Non-Invasive Glucose Detection Based on Biosensors

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Abstract. Currently, diabetes is one of the most serious and widespread diseases which has a relatively high mortality rate and needs long-lasting therapy to maintain the blood glucose level. In this case, physicians need to regularly detect patients' blood glucose levels to adjust their treatments and prescribes. The traditional measuring method for monitoring blood glucose is through pricking fingers, which is a kind of invasive method. Though measurement through blood can ensure the precision of the detection, there are still many disadvantages such as increasing the risk of infection that this noninvasive method can bring. Therefore, many scientists tend to put more effort into studying non-invasive biosensors for frequent blood monitoring. To ensure long-lasting measurements of blood glucose, biosensors are required to have high-quality, efficient, and precise. In this case, this passage will discuss different non-invasive biosensors by introducing their mechanisms, comparing the experiment data, and comparing their advantages and disadvantages.

Keywords: Glucose Monitoring, Non-Invasive Biosensor, Interstitial Fluid, Spectroscopy, Saliva.

1. Introduction

Diabetes and hypoglycemia are two of the most common disease all around the world and more than 422 million people have diabetes today. To maintain blood glucose at a normal level, people need to reduce the intake of sugar and carbohydrate. However, since sugar and carbohydrate are necessary for our body to maintain basic metabolism and provide us energy, people with diabetes need to frequently monitor their blood glucose and make a new diet. Most people today use invasive biosensors to monitor their blood glucose by pricking their fingers. This invasive method can not only increase the infection rate for patients but also reduce patients' willingness to take the detection, especially for young children. However, nowadays, many scientists and researchers have studied many non-invasive glucose detection methods that can provide regular, non-painful detection for the patient. Figure 1 shows an overview of the biosensors for blood glucose monitoring we currently have [1]. The skin-like biosensor and the GlucoWatch biographer, spectroscopy biosensor, and saliva biosensor are three of the most advanced and have the most prospect of development. This passage will first introduce the basic mechanism of each biosensor and then use the data from the experiments to compare each's advantages and disadvantages, and finally give suggestions for the future development of the non-invasive glucose detection biosensor.

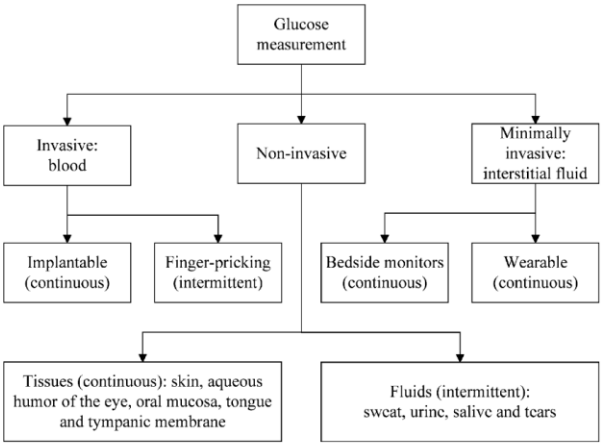

Figure 1. An overview of current glucose detection biosensors [1].

2. The main non-invasive biosensor we have today

2.1. Skin-like wearable glucose biosensor and GlucoWatch

After the emergence of some crucial techniques used in non-invasive, wearable glucose biosensors based on monitoring in interstitial fluid, recently, Wang et al. have developed a non-invasive, wearable, tattoo-based glucose detect biosensor [1]. Generally, the biosensor itself is like a tattoo, a flexible platform less than 2mm thick. It first attached a thin paper battery to the skin's surface, then create the electrochemical gradient, allowing glucose to move from the vessel to the skin's surface. Then a chip with five different layers can help transfer sugar molecules into electrical signals, which a biosensor can detect. The skin-like glucose monitoring biosensor is now proven to be effective in measuring the glucose level in a healthy person.

To be more specific, the skin-like glucose biosensor uses a kind of dual electrochemical channel (ETCs) and hyaluronic acid (HA). One channel is the anode channel and one is the cathode channel. At the anode channel, HA penetrates tissue and gets into the interstitial fluid (ISF). Since HA is a kind of biopolymer ubiquitous in biological tissue and anionic, it can be transdermally repelled into the ISF. As HA enters the ISF, the osmotic pressure will be increased [2]. ISF tends to flow from the high-pressure capillary region to the low-pressure body tissues region. Generally, the flow of the ISF in and out of the blood vessel depends on the difference in pressure between each side of the capillary wall. Normally, depending on the hydrostatic pressure, the ISF can be transported into the body tissues from the blood vessels. In contrast, osmosis pressure contributes to ISF reabsorption- the movement of ISF from body tissues into the blood vessel. Thus, the increase in osmotic pressure will disturb the filtration equilibrium and the ISF reabsorption, resulting in an increase in filtration and a decrease in reabsorption. What's more, the high concentration of glucose in ISF can also contribute to an increase in the flux of reverse iontophoresis in low-current conditions. As a result, more glucose in the ISF can be "extracted" from the capillary to the skin surface and be detected by the five-layer chip on the biosensor. Figure 2 generally shows how ISF glucose is extracted from tissue with ETCs.

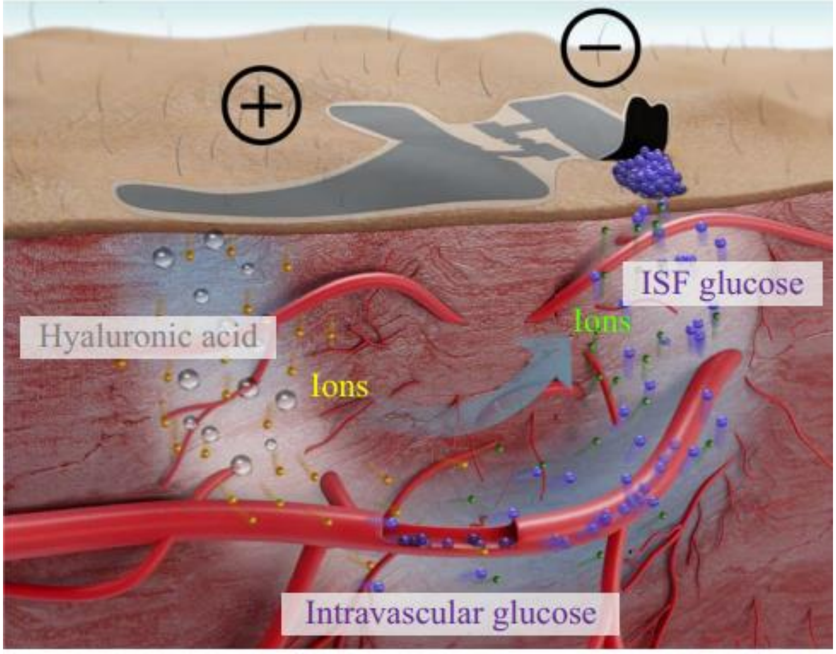

Figure 2. Schematic of the ETCs, showing HA penetration, refiltration, and outward transportation of glucose [3].

Next, the skin-like glucose biosensor can measure the glucose from the capillary. The layers of the biosensor, from bottom to top, are polymethyl methacrylate, polyimide, a nanostructured deposited gold thin film, an electrochemically deposited nanometer transducer layer, and a transfer/glucose oxidase immobilization layer [3]. With the five-layer chip, the biosensor can detect the concentration of glucose. While the ISF sample is obtained, a “rose” system is used to carry the sample and thus the glucose concentration can be detected through the sample. To be more specific, when a liquid sample is placed on the last layer of the structure, the water in the liquid will evaporate, and the liquid will stick to the edge of the layer. As more and more water evaporated, the edge of the liquid will uplift the edge of the layer. Eventually, the whole layer will be separated from the original biosensor, which can be taken and detected to measure the glucose concentration. By involving this process, the sample can be obtained with the minimum interference, and thus increase the precision of the detection.

Skin-like glucose biosensors have many advantages and calibrations to ensure precise glucose level measurement. The sensor uses a “two-electrode system” in the measurements, which can ensure high accuracy in very small current measurements. Sand dune nanostructure has also been designed to obtain nanometer-thick and high-quality Prussian blue films to ensure the toughness of the sensor. In addition, the biosensor uses a nano-structured gold layer instead of the original natural gold layer. Since the skin-like biosensor needs to be very thin to ensure its accuracy, this demand brings a challenge to the quality of the biosensor. In another word, when the structure of the biosensor is too thin, it may be more likely to break. In this case, by using the nanostructured gold layer, due to its high stiffness, the nano-gold layer can improve the whole tenacity of the biosensor [3].

Similarly, GlucoWatch uses techniques that also extract glucose from body tissue through non-invasive methods. Basically, GlucoWatch uses three separate technologies [4]. First, to extract glucose from the human body, the biosensor adopts a reverse iontophoresis technology. Since skin is negatively charged at physiological PH, sodium ions which are positively charged are the major carriers of current. The movement of sodium ions toward the iontophoretic cathode leads to an electro-osmotic flow toward this electrode. As a result, glucose can be extracted at the cathode site. Second, as the glucose has been extracted from the body, the biosensor needs to accurately measure this small amount of glucose. To achieve an accurate measurement, the GlucoWatch biographer utilizes an amperometry biosensor. Through the reaction of glucose and oxygen forming gluconic acid and hydrogen peroxide under the catalyst of glucose oxidase enzyme (GOx), the amount of the hydrogen peroxide is detected at a working electrode containing platinum via an electrocatalytic oxidation reaction to produces a current, and thus the current can be detected by the circuitry, which is the third technologies. In clinical trials under laboratory, stimulated home and actual home circumstances, the GlucoWatch can have a good performance with relatively high accuracy in glucose detection [4].

2.2. Blood Glucose Biosensor based on Raman spectroscopy

Raman Spectroscopy is a chemical analysis and a light scattering technique to provide detailed information on chemical structure, concentration, liquid constitution, and other physical or chemical properties of a substance. When light crosses a substance, it may interact with the chemical bond between its molecules and thus can receive light across the substance to determine its structure. To be more specific, when dense laser light is scattered by a molecule, most of the scattered light is at the same wavelength. However, there is still some scattered light at different wavelengths, and the wavelength is determined by the property of the molecule, and thus the scattered light, called Rama Scatter can be detected and help analyze the property of the substance [5].

Currently, since the increasing rate of diabetes, more non-invasive glucose monitoring facilities are required. In this case, various optical detecting methods have been used, and vibrational spectroscopy using near-infrared absorption and Ramen spectroscopy has been proven to be the most efficient and precise. Since glucose is an optically active substance, the light will refract to a different angle when light passes through the glucose, scattering the light, and the angle is determined by the glucose concentration [6].

The biosensor uses a quartz crystal balance sensor to detect the acetone concentration, a substance that can represent glucose concentration that is when blood glucose is low, the acetone concentration will be relatively high. A circuit is using an impedance spectroscopy circuit and multi-wavelength near-infrared spectroscopy to detect the scattered light and use the wavelength they collect to analyze the concentration of acetone in the blood [5]. To be more specific, the biosensor adopts the optical coherence tomography technique to ensure timely and precise glucose detection. The optical coherence tomography technique use interferometer can detect interferometric signals. The interferometric signal includes a portion of the light that is scattered back from the tissue and the light returned from the reference part. The combination of these two signals includes the delays of the light scattered back and the changes in scattered light varied from different glucose concentrations will be used to examine the glucose concentration [7].

However, there are a lot of challenges for vibration spectroscopy detection. While the biosensor is detecting the scattered light’s wavelength, the transition bands are very broad, which may lead to a large degree overlap of signal both from the substance that needs to be detected and other inference substances. Although some calibration modes can eliminate the interference in the detection, still since some calibrations are based on the relation of glucose detection, using the mold may also affect the precision of glucose detection. In addition, since other molecules or activities may also contribute to the different wavelengths of scattered light, the analysis based on the wavelength can be imprecise. As we study less about other factors’ relationship with the scattered light and wavelength, currently, it is nearly impossible to ratify the data [8]. Currently, a reliable and accurate non-invasive glucose monitoring biosensor that depends on spectroscopy is yet to exist. Nevertheless, there are still some advantages to the optical biosensor. For example, Raman spectroscopy has high molecular specificity, which can contribute to a harmless detection for the user and be more precise. Furthermore, the price of the biosensor is relatively low compared to other glucose biosensors.

2.3. Biosensor based on saliva measuring

Though glucose measurement through saliva drew little attention, and there is no suitable product for glucose monitoring at home or daily use, saliva glucose detection can still be a potential non-invasive alternative for undiagnosed diabetes measurement.

Experiments show that in the saliva from people at different intervals for fasting, random postprandial levels, saliva from people with diabetes tends to have high glucose levels. This demonstrates that the glucose concentration in saliva is highly statistically significant, which indicates that glucose detection through saliva is feasible [9].

Wenjun Zhang proposed a nano-biosensor with relatively high precision. The biosensor includes single-walled carbon nanotubes and multilayers of chitosan, gold nanoparticles, and glucose oxidase, using a layer-by-layer assembly technique. The researcher uses Scanning Electron Microscope to observe the detection result in a buffer solution with one layer of GOx and three layers of GOx coating with poly allylamine/ single-walled carbon nanotube suspension/(chitosan/gold nanoparticles/GOx)3 films while glucose is present in the condition. Generally, the chip monitors glucose levels by tracking the electrons that pass the glucose oxidase enzyme coated on the electrode. The adaption of SWNT-chitosan-gold nanoparticles can facilitate the electron transfer between the center of glucose oxidase and the electrode, which can eliminate the limitation of the redox effect in bio-electrocatalytic applications [10].

The result reveals that there is a significant correlation between glucose levels and saliva. After intake of glucose for two hours, the saliva has proven to be capable of measuring glucose levels. Thus, the biosensor can be adapted to monitor saliva glucose and speculate blood glucose detection.

3. Discussion

To discuss the advantages and disadvantages of all three biosensors, experiments must be taken to examine the actual efficiency of the biosensors. The experiment done for the skin-like glucose biosensor has revealed the high precision of glucose detection among healthy people. However, drawbacks remained for the biosensor. No evidence has proved that the biosensor can be used appropriately to detect people with high or low glucose levels. In addition, the skin-like biosensor is single-used and needs to be replaced by a new one after one measurement. Efforts are still required to make the biosensor for continuous, low-cost measurements. For the GlucoWatch biographer, its performance in clinical trials is relatively successful. In all three trials under a laboratory environment, stimulated home environment, and actual home environment, experiments reveal that the biographer can have a well-precise detection. In addition, by having a rich stream of glucose readings and alert function to remind patients, GlucoWatch biographer can enable their patients to better control their regimens without worry about hypoglycemia and hyperglycemia. In the experiment for spectroscopy biosensors, the result reveals that the received scattered light cannot offer a precise concentration degree, especially when detecting out from the skin layer. The limitation of the precision of the spectroscopy includes the assimilation of light from other biological chromophores, the interference brought by stratum corneum, calibration, physiological standard, environmental factors, and the wavelength that is selected to use in the sensor. In addition, Raman spectroscopy is less likely to be calibrated through different modes, which may lead to more inaccuracy of the detection, concluding that more effort needs to make to improve the calibration process of the biosensor. For saliva detection, experiments reveal that the detection is highly dependent on individuals, which means that the actual glucose can vary even though the test of saliva glucose has the same result. Still, relative research is required since the experiment do not include people with diabetes and the data on the impact that different age, gender, and health condition have brought.

4. Conclusions

There are many kinds of noninvasive biosensors for blood glucose detection that have emerged and take into an experiment to detect their efficiency. Generally, compared to invasive detection by drawing blood through pricking fingers, the non-invasive biosensor is capable for decrease the risk of infection and increasing patients' willingness to follow the detection. However, all of the biosensors that the passage discusses and the non-invasive glucose detection people currently are less precise than blood glucose detection. Since most of the non-invasive biosensors are highly individual-dependent, which means that their precision can be highly affected by individual variation and other factors such as what the patient eats and their physical state. Yet the experiments have not examined how many factors may contribute to the precision of the detection and how to calibrate these factors. Currently, GlucoWatch can be the most precise biosensor for glucose monitoring compared to others discussed in the passage. However, for all four biosensors, experiments have shown that there is still a huge gap between noninvasive detection and invasive detection, which reveal that the precision of the biosensor is the most significant issue that should be dealt with. Despite the comparison to invasive detection based on comparing their precision, many non-invasive biosensors are unable to achieve continuous glucose detection which can help patients regularly monitor their blood glucose and adjust their treatment. For example, both saliva biosensors and skin-like biosensors are unable to have long-lasting detection. Furthermore, the cost of the non-invasive biosensor can be relatively high. The skin-like biosensors have a high cost since their material. Last but not least, all three kinds of biosensors are only tested in the experiment to detect people with normal glucose levels. No experiment has demonstrated that they can also have proper functioning when detecting people with abnormal glucose levels since when too high or too low glucose concentration may also contribute to the inaccuracy of the biosensors. In conclusion, there are still many challenges for noninvasive glucose monitoring biosensors including precision, cost, and lack of experiments.

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