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A Tale of Two Compartments: Interstitial Versus Blood Glucose Monitoring

Eda Cengiz, M.D. and William V. Tamborlane, M.D.

Abstract

Self-monitoring of blood glucose was described as one of the most important advancements in diabetes management since the invention of insulin in 1920. Recent advances in glucose sensor technology for measuring interstitial glucose concentrations have challenged the dominance of glucose meters in diabetes management, while raising questions about the relationships between interstitial and blood glucose levels. This article will review the differences between interstitial and blood glucose and some of the challenges in measuring interstitial glucose levels accurately.

Not All Blood Glucose Is Created Equal

Blood glucose is generally measured as the venous plasma level. There is a 3–5 mg/mL difference between arterial and venous levels, with higher differences in the postprandial state.[1] Levels are higher in the arterial blood because some of the glucose diffuses from the plasma to interstitial fluid (IF) as blood circulates through the capillary system. Arterial blood glucose and capillary blood glucose have been shown to be almost identical in concentration,[2] even though the distribution of the glucose to the systemic capillaries does not occur instantaneously.

Glucose concentrations measured by glucose meters are whole blood levels, which can differ from plasma glucose levels by up to 11% (plasma higher). Abnormal hematocrit concentrations can result in falsely low (hematocrit >50%) or high (hematocrit <40%) glucose levels.[3] Any delay in processing or transportation of samples can decrease glucose levels by 5–7%/h.[4,5] Glucose meters use enzyme-based amperometric biosensors to measure glucose concentrations. Glucose oxidase oxidizes glucose to gluconolactone while reducing oxygen to H_2O_2. Other mediators like ascorbic acid, uric acid, acetaminophen, and salicylic acid can falsify the results by nonspecifically oxidizing H_2O_2.[3,6]

For glucose meter measurements, a skin-pricking device is used to access the dermal capillary plexus. Human skin consists of two layers—epidermis and dermis—residing above the adipose and muscle tissue. Epidermis is an avascular epithelial membrane. It has enzymes with glucose metabolizing effect.[7] Moreover, glucose is formed from the breakdown of ceramide at the stratum granulosum–corneum interface.[8] Dermis comprises many arterioles, venules, and capillaries, including a deep vascular plexus interfacing dermis and the subcutaneous tissue (Fig. 1a). Another vascular plexus located 0.3–0.6 mm from the skin surface is formed by the feeding vessels arising from the deep vascular plexus. It supplies the blood flow to the dermis and epidermis with the help of small capillary loops branching from the superficial plexus.[9] The blood sampled from the skin prick comes from the capillaries of dermis with a small amount of blood from cut arterioles and venules providing a mix concentration. Blood flow to the skin is controlled by many factors, including autonomic nervous system, temperature, hormonal changes during menstrual cycle for females, and chemical inputs.[10]

Capillary blood glucose levels at the fingertip have been shown to correlate well with systemic arterial blood glucose levels.[11] During times of blood glucose stability, identical glucose levels were demonstrated from alternate sites (e.g., forearm) as compared with finger tip samples.[12] However, at times of rapid change, mainly due to blood flow variability, levels from alternate sites differ considerably.[12,13] Capillary blood glucose measured from the forearm is lower than fingertip values at times of rapid increases (>2 mg/dL/min) in systemic blood and higher during rapid decreases.[12] Samples from the dorsal forearm have been shown to correspond better to fingertip values when compared with volar forearm samples.[14] The only exception for the alternate site testing is the palm. The skin type of the palm is in the same skin category, hairless or glabrous skin, as the fingertip, and they share the same amount of blood flow, which is considerably more (five to 20 times) than the blood flow to most alternate sites like the forearm. In that respect, blood flow to forearm and

Section of Pediatric Endocrinology and Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut.

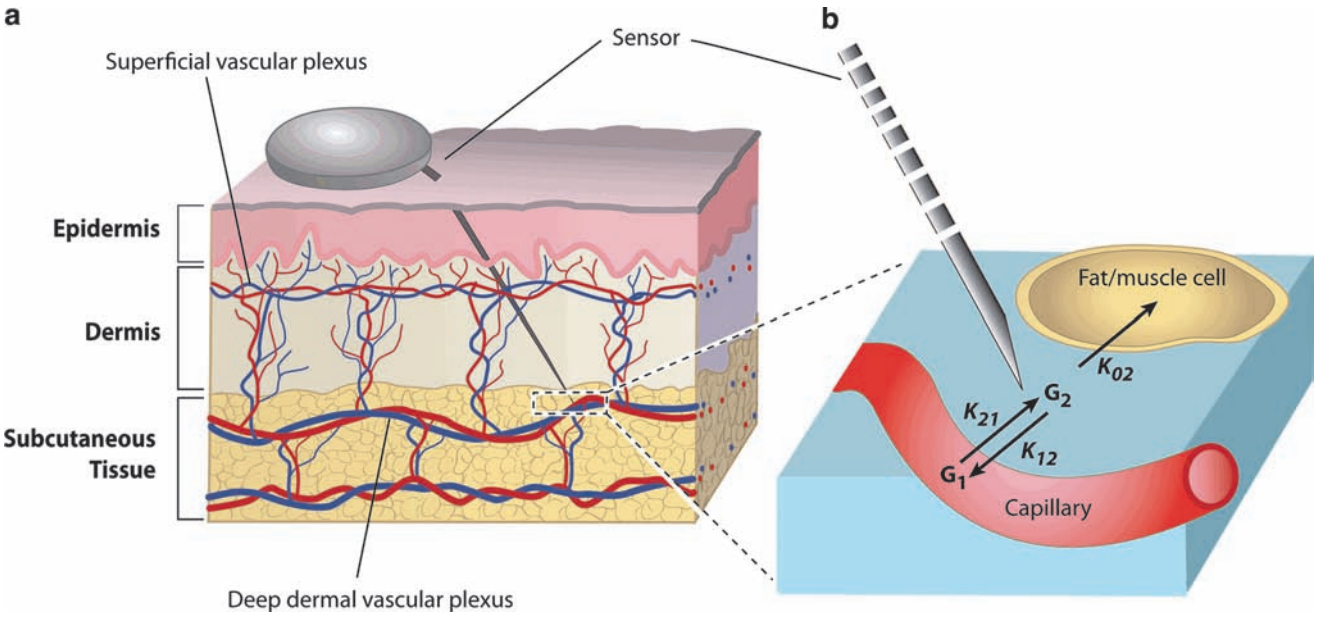

FIG. 1. Skin layers with the magnified IF space. (**a**) Vasculature in different skin layers with the CGM inserted into the subcutaneous tissue. (**b**) Diffusion of glucose from plasma to IF is in proportion to the concentration in each compartment. IF glucose is cleared by the surrounding cell uptake. Insulin may increase cellular glucose uptake after binding its membrane receptor. Adapted from Steil et al.[23] and Rebrin et al.[24]

abdomen upper dermal region has been reported to be comparable.[11]

IF constitutes approximately 45% of the volume fraction of human skin, with blood vessels contributing to the 5% of the skin volume.[9] IF is a relatively passive medium that has one-third of the total protein concentration as compared to plasma with an average albumin/globulin ratio of 1.85.[15]

The total body volume of the interstitial space is three times that of plasma; however, IF compartments around the cells are microscopic.[9] IF bathes the cells and feeds them with nutrients, including glucose, by providing a corridor between the capillaries and the cell. There is less IF in the subcutaneous tissue than in the dermis. Adipose tissue, just below the dermis, is richly vascularized with capillary walls that are relatively thinner (0.03 μm vs. 0.1 μm) than the capillaries of the dermis.[16–19] The basal membranes of the capillaries are in direct contact with the adipose cell cytoplasmic membrane.[16] The size of adipocytes might affect the amount of IF in the subcutaneous tissue, suggesting that adiposity might have an affect on IF glucose concentrations.

The Relationship Between Plasma Glucose and Interstitial Glucose

Plasma and IF have different characteristics and should be considered as separate glucose compartments. We will concentrate on the IF–plasma glucose relationship mainly in the dermal/subcutaneous tissue rather than other tissues as this is the area of interest for current continuous glucose monitoring techniques.

Glucose is transferred from the capillary endothelium to the IF by simple diffusion across a concentration gradient without the need of an active transporter.[20] Blood flow to the area dictates the amount of glucose delivered. Interstitial glucose values are determined by the rate of glucose diffusion from plasma to the IF and the rate of glucose uptake by subcutaneous tissue cells. Thus, the metabolic rate of the adjacent cells and other factors, like insulin, affecting glucose uptake by cells, the glucose supply from the blood vessel, blood flow to the area, and the permeability of the capillary that can be altered by many factors, including nerve stimulation, influence the interstitial glucose levels.[21] The time required for glucose to diffuse from the capillary to the tissue plays an important role in the lag time between changes in plasma and interstitial glucose levels, but the lag during rapid changes of blood glucose is likely due to the magnitude of concentration differences in various tissues at a time of rapid change.[22]

A two-compartment model, described by Steil, Rebrin, and co-workers,[23,24] provides an insight to the glucose dynamics between the plasma and IF compartments. As shown in Figure 1b, the equation characterizing IF glucose was described as follows: $dV_2G_2/dt = K_{21}V_1G_1 - (K_{12} + K_{02})V_2G_2$, where $G_1 =$ plasma glucose concentration, $G_2 =$ IF glucose concentration, $K_{12} =$ forward flux rate for glucose transport across the capillary, $K_{21} =$ reverse flux rate for glucose transport across the capillary, $K_{02} =$ glucose uptake into the subcutaneous tissue, $V_1 =$ volume of the plasma, and $V_2 =$ volume of the IF.

A major confounding factor in evaluating the dynamics of changes in IF glucose concentrations has been the complexity of direct sampling methods, including insertion of wicks, blister formation, lymph sampling, and ultrafiltration. Microdialysis is an indirect method of estimating IF glucose values. Lönnroth et al.[25] was the first to use this method to show that IF glucose was almost identical to venous plasma glucose in healthy individuals during steady state. Jannson et al.[26] demonstrated an increase in lag time between IF and plasma glucose when there is a rapid rise in the plasma glucose level. The data of Jensen et al.[27] revealed lower IF glucose levels than plasma glucose during clamp experiments extracting IF by suction blister technique. There are relatively

limited data on dermal IF glucose levels. Bantle and Thomas[28] demonstrated no significant difference between the dermal and plasma pre- and postprandial glucose levels in subjects with type 1 diabetes. A plasma and dermal interstitial glucose concentration lag time of 10–20 min was reported by Stout et al.[29] A recent modeling study using skin biopsy specimens of the lower leg revealed a lag time of 1–3 min in the dermis.[30] In addition to the physiological lag time, delayed availability of the glucose level depending upon the time required to collect and/or transfer the sample has been an a problem with previous methods of IF glucose sampling. Certain noninvasive methods involving optical technologies (kromoscopy, spectroscopy, etc.) to assess glucose in the IF have been in the works with their own challenges, including motion artifacts and inaccuracies stemming from inter-individual differences.[31]

Various minimally invasive or invasive methods have been used to detect glucose in IF with many of these techniques tested under different conditions (glucose infusion, glucose and insulin infusion, oral glucose tolerance test) in animal and human (with and without diabetes) studies. A wide span of accuracy has been reported from these studies, which could be due to differences in experimental conditions, methods/techniques, species, and characteristics of subjects.[32] In general, IF and plasma glucose variations were evaluated in two different conditions: steady state and non–steady state. Under steady-state conditions, IF glucose generally correlated with the blood glucose with a lag time reported to be between 0 and 45 min and an average lag of 8–10 min.[9] Increasing the blood flow to the interstitial glucose sampling site by applying controlled pressure has been shown to decrease the lag time between the blood and interstitial glucose at times of increasing plasma glucose levels.[33] The reported gradient between interstitial and plasma glucose concentrations has varied between 20%[34] to 110%.[28] During the time of decreasing glucose, interstitial glucose may fall in advance of plasma glucose[34] and reach nadir values that are lower than corresponding venous glucose levels.[35] Interstitial glucose levels have been shown to remain below plasma glucose concentrations for prolonged periods of time after correction of insulin-induced hypoglycemia.[36] These findings could be explained by the push–pull phenomenon during which the glucose is pushed from the blood to the interstitial space at times of increased blood glucose, and later on glucose being pulled from the IF to the surrounding cells during decreasing blood glucose levels.[37] This phenomenon has been a matter of debate for some time, in light of data failing to support the push–pull phenomenon and instead reporting compensation of enhanced uptake of glucose in the IF by increased plasma glucose delivery and lack of glucose removal effect of insulin in the adipose IF.[23,24]

Current continuous glucose monitoring systems have the advantage of direct insertion of electrochemical sensors into the IF space rather than transporting the sampled fluid outside the body to detect glucose concentrations. Software programs have been designed to accommodate the lag in IF glucose readings. Despite the advances in the making of sensors with new and improved designs and materials, sensor insertion causes trauma to the insertion site. It can disrupt the tissue structure, provoking an inflammatory reaction that can consume glucose followed by a repair process.[38–40] The interaction of the sensor with the traumatized microenvironment warrants the need for a waiting period for the sensor signal to stabilize, and that period varies depending on the sensor type.[21]

Because continuous glucose sensor manufacturing has not progressed to the accuracy and precision of blood glucose meter strips, sensor glucose signals must be calibrated against corresponding blood glucose meter levels. Such calibrations transforms the sensor signal into a glucose value and assumes that the plasma-to-IF glucose gradient remains relatively constant.[41] This assumption will not be valid if sensors are calibrated during rapid changes in plasma glucose, which is a major source of sensor error. The effect of sensor lag on performance is most obviously seen during periods of rapid glucose rate of change (either up or down). Sensor levels may trail glucose levels by 5–10 min during periods of rapid change, but the most important effect on lag is to introduce error during calibration, which affects long-term sensor performance. Moreover, changes in plasma–interstitial gradient in certain physiological conditions, like insulin-induced hypoglycemia, may be misinterpreted as sensor inaccuracy.[41]

Changes in sensor function that contribute to drift in sensor signal over time are due to biocompatibility problems like biofouling (obstruction of fluid exchange after nonspecific protein adsorption), passivation of electrodes (weakening of signal by reduction in conductivity), and degeneration.[42,43] The surface of the electrode can become covered with cells or other substances,[21] and the sensor can be damaged by the effects of proteolytic enzymes and free radicals.[38,40] Inflammatory cells can consume glucose around the implanted sensor,[39] and later on during the wound healing, more capillaries can supply glucose to the area.[44] Bleeding from the skin also can interfere with the sensor function.[34] Certain new technical changes like coating have demonstrated some success in preventing such sensor damage from inflammatory cells.[39,44] Recalibration at fixed intervals is currently required to deal with problems related to signal drift.[21]

Another question that needs to be addressed is if subcutaneous IF glucose measurements parallel the central nervous system glucose levels during hypo- or hyperglycemia. Nielsen et al.[45] demonstrated no differences between subcutaneous adipose tissue, muscle, and central nervous system blood and interstitial glucose levels in an animal study during hyperglycemia. Despite the lack of glucose measurement delay between these tissues during hypoglycemia, there was reduced magnitude of excursions in the central nervous system that correlated better with interstitial glucose.

Timeline for Continuous Glucose Monitors (CGMs)

Food and Drug Administration-approved and commercially available CGMs have been introduced over the last decade. The first one on the market was the MiniMed (Northridge, CA) Continuous Glucose Monitoring System (CGMS®), which stored glucose readings every 5 min up to 3 days. Sensor glucose values were available only retrospectively after downloading the sensor without the convenience of real-time values. The GlucoWatch® 2 Biographer (Cygnus Inc., Redwood City, CA) was the first CGM with real-time glucose values. However, inaccurate readings, false alarms, local irritation on the insertion site with lack of improvement in glycemic control, and hypoglycemic episodes destined the GlucoWatch to become a part of CGM history rather than a popular device in use.[46,47]

All three of the current CGM devices in common use provide sensor glucose levels in real time and use glucose oxidase-based electrochemical methods. Sensor signals are transmitted by wireless radiofrequency telemetry to the receiver. As noted above, interference with glucose readings by the sensor can occur with certain substances like glutathione, ascorbic acid, uric acid, paracetamol, isoniazid, and salicylate, which may become co-oxidized at the sensor and lead to overestimation of glucose levels.[21] Recent advances in the sensor technology were reported to overcome this problem.[48–50] The osmium complex in the wired enzyme sensor is designed to react at a relatively low potential, 40 mV, compared to the 500 mV required to reduce H_2O_2. Substances such as uric acid or acetaminophen react at higher voltages, and the interference is minimized by the low operating potential.[50]

Overall percentage of error for the CGM runs around 15%. As mentioned before, accuracy depends on multiple factors like current glucose concentration and rate of change of glucose values, with poor correlation during hypoglycemia and times of rapid change. Percentage of error for individual sensors have been reported as 17% for the Guardian® REAL-Time (Minimed, Northridge, CA),[51] 11–16% for DexCom STS (DexCom, San Diego, CA),[52,53] and 12–14% for the Navigator (Abbott Diabetes Care, Alameda, CA).[48,49]

The CGM has been declaring its use as a valuable tool for the management of diabetes therapy slowly but surely for the past couple of years. This underscores the importance of correctly interpreting and utilizing the glucose sensor data to make insulin adjustments. Patients might have a tendency to bolus insulin excessively when they experience high blood glucose alarms without taking into consideration the residual insulin from the premeal bolus or respond to declining glucose levels by decreasing the basal insulin infusion unnecessarily.[54] Even though there is not a true and tried guideline for modifying insulin dose depending on the sensor glucose levels, the feasibility of certain algorithms has been shown to be effective.[55] According to this algorithm the insulin bolus dose should be adjusted by 20% (decrease with declining glucose levels and increase with raising levels) for glucose changes >2 mg/dL. An adjustment of 10% insulin bolus is recommended for a change in glucose levels of ± 1–2 mg/dL.[55]

Clinical studies demonstrating the benefit of using CGM as an adjunct to detect glucose trends for various patient populations with and without diabetes are likely to broaden CGM use in medicine. Sensors have been used successfully to detect abnormal glucose levels in the intensive care setting despite the confounding factors like edema, hypothermia, or multiple medication use.[56] Outpatient studies including the use of CGM for diagnosing gestational diabetes and later on guiding therapy for pregnant women demonstrated promising results suggesting the possible future use of CGM in these settings.[57–60]

What Does the Future Hold?

The introduction of new continuous glucose monitoring systems has opened up a new compartment that has not been heretofore accessible—the IF space. Most clinicians are very comfortable in interpreting changes in plasma glucose because the intravascular space has been readily accessible. Changes in plasma glucose usually precede changes in interstitial glucose and thus provide an earlier warning signal regarding evolving hypo- and hyperglycemia. Nevertheless, there are a number of circumstances where there are discrepancies between plasma glucose levels and clinical symptoms. A prime example is persistence of impaired cognition for prolonged periods of time after correction of hypoglycemia, which may be related to delays in the correction of IF glucose concentrations. In circumstances such as these, it can be argued that accurate and precise measurements of interstitial glucose levels may be more important clinically. Advances in sensor technology that do away with the need to calibrate sensor signals against plasma glucose levels will eliminate a major source of sensor error and allow us to measure the concentrations of glucose that are directly available to cells much more accurately. It will also require clinicians to develop a new set of metrics to evaluate normal, as well as clinically relevant high and low, interstitial glucose levels. Even the terminology may need to change. For example, in the future, *glucopenia* rather than *hypoglycemia* may be a major obstacle to successful treatment of type 1 diabetes.

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E.C. does not have any disclosures. W.V.T. is a member of the advisory board to Medtronic and Abbott Diabetes Care and a member of the speaker's bureau for Medtronic.

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Address reprint requests to:
Eda Cengiz, M.D.
Yale University School of Medicine
333 Cedar Street, LMP 3103E
P.O Box 208064
New Haven, CT 06520

E-mail: Eda.Cengiz@yale.edu