A New Approach to Glucose Monitoring Using a Non-Invasive Ocular Amperometric Electro-Chemical Glucose Sensor for the Diabetics

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Abstract: A non-invasive method of monitoring blood glucose would present major advantages over existing methods, since the problems listed in this study are specific to invasive testing procedures. Our group will attempt to develop a new technology for the non-invasive monitoring of tear glucose levels, potentially blood glucose monitoring, using a disposable contact lens embedded with glucose sensing metal that is fast and simple, and is more economical than existing methods. Our precision tear glucose sensing system is based on measuring the tiny electric current, probably nano- or pico-ampere scale, in order to monitor the tear glucose concentration by using an electrochemical detection technique. The proposed study with a glucose sensing contact lens with implanting the metallic sensor on top of lens is capable of monitoring glucose accurately enough to satisfy medical use criteria. The cost to patients of such a method would be significantly less over time than existing methods because only a monitor with contact lens would be required, and the high monthly expense of testing strips would be avoided. In addition, patient acceptance would be very high because of the non-invasive nature and the simple and safe use of the procedure.

Key words: Glucose Monitoring, Electro-chemical Sensor, Contact Lens, Diabetes

Identification and Significance of the Problem

Diabetes mellitus represents one of the major health problems in the society. Often, diabetes leads to such problems as renal failure, foot problems, heart disease, and vision impairment. According to the American Diabetes Association, the estimated cost of diabetes-related health care in the United States is approximately $91.8 billion annually, including $23.2 billion in direct medical costs. The recent multi-center NIH studies have indicated that the health risks associated with diabetes are significantly reduced when the blood glucose levels are well and frequently controlled, indicating that it is prudent to measure the blood glucose as often as five or six times a day. Thus it is very important that proper monitoring be done by diabetics at home or at work [1,2].

At present, all existing methods of home blood glucose monitoring require obtaining a blood sample by pricking a fingertip with a needle or lancet (referred to as a "stick"), allowing the puncture to bleed until a testing strip is adequately covered with blood, and then placing the coated strip into a glucose monitor for testing. This method strongly discourages patients’ compliance and has the following serious drawbacks:

1) The procedure is invasive. For many people, the prospect of performing 5 or 6 "sticks" daily is intimidating and painful. In addition, it provides a significant risk for infections.
2) The procedure for testing is laborious and it requires thorough hygiene (washing the hands, cleaning the area that is to be "stuck", etc.). Many people have trouble learning how to test their own blood for glucose.

3) There is a very small margin for errors in the testing procedure, and thus many individuals do not obtain accurate results due to poor testing practices.

4) The procedure is expensive. Although the current marketing strategy employed by most manufacturers is to sell the monitor rather inexpensively, the test strips remain expensive, routinely costing about 80 cents each. Thus frequent blood glucose tests, requiring 5 or 6 strips daily, can cost patients over $1,000/year.

Clearly, non-invasive or less invasive methods of monitoring blood glucose levels would present major advantages over existing methods. We will develop a new technology for a non-invasive monitoring of glucose levels in tears using a disposable contact lens type electrodes and electrochemical detection. Our tear glucose sensing system is based on measuring a very low current, probably in a nano- or pico-ampere scale. This current would be directly proportional to the tear glucose levels, and therefore, should reflect directly glucose levels in blood. The proposed glucose sensing contact lenses with implanting the metallic sensor should be capable of monitoring very low glucose levels with the accuracy and precision that would satisfy medical use criteria; and this method is expected to be fast and simple. The cost of the proposed testing device would be significantly lower than for existing methods because only a monitor with contact lens would be required, and the high monthly expense of testing strips would be avoided. In addition, the patient acceptance for this new methodology is expected to be high due to its non-invasive nature, and its simple and safe sampling and testing procedure.

**Background**

There has been an increasing demand for continuous, non-invasive glucose monitoring techniques due to the increasing number of people diagnosed with diabetes and the recognition of the fact that the long-term outcome of these patients can be dramatically improved by a careful frequent and accurate glucose monitoring and control. In this part of the proposal, we will review several of the newest minimally invasive and non-invasive glucose monitoring technologies under development or introduced to current market.

- **Near infrared (NIR) spectroscopy:** Near infrared (NIR) spectroscopy utilizes an external light source with wavelengths in the infrared spectrum near the wavelength of visible light that penetrates a body part. Part of the penetrating light is absorbed by glucose. The amount of energy absorbed is analyzed by a technique called spectroscopy and is compared to a detection beam and then is converted into a blood glucose value. The major problems with using this technique are the frequent recalibration, the relatively low level of radiation absorbed by glucose and the possible absorption of energy by other substances or medications [3,4].

- **Mid infrared (MIR) spectroscopy:** The body emits thermal radiation. When the energy exits the body, part of it is absorbed by glucose. The absorption in the "glucose band" is related to its concentration. The amount of energy absorbed is determined by spectroscopy and converted to a blood glucose value. The main difficulties of this technique are very small signal size of human thermal emissions and inconvenient procedures of the prototype device [5,6].
• **Radio wave impedance:** When an alternating electric current penetrates a solution, the amplitude and phase of the current are attenuated (thinned) in proportion to the concentration of the solution. In blood, glucose is the substance present at the highest concentration compared to other solutes. The radio wave or current is applied to a body part like a finger and the exiting current is compared to the reference current and the difference represents the impedance caused by glucose. The glucose concentration in blood can be calculated from a measurement of the impedance to radio wave energy of a fingertip. A major potential problem occurs when impedance is also affected by factors other than glucose, which must be accounted to determine the relationship between impedance and blood glucose concentration [7].

• **Optical rotation of polarized light:** The aqueous humor of the eye is the transparent liquid present between the cornea and the lens and its concentration of glucose is proportional to that of the blood. If this technique applies a beam of linearly polarized light to the aqueous humor solution, the beam is shifted by an angle proportionate to the concentration of glucose. This angle can then be converted to a glucose concentration. Since the concentration of glucose in this tissue is very small, the angle of rotation is also very small and one needs a highly sensitive system to convert this angle into actual blood glucose equivalent. Also, there is a delay between blood glucose and aqueous humor glucose. In vivo application in humans has not been performed [8,9,10].

• **Fluid extraction from the skin:** This technology extracts and measures tissue fluid from skin known as reverse iontophoresis. Reverse iontophoresis involves application of an electrical current to the skin followed by extraction of fluid. The glucose concentration of this extracted fluid can be measured and is proportional to that of blood. Although this technique is the only noninvasive glucose monitoring method capable of measuring blood glucose levels continuously without patient effort, there are several problems to be used as a method for blood glucose measurement. First, there is a lag time of at least 20 minutes between blood glucose and skin fluid. Second, the technology should be highly sensitive and accurate enough to monitor the glucose concentration in this fluid which is 1/1,000 that of blood glucose. Third, wrist skin can be adversely affected by prolonged reverse iontophoresis. However, the system using fluid extraction technique, called GlucoWatch, has been introduced to the market and reported to produce clinically acceptable results for 95% of its measurements [11, 12].

• **Interstitial Fluid Harvesting:** This technology for noninvasive monitoring involves transcutaneous harvesting and measurement of interstitial fluid from skin. Prototype devices using this technology are accurate and small in size. While previously mentioned technologies produce neither skin trauma nor pain, transcutaneous harvesting of interstitial fluid can be accomplished with nearly no skin trauma and minimal sensation. Therefore, this technology is classified as invasive method. This method, known as MiniMed, uses a small sterile electrode containing the enzyme glucose oxidase. This is inserted under the skin or the abdomen with a introducer-needle, then sealed and secured in place with a medical dressing. When glucose in the interstitial fluid reacts with the enzyme, there is generation of electrons, which produce an electrical microcurrent. The concentration of interstitial fluid glucose has been shown to be equivalent to that of blood glucose when blood glucose level is stable. Since interstitial fluid technology shares a problem with invasive methods for blood glucose monitoring, this method may potentially harm the skin [13].
Glucose sensing contact lens with fluorescence detection: This new technology has been developed for the non-invasive monitoring of tear glucose using a daily use, disposable chemical contact lens, embedded with sugar-sensing boronic acid containing fluorophores. This sensing technique uses a concept that glucose levels in tears correlate well with blood levels and can be used routinely in monitoring glycemic control. The contact lens is made using a meshwork that traps fluorescent molecules inside the lens. The diabetic inserts the contact lenses in the usual way, and then holds the light device up to the eye and activates it, sending a small burst of glowing light into the contact. The fluorescent molecules in the lens bind to and react with the glucose in the diabetic’s tears. The device “reads” the wavelength of the fluorescence reflected from the contact lens and translates the reading into a measure of the glucose. Higher levels of fluorescence mean higher levels of glucose. The lenses have a 90% response time of about 10 minutes, allowing the continuous and non-invasive monitoring of tear glucose levels. Although this method employs an excellent idea, it requires too many complicated steps to be used by diabetes patients. It would be a major problem to many diabetics since this technology requires patients to wear a chemical contact lens permanently for the continuous monitoring of tear glucose [14, 15].

The promising technologies listed above are currently investigated as non-invasive tools to detect blood glucose levels. Although recent advances in basic research and clinical applications in the noninvasive glucose monitoring are very encouraging for the future of this field, the results of currently introduced techniques in this field are still far from satisfying requirements in terms of a noninvasive glucose sensor. Therefore, it is necessary to develop a new technique satisfying the criteria such as accuracy, low cost, simplicity in sampling and testing, portability, and safety in use.

Plan of Study and Methodology
Michail and co-workers [16] first demonstrated elevated tear glucose levels during hyperglycemia. They have also shown that the tear glucose concentration follows blood glucose level, and the glucose between blood and tissue fluid exists in an analogous manner to the equilibrium. Many scientists have reported that actual glucose concentrations in tears are low and in the range of 50-500 \( \mu M \). More recently, Chatterjee et al. [17] and Zhu et al. [18] attempted to find out the relationship between tear and blood glucose concentrations and to develop a rapid method of detection of tear glucose level semi-quantitatively with glucose oxidase enzyme impregnated strips and to evaluate its role as an indicator of blood glucose level. The concept of using tear fluid glucose will be employed as a way to follow the level of blood glucose in this study.

An invasive but continuous glucose monitoring system, known as interstitial fluid harvesting, involves placing a needle under the skin, which sends data through a wire running through the skin to a monitor worn by the patient. This system uses an adhesive to stick to the skin to allow it to come in contact with a small electrical current that begins a process called reverse iontophoresis uses electric current to introduce ions into the body. Although this method gives highly accurate results, it has some limitations; since a swelling around the needle occurs very frequently, this device requires frequent calibration via fingerstick tests and frequent replacement of a needle. Additionally, this device may result in some local skin irritations after its use. This electrochemical methodology will be employed in this work to monitor tear glucose concentrations in conjunction with a non-invasive testing that can eliminate problems listed above.
The study presented here will introduce and provide basic scientific and engineering data on a new approach using an electrochemical contact lens sensor that measures glucose levels in tears. Changes in the glucose concentrations can be monitored by measuring the amount of electrical current with varying the frequency in order to optimize the impact of tear glucose on the electrical current. (The measured current is proportional to the glucose concentration). We will create an electronic contact lens that will contain a metallic glucose sensor at the edge of the contact lens that can be instantly worn by a diabetic patient in order to measure his or her blood glucose levels. The proposed research will introduce the concept of using the glucose concentration in tears as a detection of the blood glucose concentration. This project is based on two basic facts: (1) the concentration of glucose in tears is directly proportional to the blood glucose level and it follows the changes in the glucose level without a significant delay and (2) an amperometric glucose microsensor can detect the level of current which is proportional to the glucose in human blood serum. The new contact lens with embedded electrochemical sensor, which can detect the tear glucose level, will be constructed and applied to provide preliminary results for the future applications.

In an electrochemical glucose sensor, an enzyme, glucose oxidase, acts as a biorecognition element, which recognizes glucose molecules. Molecules of this enzyme are immobilized at the electrode surface, which acts as a transducer. As soon as the enzyme recognizes the glucose molecules, it acts as a catalyst to produce gluconic acid and hydrogen peroxide, \( \text{H}_2\text{O}_2 \), from glucose and oxygen from the air. At appropriate potentials, \( \text{H}_2\text{O}_2 \) is reduced at the electrode surface (see Scheme 1). The total electrode current is directly proportional to the number of electrons transferred due to the reduction of hydrogen peroxide, \( \text{H}_2\text{O}_2 \) (2 electrons per one molecule of \( \text{H}_2\text{O}_2 \)); this electron flow is directly proportional to the number of glucose molecules concentration present in blood. First, we will investigate electrochemical glucose electrodes to find the sensitivity between current and glucose concentration by using electrochemical instrument\(^1\) as shown in Figure 1.

**Scheme 1:**

\[
\text{Glucose} + \text{O}_2 + \text{H}_2\text{O} \rightarrow \text{Gluconic acid} + \text{H}_2\text{O}_2 \quad \text{(enzyme present)}
\]

\[
\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}^+ + 2e^- \quad \text{(electrode reaction)}
\]

**Figure 1:** Schematic drawing of an initial design for the glucose sensor.

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\(^1\) Electrochemical analyzer
Our goal is to produce a new non-invasive glucose-monitoring device that can be used instantly by the diabetic patients. The block diagram of the glucose sensing system including main components is presented in Figure 2. A precision voltage controlled oscillator is used to provide various frequency signals. The signal is then pass through a medium filled by d-glucose solution. The magnitude and phase of the signal from the electrochemical sensor through the medium are proportional to the concentration of the d-glucose. The lock-in amplifier will provide an output signal that will be a dc voltage proportional to the amplitude and phase of the applied signal present in the detected signal from the electrochemical sensor. This dc output voltage will be finally monitored by the precision oscilloscope. Therefore, the lock-in amplifier will provide very accurate output dependent on detected and reference signal as a phase and frequency locked detection of the applied signal component. Second, we will demonstrate system and apply additional dc current directly to the electrochemical electrode in order to stimulate more electrochemical activities and investigate the relationship among conductance, current, and glucose concentration by utilizing very high sensitive conductivity and current sensors 2,3.

**Figure 2:** Block diagram of the precision electrochemical glucose sensing system.

Third, we will also develop a new specially designed sensor such as disposable plastic electrochemical contact lens embedded with glucose sensing electrode, as shown in Figure 3. This sensor will produce very low currents as a response to the glucose presence in tears of an eye (according to Scheme 1). We will combine the contact lens sensor with electrical measuring system shown in Figure 2. Then we will test this system with glucose solution of various concentrations. In the preliminary phase of this research, fresh solutions of deionized water with 50, 100, 150, 200, and 250 mg/dl glucose will be used; these levels are considered as a physiological range for glucose in blood. Later on in our studies we will test much lower concentrations of glucose, and we will introduce other ions that would mimic a physiological composition of human tears (e.g., Na⁺, K⁺, Cl⁻). The lens will be able to trach tear glucose level because the output electrical current, in a nano- or pico-ampers range, is directly proportional to the glucose concentration.

**Figure 3:** Schematic drawing of an electrochemical contact lens.

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2 Accumet AB30, Fisher Scientific  
3 Pico-ammeter, Keithley
Contact Lens Design

The proposed new concept of monitoring blood glucose for the diabetic patient is both innovative and challenging. As a contact lens clinician point of view, there are two challenges using a soft disposable contact lens with a new electrochemical glucose sensor. First, how do we get the electrochemical sensor to stabilize on the eye to take a glucose concentration level? In the Figure 4 (a) and (b), both pictures show how a rigid and soft contact lens normally fit on the cornea of a patient. By applying the sensor on top of both lenses, in Figure 4 (a) and (b), the sensor would move and cause inaccuracy of readings. The proposed answer to this question is to have a disposable lens designed so that the electrochemical sensor would piggyback the contact lens in the proposed cutout of the lens as shown in Figure 4 (c). The second challenge in this study is to determine which lens material would be appropriate that would absorb the very low currents as a response to the glucose presence in tears of any eye. Various lens materials will have to be tested in order to see which material will be the most sensitive for monitoring glucose levels in the tears. Results of our tests will enable the research team to have a disposable contact lens designed that will be sensitive to the electrochemical sensor readings in order to determine the glucose levels in the tears.

![Figure 4: Potential methods for the implanting electrochemical sensor on top of contact lens.](image)

Conclusion

The proposed new electrochemical glucose sensing technique using the contact lenses has many potential advantages over currently existing invasive and non-invasive methods. A highly precision voltage source, accurate electrical components including electronically embedded contact lens, and a sophisticated analyzing system such as precision current monitor will be used in this study. The contact lens glucose sensing method introduced in this work can be miniaturized using current integrated circuit and semiconductor technology, and has the potential to provide a low cost, fast, stable, and compact non-invasive glucose sensor for the diabetic patients within near future.
References:


