation) might be absorbed into the circulation before they can increase glucose uptake locally. In addition, negative cooperativity of insulin action (a lower than expected effect of very high insulin concentrations)may play a contributing role. Other factors to be considered include dilution of interstitial fluid by the insulin vehicle and the possibility that some of the local decline in glucose might be due to the systemic effect of insulin. With regard to future research, redundant sensing units might be able to quantify the effects of proximity, leading to a compensatory algorithm. In summary, when measured at the site of insulin delivery, the decline in subcutaneous glucose level appears to be minimal, though the literature base is not large. Findings thus far support (1) the development of integrated devices that monitor glucose and deliver insulin and (2) the use of such devices to investigate the relationship between subcutaneous delivery of insulin and its local effects on glucose. A reduction in the number of percutaneous devices needed to manage diabetes would be welcome.

Keywords

continuous glucose monitoring, type 1 diabetes, adipocytes, glucose uptake, insulin delivery

Many people with type 1 diabetes use both a continuous subcutaneous (SC) glucose monitor and a pump that delivers insulin subcutaneously. However, for concurrent use of both devices, there is currently a need for 2 skin punctures. Due to this inconvenience, there is interest in the development of a single catheter that would serve both purposes. Another reason for interest in a dual use device is the development of closed loop systems (currently not FDA cleared for general use) that require the concurrent use of a continuous glucose monitor and continuous hormone delivery.[1-8]

Many patients find that wearing a transcutaneous device leads to concern about possible dislodgement, especially during rapid motions. The need for multiple devices often impairs freedom of movement and can lead to a general sense of frustration. In addition, bacterial colonization and infection at insertion sites is always a concern,[9] and such a risk is proportional to the number of puncture wound sites.

For these reasons, several research groups have investigated the use of a single catheter that allows both glucose sensing and insulin delivery, or the use of 2 such devices in close proximity. The primary purpose of this article is to review the scientific theory and literature that address the concept of sensing glucose at or near the site of insulin delivery.

Can Glucose Be Measured Accurately At or Near the Site of SC Insulin Infusion?

Insulin regulates glucose transporters in fat and muscle cells and promotes uptake of glucose into these cells.[10,11] Thus, one might expect that glucose could not be measured accurately at the site of SC insulin delivery. In 2008, Hermanides et al[12] addressed this issue in humans who were using continuous SC insulin infusion. Each subject had 2 microdialysis sensors, one very close (9 mm) to the insulin delivery catheter and one much farther away. Blood glucose was raised and lowered during the experiments. Interestingly, this group found that the results for the near and far sensors were nearly identical. There was a trend for the delay of near sensors to be greater than far sensors, though this difference did not reach statistical significance. Calibrated data for near and far sensors in each of the 10 subjects showed that sensor

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measurement error (mean absolute relative difference, MARD) values were similar, typically 8-10%.[12] The authors concluded that continuous glucose monitoring (CGM) by microdialysis can be accurately performed at a mean distance of 9 mm from an insulin infusion catheter in the normoglycemic and hyperglycemic ranges.

Shortly thereafter, Lindpointner et al[13] addressed the same general question. Microdialysis catheters were inserted into normal volunteers who underwent euglycemic clamp experiments. Insulin was delivered through the catheters at 3 different rates, before and after which the catheters were perfused with an insulin-free solution. After beginning insulin delivery, the ratio of tissue glucose to plasma glucose (TPGR) began to decline, consistent with a local insulin effect. However, the reduction was small (15-20%) and it remained constant at this level after the 1 hour equilibration phase until insulin was stopped. Interestingly, the degree of reduction in TPGR was the same for all 3 insulin infusion rates. One explanation of this latter result is that when local concentration of insulin rises to very high levels, uptake of glucose into local adipocytes becomes maximal (saturated).[13]

In a second study from the same group, insulin delivery was periodically interrupted to extract interstitial fluid (ISF) from a SC catheter and to measure glucose. Using this method, the ISF glucose levels were quite similar to those obtained from blood, suggesting that delivery of insulin at the glucose sampling site did not lead to systematic error.[14]

In a very recent study, Hajnsek et al[15] also studied a catheter designed both for insulin delivery and for continuous measurement of glucose in SC tissue. The sensing chemistry included a glucose oxidase-bound layer of a luminescent dye. A reference oxygen sensor was included to compensate for fluctuations in tissue oxygen tension. In pigs, by optically interrogating the dye, they did not find major differences in glucose measurement accuracy among sites near insulin delivery, sites near saline delivery, and sites without a nearby infusion. More specifically, the median absolute relative errors averaged 22%, 18%, and 19% for these 3 groups. Mean absolute relative errors, which typically are greater than median values, were not reported; the degree of error for the 3 conditions was higher than with other previously published methods.[15]

We are aware of only 1 study that evaluated how the proximity of the insulin injection site relative to nondialysis amperometric sensors influenced local glucose levels. In this study, Rodriguez et al compared the effect of sensors placed as close as 5 mm to insulin injection sites ("near sensors") to sensors at greater distances ("far sensors"). In terms of the response time for the hypoglycemic effect, no significant differences were found. In terms of the percentage decline in measured glucose for near versus far sensors, there was a *lesser* decline in near sensors located 0.5 and 3 cm from the insulin injection site but not in the 2 near sensors at 1 and 2 cm from the site. These results are difficult to explain. Clearly, there is no evidence of a greater decline in sensors near the site of an insulin injection (which is what one would expect if there were local stimulation of glucose uptake by fat cells).[16] The limitations of this study included failure to provide calibrated data and the use of highly diluted insulin (10 units per ml), the purpose of which was to allow more accurate dosing. Due to the great dilution of the insulin, it may not be possible to extrapolate results from this study to standard insulin concentrations (100 units per ml).

A team from Medtronic has developed a glucose sensor and insulin delivery port situated on the same platform and in close mutual proximity (11 mm). Pump users with type 1 diabetes wore this Combo-Set in 1 location and a standard amperometric sensor without nearby insulin delivery in another location. The accuracy of the Combo-Set (97% of values in Clarke A + B) and the standard sensor (93%) were very similar, and the postprandial insulin kinetics related to the Combo-Set were typical of standard insulin kinetics.[17]

For a tabular summary of published articles on this general topic, see Table 1.

Possible Reasons for a Smaller Than Expected Effect of Local Insulin on Glucose Uptake

Given its very high local concentration in SC fat, one might expect a very large effect of SC-delivered insulin to markedly lower the local concentration of glucose. In support of this notion, manufacturers of glucose sensors typically state that users should locate a sensor at least 2 inches away from the site of insulin infusion.[18] Nonetheless, in the reports mentioned above, such an effect was small. What are possible reasons that could explain such an effect?

Possible Reason 1: Maximal Glucose Uptake Into Human Adipocytes Is Low. Despite a substantial fat mass in most humans, most of our glucose is taken up into muscle tissue.[19] At one time, based on rodent studies, it was thought that uptake of glucose into adipocytes was brisk in all mammals. However, a recent report found that glucose uptake in rodents is not typical of human physiology. Using photolabeling, Kozka et al found that the maximal uptake rate of a glucose mimic (3-O-methyl-D-glucose) was 15-fold lower in human adipocytes than in rat adipocytes. They determined that the cause of such a disparity was the much greater abundance of GLUT4 transporters in rodent adipocytes.[20] Even if injected insulin exerts a local effect before it is absorbed into blood, that effect may well be very small.

Several groups have investigated the magnitude of insulin-induced glucose uptake in fat and muscle. A report from Bjorntorp et al from the 1970s found that adipose tissue was responsible for less than 1% of glucose uptake in hyperinsulinemic nondiabetic humans.[21] The magnitude of glucose uptake into muscle tissue is far greater. Several groups have used direct muscle perfusion to quantify glucose uptake into muscle during hyperinsulinemic euglycemic glucose clamps. For example, DeFronzo et al found that glucose uptake by muscle was about 75 times greater than estimates of uptake

Table 1. A Summary of Key Publications and Findings With Regard to Continuous Glucose Measurement at or Near the Site of Insulin Delivery.

Key publication, year	Subjects, species	Glucose level	Insulin delivery	Distance insulin, sensor	Method	Observation
Hermanides et al,[12] 2008	N = 10, humans	Euglycemic, hyperglycemic	Bolus and infusion	9 mm	Microdialysis	Near and far sensors show identical readings
Lindpointner et al,[13] 2010	N = 5, humans	Euglycemic	Infusion	Co-localized	Microdialysis, microperfusion	15-20% drop in interstitial glucose during insulin
Rodriguez et al,[16] 2011	N = 10, minipigs	Euglycemic, hypoglycemic	Bolus	5-30 mm	Amperometric	Glucose decline was not greater in near vs far sensors
Hajnsek et al,[15] 2013	N not given, pigs	Hypoglycemic, hyperglycemic	Infusion	Co-localized	Glucose oxidase luminescence (optical)	Sensor accuracy not adversely affected by insulin delivery
Regittnig et al,[14] 2013	N = 13, humans	Euglycemic, hyperglycemic	Infusion	Co-localized (but asynchronous measurement)	ISF withdrawal	Sensor accuracy not adversely affected by insulin delivery
O'Neal et al (Medtronic),[17] 2013	N = 10, humans	Euglycemic, hyperglycemic	Bolus and infusion	11 mm	Amperometric	Sensor accuracy not adversely affected by insulin delivery

into fat taken from the literature.[22,23] In view of these quantitative studies, it is not surprising that recent studies found little perturbation of local glucose concentrations during SC insulin delivery.

Possible Reason 2: Absorption Into Circulating Blood Might Successfully Compete Against a Local Insulin Effect. After its injection into the SC space, the tissue diameter of a substantial insulin bolus is roughly 5-10 mm in diameter, as found by Trajanoski et al[24] and Linde and Philip.[25] However, the details of the fate of injected insulin are more complex, as reviewed by Trajanoski et al[24] and Wilinska et al.[26] The Wilinska et al study found that inclusion of a local SC degradation element (suggesting local action and uptake into adipocytes) improved the fit of their insulin absorption model. Nonetheless, their estimate of the magnitude of local degradation was quite small, about 2 mU of insulin per minute. We believe that the most likely cause of local insulin degradation is a result of its physiologic insulin action. After binding, the ligand-insulin receptor complex is internalized, then degraded in an acid environment of endosomes.[27] Although some of the insulin is taken up in this manner, we believe that the weight of evidence favors direct absorption of injected insulin into capillaries, after the slow process during which insulin hexamers dissociate into monomers and dimers.[28] Systemic absorption will thus prevent the local direct effect of insulin on adipocytes. In fact, there are 2 investigations that found local insulin degradation to be almost zero,[29,30] in contrast to the Wilinska et al report. Capillary blood flow to human adipose tissue is large (3-5 ml per 100 g of tissue per minute), which is 2- to 3-fold higher than in muscle tissue.[31] When monomers and dimers are finally made available as the hexamers degrade, this large degree of flow might well be expected to allow rapid absorption into plasma rather than the competing effect, exertion of a direct local effect on adipocytes.

Possible Reason 3: At High Concentrations, the Effect of Insulin (per Unit) Is Probably Much Less Than at Low Concentrations. DeMeyts et al discovered that when insulin-responsive cells were exposed to very high concentrations of insulin, their response per unit of insulin immediately fell to very low levels.[32] He called this phenomenon negative cooperativity, and it was later verified by Olefsky et al[33] and by Arner et al.[34] When local insulin concentrations are very high, there appears to be some degree of inherent protection against high glucose uptake. However, in contrast to the effects of large doses of some hormones originating from the pituitary and hypothalamus,[35] there is no evidence that this effect of insulin overtly blocks hormone action. Instead, it means that the incremental increase in insulin effect, as concentration increases, is less at high versus low concentrations. Thus, by itself, this concept is unlikely to account for a very low action of insulin at the site of injection, but could very well be a contributory factor. Interestingly, this effect is essentially never operative during normal physiology; it is only during artificial circumstances such as injection into fat tissue that this effect becomes important.

Other Relevant Concepts

Dilution of Glucose by Local Insulin Delivery

In addition to its physiologic effect, it is quite possible that insulin affects local glucose concentration by diluting the ISF. For this reason, in terms of experimental design, it is

important to include a control during which a non-insulin-containing fluid is infused locally in a volume equal to that of insulin. Given the fact that many of the reports cited above did not have such controls, it is difficult to report with certainty the effect of dilution. An article from Lindpointner et al[13] suggested that the effect of an insulin infusion to dilute the local ISF was minimal given their finding of no effect of insulin infusion on catheter recovery (exchange efficiency). In another article from the same group, it was determined that there was some dilution of glucose during insulin boluses but not during basal delivery.[36] To the extent that there is a degree of interstitial dilution from the insulin, it is quite likely that this glucose-lowering effect is transient. An insulin bolus is diluted rapidly as it spreads through the SC space. The further it diffuses away from the sensing elements and the more rapid its absorption into the circulation, the less effect it will have to dilute local glucose concentrations.

To the degree that there is a transient local effect of insulin delivery to perturb glucose measurement, there may be a short period of time after an insulin injection during which glucose measurements would be falsely low. If this dilution effect can be precisely defined, it is likely that a model could account for this effect and minimize the error. Even without such a correction, errors during this time frame are unlikely to be dangerous. In the event that a bolus is not followed by an anticipated meal, one can at least take comfort that falsely low glucose readings in the postbolus period would not lead to overdelivery of insulin.

Systemic Insulin Effects Might Contribute to Reduction in Local Glucose Concentration

As noted above, scientists from Graz reported that after the onset of insulin delivery, interstitial glucose underwent a small decline compared to blood glucose. Their data analysis found that the kinetics of the decline were more consistent with a local effect (rapid decline) than with a systemic effect (slower decline) of insulin.[13] However, a number of studies found that the ratio of interstitial to blood glucose is also affected by systemic insulin levels, raising the question of whether systemic effects of insulin could contribute to declines in local interstitial glucose concentration when insulin is given locally by the SC route. The earliest report of which we are aware found that in humans, SC interstitial glucose (as measured by a sensor) was lower when glucose was falling compared to when it was rising. This phenomenon led to a shorter delay of sensor glucose (behind blood glucose) when glucose was falling versus rising. Since falling glucose levels are associated with high systemic insulin levels, this finding suggested that high insulin levels reduced interstitial glucose to a greater extent than blood glucose.[37] Shortly after this report, a similar finding was reported in animals by Thome-Duret et al.[38] This French group hypothesized that, during the high insulin effect, the decline in plasma glucose results from glucose transport from the ISF into cells (the "pull" effect). In contrast, during low insulin effect and low peripheral glucose uptake, glucose is transported from the liver or gut into plasma, then *later* diffuses into the ISF (the "push" effect). One can easily imagine a situation in which, during a very high insulin effect, the fall in interstitial glucose might actually precede the fall in blood glucose. A team from Cygnus reported findings similar to those of Sternberg et al and Thome-Duret et al during tests with a transdermal amperometric sensor.[39]

More recently, using data obtained from closed loop studies and meal delivery studies in subjects with type 1 diabetes who used Dexcom sensors, some of us addressed this issue. To avoid the confounding effects of calibration error, we limited the analysis to data in which accuracy was good; poor accuracy due to calibration error can masquerade as a lead or a lag. In this study, we measured lag using 2 methods: (1) the time delay at the vertical midpoint of the glucose change (regression delay) and (2) determination of the optimal time shift required to minimize the difference between glucose sensor signals and blood glucose values drawn concurrently. The 2 methods largely agreed with one another. In confirmation of the push-pull hypothesis, we found a substantially greater lag during rising segments (average of 7-10 minutes) than falling segments (average of 0-3 minutes). As one might expect, with the lower lag during falling segments, sensor accuracy was greater in this condition. We concluded that in persons with type 1 diabetes, when noise and calibration error are minimized to reduce confounding effects, SC amperometric glucose sensors demonstrate a shorter lag duration and greater accuracy when insulin effect is great and glucose is falling versus rising.[40] This finding suggests that an effect of insulin to lower local interstitial glucose level more than the blood glucose level might be due, at least in part, to its systemic effect.

In contrast with these findings, other groups found that the lag of sensor glucose behind plasma glucose occurred regardless of whether glucose was rising or falling and regardless of systemic insulin effect.[41-43] Several workers addressed the sources of these disparities and concluded that the best explanations are differences in sensor technology and in experimental design.[43-45]

Clinical Relevance of a Dual Use Catheter

The idea of measuring glucose at or near the site of insulin delivery is relevant to several clinical situations. For example, in patients with diabetes who now use both an insulin pump and a continuous glucose monitor, the inclusion of a sensing capability in the insulin delivery catheter itself would greatly increase convenience. Similarly, in an insulin-only closed loop system, a user would not need a separate body-worn sensor. One can easily imagine a system in which there was only 1 inserted device (the sensing catheter) and 1 electronic device carried in a pocket: a device that pumps insulin, receives continuous glucose

data, and houses both the algorithm controller and user interface. For a dual hormone system (eg, insulin and glucagon), the situation is more complex but not daunting. It is quite possible that both hormones could be delivered through a single catheter, though the dead volume would need to be kept to a minimum to minimize unwanted delivery of a hormone when the pump switches to delivery of the other hormone. In addition, it would be necessary to demonstrate the mutual biochemical compatibility of the 2 formulations since there would likely be at least a small amount of mixing. Finally, it would be necessary to show that the hormone formulations were compatible with the fluid path of the pump.

Future Studies: Potential Benefits of Sensing Unit Redundancy

In a variety of fields, the concept of sensor redundancy is used to increase accuracy.[46,47] In 1996, Schmidtke et al found that by using data from pairs of wired enzyme glucose sensors, accuracy was improved compared to use of a single sensor.[48] Our group found that an array of 4 glucose sensing units in close proximity led to accuracy benefits[49] and that the use of 4 separate Dexcom glucose sensors worn concurrently markedly reduced large ("egregious") errors.[50]

We believe that the concept of sensing unit redundancy will be a fruitful area for research in the area of catheters designed both for sensing and insulin delivery. For example, the use of multiple sensing units might be useful to further investigate the proximity effect: Does the specific distance between the sensing unit and the insulin delivery site affect the accuracy with which glucose is measured? If so, an algorithm that uses data from multiple sites might well reduce sensor inaccuracy. The topic of sensing error is especially relevant to the field of the artificial pancreas. The reduction of egregious errors will help reduce the chance of serious adverse clinical outcomes, such as those due to overdelivery of insulin. In addition, multiple distributed sensing units that provide "tissue averaging" could prove provide increased accuracy in vivo. The general idea here is that there is heterogeneity in tissue characteristics such as capillary density—the use of multiple sensors might average out these effects and provide a better metric of whole body glucose.

In summary, a recent series of investigations suggests that the perturbation of SC interstitial glucose levels by local delivery of insulin is much less than what was originally believed. Several biological concepts, including the concepts of negative cooperativity and competition between insulin absorption and local action, could explain a minimal local effect of insulin in SC fat. In conclusion, the development of a dual purpose device for sensing glucose and infusing insulin is plausible and would provide a usability benefit to persons with diabetes.

Abbreviations

CGM, continuous glucose monitoring; GLUT4, glucose transporter 4; ISF, interstitial fluid; MARD, mean absolute relative difference; SC, subcutaneous; TPGR, tissue to plasma glucose ratio.

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