Detection of Trace Glucose on the Surface of a Semipermeable Membrane Using a Fluorescently Labeled Glucose-Binding Protein: A Promising Approach to Noninvasive Glucose Monitoring

Xudong Ge, Ph.D.,1 Govind Rao, Ph.D.,1 Yordan Kostov, Ph.D.,1 Sunsanee Kanjananimmanont, B.S.,1 Rose M. Viscardi, M.D.,2 Hyung Woo, M.D.,2 and Leah Tolosa, Ph.D.1

Abstract

Background:
Our motivation for this study was to develop a noninvasive glucose sensor for low birth weight neonates. We hypothesized that the underdeveloped skin of neonates will allow for the diffusion of glucose to the surface where it can be sampled noninvasively. On further study, we found that measurable amounts of glucose can also be collected on the skin of adults.

Method:
Cellulose acetate dialysis membrane was used as surrogate for preterm neonatal skin. Glucose on the surface was collected by saline-moistened swabs and analyzed with glucose-binding protein (GBP). The saline-moistened swab was also tested in the neonatal intensive care unit. Saline was directly applied on adult skin and collected for analysis with two methods: GBP and high-performance anion-exchange chromatography (HPAEC).

Results:
The amount of glucose on the membrane surface was found (1) to accumulate with time but gradually level off, (2) to be proportional to the swab dwell time, and (3) the concentration of the glucose solution on the opposite side of the membrane. The swab, however, failed to absorb glucose on neonatal skin. On direct application of saline onto adult skin, we were able to measure by HPAEC and GBP the amount of glucose collected on the surface. Blood glucose appears to track transdermal glucose levels.

Conclusions:
We were able to measure trace amounts of glucose on the skin surface that appear to follow blood glucose levels. The present results show modest correlation with blood glucose. Nonetheless, this method may present a noninvasive alternative to tracking glucose trends.


Author Affiliations: 1Center for Advanced Sensor Technology, Department of Chemical, Biochemical, and Environmental Engineering, University of Maryland, Baltimore County, Baltimore, Maryland; and 2Division of Neonatology, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland

Abbreviations: (GBP) glucose-binding protein, (HPAEC) high-performance anion-exchange chromatography, (NICU) neonatal intensive care unit, (PBS) phosphate-buffered saline, (PED) pulsed electrochemical detection, (SC) stratum corneum, (TEWL) transepidermal water loss, (TG) transdermal glucose

Keywords: blood glucose, fluorescence, glucose-binding protein, neonate, noninvasive

Corresponding Author: Leah Tolosa, Ph.D., Center for Advanced Sensor Technology, Department of Chemical, Biochemical, and Environmental Engineering, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, Maryland 21250; email address leah@umbc.edu
Introduction

This article describes our initial efforts to develop a noninvasive method to determine glucose levels in low birth weight and preterm neonates. The primary objective was to develop a glucose sensor that is noninvasive/painless, is more accurate and sensitive than current sensors, is easy to use by staff, and produces rapid results. The method of sampling takes advantage of the high permeability of the underdeveloped cutaneous layer of neonatal skin. We hypothesized that this permeability will allow small molecules like glucose to diffuse passively to the surface of the skin and be available for sampling, albeit in small amounts. The glucose biosensor for this method is a recombinant fluorescent glucose-binding protein (GBP), which, in nature, is responsible for chemotaxis in gram-negative bacteria and, therefore, has undergone natural selection to be sensitive to very low (µm) levels of glucose and be highly glucose selective, even in complex media. Our group has labeled the GBP with fluorescent dye(s) and has previously demonstrated optical sensing of glucose using this biosensor.

The primary motivation for noninvasive glucose sensing is that current blood glucose monitors require intermittent blood collection through a skin-penetrating prick on the finger or the heel of neonates. This procedure is painful, messy, and not conducive to good patient compliance. The same point-of-care devices for glucose testing in adults are currently used for neonates. Thus they present added issues specific to neonates, such as threat of infection, long-term effects of pain, and potential anemia from frequent blood draws. A true noninvasive, painless, and accurate glucose sensor is a “holy grail” not only in neonatal glucose monitoring, but in adults as well. Several spectroscopic methods have been in development for years, including near-infrared, mid-infrared, Raman, photo acoustic, and terahertz spectroscopy. The methods generally involve exposing the skin to radiation and teasing out the minute signal from the blood and tissue glucose. These noninvasive methods suffer from large background interferences (generally from water but also molecules with glucose-like structures), requiring multiple corrections on the hardware and software. None have resulted in a commercial device. Previous attempts to collect and measure transdermal glucose (TG) were based on diaphoretics or external forces to enhance the excretion of glucose through the skin. The closest success among these, reaching Food and Drug Administration approval, is the Cygnus Glucowatch™. This device extracted glucose across skin by iontophoresis, but the device never made it to market. Another TG monitor developed by Echo Therapeutics Inc. uses a “skin preparer” to abrade the stratum corneum (SC) for access by a glucose oxidase sensor. This is clearly not applicable to neonates or very young children. Other workers have looked at ultrasound and chemical skin disrupters as well as application of adhesive tape to peel off the SC to increase the amount of glucose extracted through the skin. In contrast, the method for noninvasive TG monitoring described in this article is simply based on collecting the glucose that passively diffuses through skin by gently washing the skin with water.

Our earliest design for collecting passively diffusing TG is a buffer-moistened swab. To test whether glucose on the skin’s surface will be absorbed by this swab, cellulose acetate dialysis membrane was used as preterm neonatal skin surrogate. Additionally, this simple model is meant to show that varying the glucose concentrations inside the membrane is reflected in the glucose levels collected on the surface of the membrane. Initial testing of the swab on patients in the neonatal intensive care unit (NICU) proved to be disappointing, probably due to the drying of the outer layer of the swab, which created a barrier to glucose diffusion. This led us to try a more efficient direct sampling procedure based on washing the skin for a set time period and allowing glucose to diffuse. We unexpectedly found that we can pick up traces of glucose even on adult skin. These findings suggest that this method is applicable not only to neonates but also to a broader population of patients.

Methods

The Acrylodan-Labeled Glucose-Binding Protein

The fluorescently labeled GBP used in this study was prepared as described previously. Before analyzing the samples, the GBP was calibrated using standard glucose solutions. Standard solutions were prepared by dissolving D-glucose (>99.5% purity) obtained from Sigma-Aldrich (St. Louis, MO) in phosphate-buffered saline (PBS). Volumetric flasks were used to make the stock solution (100 mM) and the following dilutions: 0.5, 1.0, 2.0, 4.0, and 8.0 mM.
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The fluorescently labeled GBP has micromolar sensitivity to glucose, and its accuracy has been previously validated by high-performance anion-exchange chromatography (HPAEC) with pulsed electrochemical detection (PED) for sugar analysis. For micromolar glucose analysis, GBP has a similar accuracy with a much faster response (less than a few seconds versus ~20 min).

The Test Vessel and Sampling Swabs
To test the feasibility of collecting glucose on the external surface of a semipermeable membrane, we designed an appropriate test vessel as shown in Figure 1. The vessel is composed of two pieces (1 and 2) made of poly(methyl meth-acrylate) (Professional Plastics, Fullerton, CA). A sheet of dialysis membrane (3) with a molecular weight cut off of 3000 (PIERCE, Rockford, IL) was placed between the two plastic pieces, which are then tightly clamped together with screws to prevent leaking. The molecular weight cutoff of 3000 was chosen based on its comparability to the skin of a preterm neonate. The water loss rate of this membrane was measured to be 59 g/m²/h at room temperature. This is comparable to the transepidermal water loss (TEWL) rate of a 26-week gestational aged neonate. The inside volume of the chamber (4) is 50 ml, which is filled with glucose solution of known concentration. The swab to collect the glucose from the surface is shown in Figure 2. It was fabricated in the laboratory according to the following procedure. A piece of chromatography paper (Whatman, Piscataway, NJ) was first laminated with a layer of 75 μm thick polyethylene film (3M, St. Paul, MN) on one side. A piece of double-sided adhesive tape (Adhesive Research, Glen Rock, PA) of approximately the same size was attached onto the polyethylene side. The laminated paper was then cut into 1 cm wide strips. The protective layer was peeled off the adhesive tape on one of the strips and was adhered onto a strip of 5 cm wide polyester transparency film. Finally, the described assembly was cut into 1 cm wide strips and the swabs were stored in a petri dish.

Swab Sampling Procedure
The surface of the membrane in Figure 1 was first thoroughly rinsed with deionized water. Then the water on the surface was removed with glucose-free absorbing material, and the surface was allowed to dry at room temperature. Next, 30 ml of glucose solution was added to the chamber. A swab was placed on a clean surface with the paper side facing up and 25 μl of PBS buffer was uniformly applied onto the swab using a pipette. After the buffer was completely absorbed into the paper (~5 s), the swab was pressed onto the clean membrane surface and held for a specified amount of time. The swab was then removed from the surface and placed facing up on a clean surface. After 250 μl of PBS was added to a cuvette, the swab was dipped into the buffer, and the cuvette was shaken for 2 min. Finally, the swab was removed from the buffer, and the buffer was then transferred to a 1.5 ml plastic vial for glucose analysis with the GBP.
**Direct Sampling Procedure**

The skin surface was first washed with soap and thoroughly rinsed with deionized water. The water on the surface was removed with glucose-free absorbent material, and the surface was allowed to dry at room temperature. To delineate the sampling area, a 1 cm² plastic ring was placed onto the skin surface and held in place by a finger. We introduced 125 μl of PBS buffer on the skin surface, being careful to keep it within the area of the ring. The buffer was pipetted up and down for 5 min to thoroughly wet and “wash” the surface. The buffer was then withdrawn and transferred to a 1.5 ml plastic vial.

**Transepidermal Water Loss Measurement**

The TEWL values were measured by a Delfin Vapometer (Delfin Technologies, Finland) as instructed.

**Fluorescence Measurement Procedure**

Fluorescence intensities were measured on a Varian Cary Eclipse Fluorescence Spectrophotometer (Varian Instruments, Walnut Creek, CA). A total of 250 μl of GBP solution (~1.5 μM) was added to a 1.5 ml quartz cuvette, and the fluorescence was measured 20 times consecutively. Then 50.0 μl of glucose solution was added. After the mixture was gently vortexed for 10 s, the cuvette was then placed on the spectrophotometer and the fluorescence was again measured 20 times. The average fluorescence intensity before and after adding the glucose sample was calculated, and the signal change was obtained. The assay was performed in triplicate for each solution. All measurements were made at the same instrumental conditions: excitation wavelength 380 nm, emission wavelength 510 nm, excitation slit width 5 nm, emission slit width 5 nm, photomultiplier-tube detector voltage 900 V, and average time 0.1 s.

**High-Performance Anion-Exchange Chromatography and Pulsed Electrochemical Detection**

A DX-500 microbore liquid chromatography system (Dionex Corporation, Sunnyvale, CA) with a Dionex Model ED40 electrochemical cell and pulsed electrochemical detector was used to measure glucose in the sample solutions. The electrochemical detector was equipped with a gold electrode, a combination pH and Ag/AgCl reference electrode, and a titanium auxiliary electrode. Separation was achieved using a DionexCarboPac PA10 guard and PA10 2 × 250 mm² analytical column. The mobile phase was 0.150 M NaOH, which was obtained by mixing 0.200 M NaOH (75%) and deionized water (25%), and delivered isocratically. All solvents were degassed and kept under pressure (N₂, approximately 10 psi). Samples were introduced by an AS3500 autosampler (Spectra-Physics, Mountain View, CA) onto an injection valve (Model 9010, Rheodyne Inc., Cotati, CA) fitted with a 25 μl injection loop. Glucose was analyzed using a pulsed potential waveform controlled by Peaknet software (Dionex, version 5.21). Under the experimental conditions, glucose elutes in 4.1 min. Samples were run in triplicate, and the glucose concentration in the solution was quantified by using peak area data from the chromatogram.

**Results and Discussions**

The GBP used in this study has a single cysteine mutation at 255 where the polarity-sensitive probe acrylodan is covalently attached. The labeled acrylodan emits strong green fluorescence (510 nm) when excited with violet light (380 nm). In the presence of glucose, the fluorescence intensity of acrylodan decreases with glucose concentration. The signal change is defined as \( \frac{F_0 - F}{F_0} \) where \( F_0 \) and \( F \) are the fluorescence intensity of GBP in the absence and presence of glucose, respectively. A typical calibration curve of the glucose biosensor is shown in **Figure 3**. It can be seen that the calibration curve is almost linear at low glucose concentrations but

![Figure 3](https://www.journalofdst.org)
gradually saturates at higher glucose concentrations. The glucose concentrations in the standards before addition to the GBP solution were 0.00, 1.00, 2.00, 4.00, and 8.00 µM, respectively. Volumes of 50.0 µl of these standards were added to a 250.0 µl protein solution. Thus the final total glucose concentrations in the assay, including bound and free glucose, were 0.00, 0.199, 0.397, 0.787, and 1.55 µM.

**Figure 4** shows the effect of the time interval between when the surface is cleaned and when the surface is sampled (lapse time) on the glucose concentration in the collected samples. It can be seen that the glucose concentrations in the collected samples increase with the lapse time and gradually level off. When the surface is freshly rinsed, glucose diffuses readily across the membrane and accumulates on the surface. At 2 h, there is less glucose permeating through the membrane. The reason for this is not clear. Nonetheless, these longer lapse times are only for purposes of demonstration. At the point of care, it is practical to sample at no more than a few minutes.

**Figure 5** shows the effect of time the swab is allowed to dwell on the membrane surface on the glucose concentrations in the collected samples. As expected, the glucose concentration in the collected sample is approximately proportional to the contact time. The longer the contact time, the more glucose the test strip can collect.

**Figure 6** shows the relationship between the glucose concentrations in the chamber and the glucose concentrations in the collected samples. These data were collected at a lapse time of 30 min after surface rinsing, and the swab was allowed to be in contact with the surface for 30 s. The glucose concentration in the samples is linearly correlated to the glucose concentration in the chamber with $R^2 = 0.9666$. This implies that, by measuring the glucose on the surface of a semipermeable membrane, the glucose concentration inside the membrane can be calculated with appropriate calibration.

We hypothesized that the underdeveloped skin of the neonate should behave like the semipermeable membrane, which we chose based on the same rate of water loss of 59 g/m²/h. To test this hypothesis, we collected some samples from the skin surface of neonates in the NICU using the swab sampling procedure. It was found that the glucose concentrations in the samples collected by the swab were too low to be detectable. It is possible that, from the time the buffered saline was added to the filter paper to the time the swab was applied on the baby, the outer layer of paper dries and becomes a barrier to glucose diffusion. Indeed, we found that the swab could collect only part of the glucose on the surface. Conversely, only a fraction of the glucose that manages to diffuse to the filter paper is released to the wash buffer prior to analysis. We observed this when serum of known glucose concentration was
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Glucose molecule present in the interstitial fluid cannot penetrate through the dermis and the adipose tissues beneath the epidermis. Without some kind of chemical or physical enhancement, the general belief was that sufficient surface collection of glucose is not possible.

Up to this point, the results on the cellulose acetate semipermeable membrane support the idea that the glucose that diffused on the surface of the membrane is directly proportional to glucose inside the membrane. However, human skin is of a more heterogeneous composition than a simple inanimate membrane. Human epidermis is composed of the basal layer, keratinocytes, and an outer SC. The prevailing notion is that the SC consists of hornified cells with no interstitial fluid and, thus, is presumed to be of little value to TG sensor development. In reality, the SC is involved in dynamic processes. It is also assumed that the highly hydrophilic glucose molecule present in the interstitial fluid cannot penetrate through the dermis and the adipose tissues beneath the epidermis. Without some kind of chemical or physical enhancement, the general belief was that sufficient surface collection of glucose is not possible. With all these caveats, we nevertheless decided to test direct sampling of the skin on an adult, primarily because neonates are not as accessible for immediate testing.

First we measured the total TEWL at different sites on the body. The highest TEWL was at the tip of the fingers (~200) and lowest on the belly (~10). Based on the TEWL rates, we estimated the glucose concentrations in samples for 125 µl water to wash 1 cm² skin. The calculated results are shown in Table 1. Table 2 shows the actual glucose concentrations in the collected samples measured using the HPAEC-PED. Comparing the data for finger (in bold) in both tables and the data for the wrist (in bold/italic) in both tables, we can see that they are comparable. This shows that the glucose diffusion rate through the skin is related to the TEWL rate.

Next, we collected some samples from the skin surface of an adult before food intake and 1, 2, and 3 h after food intake. At the same time, blood glucose concentrations were measured with a Precision Xtra glucometer produced directly applied to the swab. Approximately 50% of the glucose remains in the swab, and approximately 50% is available for analysis. Thus the swab turned out to be a poor vehicle for collection of skin glucose. Consequently, the swab was completely eliminated for sampling. Instead, buffered saline was directly applied on the skin, circulated for a period of time, collected, and analyzed.

![Figure 6. Relationship between the glucose concentration in the sample and the glucose concentration in the test vessel. The error bars are the standard deviation of three different samples. The samples are collected 30 min after surface rinsing, and the sampling time is 30 s.](image)

Table 1. Estimated Amounts of Glucose Diffusing to the Skin (ng/cm²)

<table>
<thead>
<tr>
<th>Duration (min)</th>
<th>Finger</th>
<th>Palm</th>
<th>Toe</th>
<th>Wrist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3</td>
<td>0.8</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>1.7</td>
<td>3.3</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>10.0</td>
<td>2.5</td>
<td>5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>13.3</td>
<td>3.3</td>
<td>6.7</td>
<td>0.7</td>
</tr>
<tr>
<td>5</td>
<td>16.7</td>
<td>4.2</td>
<td>8.3</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>20.0</td>
<td>5.0</td>
<td>10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>23.3</td>
<td>5.8</td>
<td>11.7</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>26.7</td>
<td>6.7</td>
<td>13.3</td>
<td>1.3</td>
</tr>
<tr>
<td>9</td>
<td>30.0</td>
<td>7.5</td>
<td>15.0</td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>33.3</td>
<td>8.3</td>
<td>16.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>
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Table 2. Measured Amounts of Glucose on the Skin (ng/cm²)²

<table>
<thead>
<tr>
<th>Time</th>
<th>Forefinger (site 1)</th>
<th>Wrist (site 2)</th>
<th>Site 1/site 2²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Standard deviation</td>
<td>Average</td>
</tr>
<tr>
<td>Before a meal</td>
<td>15.84</td>
<td>0.32</td>
<td>0.34</td>
</tr>
</tbody>
</table>

² The duration of the collection is 5 min.

b The ratio of the amount of glucose collected at site 1 to that collected at site 2.

by Abbott (Alameda, CA). Figure 7 shows the comparison between the blood glucose levels and the amounts of glucose collected on the skin surface and measured by GBP. The two sets of data appear to follow the same trend. Although it is premature to assert that the blood glucose can be estimated from the TG, we contend that this method is a potential noninvasive tool for tracking trends in blood glucose. The correlation between skin glucose and blood glucose in these sets of data (although repeatable) is not yet compelling. Factors that can affect the glucose collected on the skin include the reproducibility of the sampling method, which, at present, is done manually. We are currently working on an automated sampling device to ensure uniform sampling. The SC is known to have inherent glucose from the hydrolysis of glucosylceramide. However, the rate of this reaction is slow (~3–5 µmol/h/g tissue) and, by our calculations from the time of sampling and the area of SC sampled, contributes only marginally to the collected glucose. Lastly the commercial glucose monitor is not the best tool for measuring blood glucose. For this, the gold standard YSI glucose electrode is the method of choice. We are currently conducting such tests.

Note that the amount of glucose diffusing to the adult’s skin surface is 1.6–3.2 ng/cm²/min. Such trace amounts of glucose cannot be measured with the conventional glucose-oxidase-based sensor. An extremely sensitive glucose sensor such as the GBP (Kₐ = 0.4-1.2 µm) is required. Another interesting observation is that the glucose diffusion rate through the skin is much slower than through the semipermeable membrane, even when the latter has a similar water loss rate as the skin. This means that, although water loss rate is related to the glucose diffusion rate, it is only one of the many factors affecting the glucose diffusion rate. These factors include pore size and distribution, thicknesses of the dermis and epidermis, and vascularity of the subcutaneous layer, which will require more in-depth study of skin physiology beyond this article.

To verify that the GBP results can be duplicated using a standard analytical method, we repeated the sampling procedure and analyzed the collected TG samples using HPAEC-PED. Figure 8 shows the comparison between the blood glucose levels and the amounts of glucose diffusing to the skin surface measured by HPAEC and PED. These two sets of data again clearly follow the same trend. These results confirm our findings using GBP shown in Figure 7. It should be noted that, although HPAEC and PED has the same sensitivity as GBP, it is not amenable

![Figure 7](image1.png)  
**Figure 7.** The amounts of glucose diffusing to the skin surface measured by GBP versus the blood glucose concentrations. The error bars are the standard deviations of three repeated assays.

![Figure 8](image2.png)  
**Figure 8.** The amounts of glucose diffusing to the skin surface measured by HPAEC and PED versus the blood glucose concentrations. The error bars are the standard deviations of three repeated assays.
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for quick glucose monitoring, as each analysis takes approximately 20 min. Additionally, conversion to a low-cost, miniaturized point-of-care device is realistic for the GBP but not HPAEC.

Conclusions

We showed that trace amounts of glucose that passively diffuse to the surface of a semipermeable membrane can be collected with a simple moistened swab or by direct sampling procedure. Measurements of the trace glucose levels are made possible with the highly sensitive fluorescent GBP and verified by the standard high-performance liquid chromatography method. The glucose concentration on the surface increases with the time after surface cleaning but gradually levels off. The sampling time also affects the glucose concentration in the sample collected. At a fixed lapse time after surface cleaning and a fixed sampling time, the glucose concentration in the collected sample is linearly proportional to the glucose concentration in the chamber. Because the skin is a semipermeable membrane, it is expected to behave somewhat similarly as the surrogate membrane. The TEWL of skin at various parts of the body correlates with glucose collected. Preliminary studies on adult skin before and after a meal showed that the amount of glucose diffusing to the surface of human skin follows changes in blood glucose. Note that this procedure samples the passive diffusion of glucose through the SC, and no external force (e.g., iontophoresis or ultrasound) was employed. One can argue that bathing the skin surface with buffer softens the hornified cells on the SC and induces diffusion through the concentration gradient. Nevertheless, the process is no harsher than washing the skin with water and should not produce adverse effects on the skin surface.

Automation, standardization and further optimization of the sampling device are now being undertaken and should lead to a novel, noninvasive method of glucose monitoring. Additionally, larger population studies are currently being conducted for noninvasive blood glucose monitoring using the direct sampling procedure versus YSI.

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Acknowledgments:

We thank Ms. Karuna Sri Mupparapu for the preparation of the GBP, Mr. Michael Tolosa for fabrication of the experimental chamber, and Dr. William La Course for the use of the HPAEC-PED. We dedicate this article to Dr. Freeman Hrabowski, University of Maryland, Baltimore County, president, on his 20-year anniversary as a transformational leader in higher education.

References:

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