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포도당 모니터링을 위한 비침습적 정량화 방법

Non-invasive quantification methods for glucose monitoring

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Abstract

Diabetes mellitus is an abnormally high glucose level in the bloodstream. Several pharmaceuticals are administered to diabetic patients to control their glucose levels. Early diagnosis and proper glycemic management are essential in this situation to prevent further progression and complications. Biosensor-based detection has progressed and shown potential in portable and inexpensive daily assessment of glucose levels because of its simplicity, low cost, and convenient operation without sophisticated instrumentation. This review discusses various systemic aspects of non-invasive glucose monitoring, including materials for monitoring and managing diabetes.

Keywords: glocose, biosensor, diabetes, non-invasive

1. Introduction

Diabetes mellitus is a metabolic disorder caused by a lower level of insulin hormone, which is generally secreted from the pancreas organ. Diabetic patients show several kinds of complications unless properly managed[1]. Early diagnosis and proper glycemic management are crucial to control and prevent further progression and complications in diabetic patients[2]. In general, in order to manage the blood glucose level of a diabetic patient, blood should be collected using a needle at the tip of a finger several times every day. Since the glucose in the blood can be measured directly, the most accurate measurement of the blood of diabetic patients. However, blood collection through fingertip punching repeatedly every day can cause mental trauma to the patient as well as infection and fingertip inflammation. Therefore, recently, in addition to these methods, noninvasive methods for measuring blood glucose levels have been developed[3].

Nowadays, developing a practical glucose biosensor with high reliability and sensitivity must be a top consideration for the biosensor industry. Various noninvasive glucose biosensors have been developed including optical[4, 5], electrochemical[6], transdermal[7, 8], colorimetric assay[9], luminescent detection[10], magnetic signal detection[11, 12], and microwave approaches[13, 14]. With the emergence of nanomaterials, significant advances have been made in fabricating glucose biosensors. However, conventional glucose biosensors suffer from expensive instrumentation, complex handling nature, and high fabrication cost, hindering their commercial use.

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Thus, robust, sensitive, economically sustainable, and low-cost fabrication of glucose biosensors is required for on-site commercial applications. This review highlights important advances in biosensor-based glucose detection, various mechanisms, analysis methods, and their applications in biosensors.. Finally, we address future development requirements for monitoring glucose levels.

2. Glucose monitoring techniques

2.1 Transdermal reverse iontophoresis (RI)

Transdermal reverse iontophoresis (RI) is a needle-free technique[15] that can extract biomolecules and drugs through intact skin to achieve whole blood glucose detection. In the RI principle, migration of Na^+ and Cl^- ions creates an electro-osmotic flow from beneath the skin toward the cathode and anode electrodes, respectively, as shown in Figure 1. Glucose concentration can be measured by the transportation of glucose molecules[16]. The electrodes are easily placed on the skin, and skin ISF (Intracellular fluid) transports the necessary proteins to the cell matrix through diffusion, which leads to a reliable correlation between ISF and whole blood glucose concentration[17]. However, devices adopting RI have limitations, including a long warm-up time, the need to change gaskets every 12 hours, difficulty of use during sweating, and potential inflammation of the user's skin.

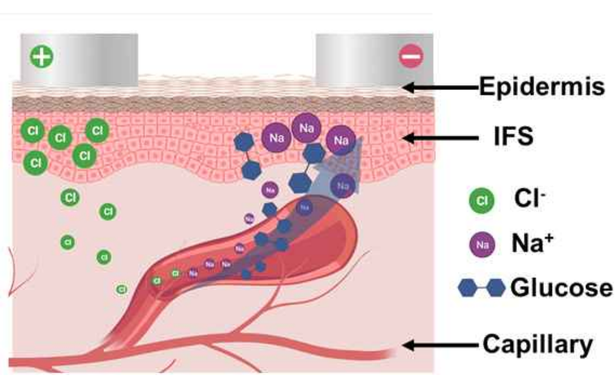

Fig. 1 Working principles of reverse iontophoresis (RI).

2.2 Electrical impedance spectroscopy (EIS)

Another method, electrical impedance spectroscopy (EIS), also known as bioimpedance spectroscopy, has been developed to continuously monitor glucose concentrations[18]. This technique involves the measurement of impedance variation with skin tissue composition and structure as a function of frequency, as shown in Figure 2. The glucose oncentration can be estimated from impedance analysis conducted over several band frequencies due to skin impedance variation. Although the performance of EIS-based glucose concentration estimation has improved significantly, the overall accuracy and sensitivity are still not high enough for commercial use. While transdermal glucose monitoring methods are painless, minimally invasive, and portable, the developed devices suffer from drawbacks, including limited sensitivity, long-term instability, electrode degradation, and long warm-up time (1 hour). Moreover, the fundamental challenges of impedance based EIS and RI methods are improving the specificity to glucose detection and reducing equilibrium processing time and interference from the experimental conditions to the end-user. An ideal transdermal glucose monitoring method requires a wider measurement concentration range, higher sensitivity, faster response, more specific selectivity, high biocompatibility, long-term stability, and continuous monitoring capability.

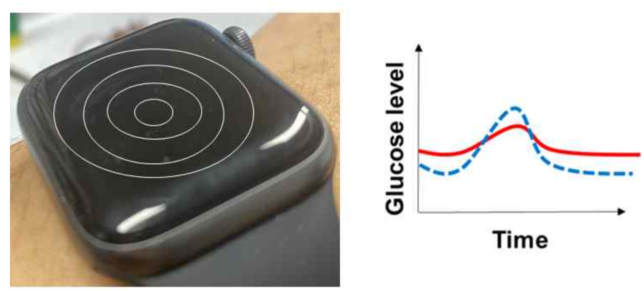

Fig. 2 Impedance spectroscopy for glucose monitoring.

2.3 Electrochemical glucose monitoring

Electrochemical glucose biosensors have been used dominantly over the last 40 years because of their superior sensitivities and selectivity. Also, electrochemical techniques offer low detection limits, fast response times, long-term stability, and cost-effectiveness. An electrochemical glucose biosensor comprises the biological recognition elements, electrochemical transducer, and the signal processing and display unit, as shown in Figure 3. The electrochemical methods usually measure the glucose concentration from body fluids and convert the amount of glucose into an electrical signal (current or voltage)[19]. In 1962, Clark and Lyons proposed the concept of a glucose oxidase (GOx) electrode. There have been extensive studies on electrode materials, electrode coatings, enzyme-curing methods, and electrode construction. Enzymatic glucose sensors have been popular due to the high sensitivity and selectivity of enzymes to enhance electron transfer rates. The development of electrochemical glucose biosensors has evolved over several generations (Figure 4). The first generation applied GOx-modified platinum (Pt) developed by Clark. The basic principle relies on the following reaction process.

$$\text{Glucose} + O_2 \rightarrow \text{Gluconic acid} + H_2O_2 \quad (1)$$

$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^- \quad (2)$$

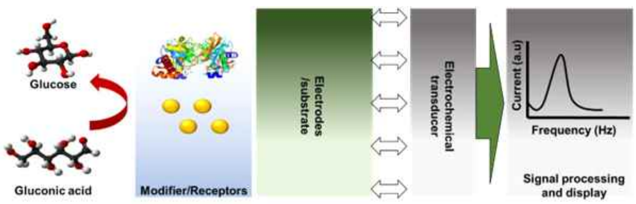

Fig 3. General scheme of electrochemical glucose detection.

The first generation involves GOx-catalyzed glucose oxidation by molecular O_2 with gluconic acid and H_2O_2. The generated H_2O_2 is oxidized at the Pt electrode to generate free electrons. The amount of glucose consumed is proportional to the produced hydrogen peroxide or consumed oxygen. The first-generation glucose biosensor has been widely used for self-monitoring glucose concentrations. However, there are limitations including the solubility of O_2, humidity-induced variations, and side reactions. The second-generation glucose devices replaced O_2 with a redox mediator that directly interacts with a GOx enzyme[20]. As the artificial electron acceptors replace oxygen and directly transfer electrons, they provide higher sensitivity, shorter response time, and broader application range than the first-generation devices with development of screen-printing technology[21]. Electronic mediators and oxygen affect the selectivity and sensitivity of glucose detection, leading to third-generation glucose biosensors with direct electron transfer between the electrode and GOx without medium, resulting in even faster response times and higher sensitivity. Even though these second- and third-generation devices successfully overcome the O_2 problems, the stability of GOx remains an issue[22]. In addition, in terms of manufacturing, the immobilization process of GOx is complex and has limited storage area and utilization[22]. Recently, non-biological catalysts (enzyme-free) have been introduced to resolve the limitations of the previous generations of glucose biosensors.

However, the inherent problems of enzyme degradation are external environmental factors[23], leading to unreliable glucose concentration readings[24]. Moreover, the most severe problems are insufficient stability and lower reproducibility, which are difficult to overcome.

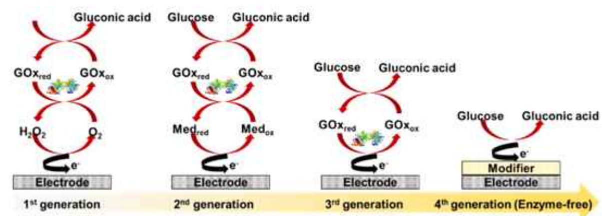

Fig 4. First to fourth generations of electrochemical glucose sensor for a generation.

2.4 Colorimetric-based glucose monitoring

Colorimetric detection uses specific nanomaterials interacting with molecules of interest and changing color easily monitored by naked eye as shown in Figure 5. The original color pieces of information are recorded with a charge-coupled device (CCD) or complementary metal-oxide-semiconductor (CMOS). The CCD camera is one of the most sensitive cameras to record the image and convert the photons into electrons divided into two-dimensional grids, known as pixels. The electrical signal processed by image processing software reads the information and assigns every pixel a shade of color in Figure 5. The digital images are acquired into final images in JPEG, PNG, TIFF, and BMP formats[25]. These sensors are widely used in the colorimetric glucose monitoring area using digital cameras, scanners, and smartphones. Current smartphones have significant advantages because they have high-capacity internal memories, high-resolution image sensors, wirelessly communicate with other devices, and are equivalent to a microcomputer[26, 27]. As well as the recent smartphone has significant advances, it makes them useful for colorimetric assay, including spectroscopy applications and fluorometric detection[27].

Fig 5. The method of image acquisition to detect colorimetric reaction: (left) CCD-based digital camera (right) the naked eye.

2.5 Magnetic signal detection

While colorimetric and fluorescence-based nanoparticles can only detect surface regions of the captured image, magnetic nanoparticles (NPs) can detect the entire volumetric magnetic signal in test regions [28]. In general, Fe- and Ni-based magnetic nanomaterials are used as they exhibit no hemolytic activity or genotoxicity while demonstrating biocompatibility, superior interactions with target biomolecules, and remarkable catalytic oxidation activity[29]. In addition, a set of thin-film induction coils serves as measurement units for magnetic force. This platform allows increased quantitative detection with high sensitivity and rapid test results with a relatively low error range. However, magnetic signal detection requires metallic shielding to effectively block external electromagnetic waves, which is a source of interference error, and an ultrasensitive magnetic sensor, which is costly.

2.6 Microwave

Microwaves can easily penetrate biological tissues utilizing electromagnetic waves with wide wavelength (1 mm to 1 m) and frequency (300 GHz to 300 MHz) ranges. Several microwave techniques have been introduced to measure glucose concentration because they influence the magnitude of the complex permittivity of whole blood and body fluids. The glucose concentration affects the orientational polarization, causing a shift in relaxation behavior applications. The success of biosensors for glucose detection in diabetic patients requires high accuracy and user-friendly device portability, biocompatibility, and ease-of-use in image acquisition. Therefore, a wide variety of frequency ranges has been reported to analyze the influence of glucose concentration on the permittivity of glucose solutions. In general, the microwave's reflection, transmission, and absorption are closely related to the dielectric property of tissues and the variation of the dielectric constant depending on glucose concentration fluctuations[30]. Currently, the correlations between glucose concentration in whole blood or body fluids and its dielectric properties have been investigated and led to further research involving microwave sensors due to their rapid, wireless, and affordable nature. Studies of spiral-shaped resonators have been carried out with aqueous glucose solutions and biological phantoms[31]. Also, patch resonators, microstrip line-based resonators, or closed-loop rings have been studied for glucose sensing in human biological solutions [32]. However, the central issue of microwave biosensors is finding a strong correlation between whole blood glucose concentration and effective permittivity. Therefore, current research focuses on improving the sensitivity and selectivity. Recently, multi-sensor integration, big data computing, and machine-learning algorithms were reported to resolve these issues[33]. However, more precise whole blood glucose concentration measurement might only resolve the sensitivity issues.

3. Conclusion and future direction

Recent research of biosensor for non-invasive glucose monitoring has overwhelmingly increased, expanding the scope of applications. The success of biosensors for glucose detection in diabetic patients requires high accuracy and user-friendly device portability, biocompatibility, and ease-of-use in image acquisition. However, conventional glucose detection methods suffer from expensive instrumentation, and high fabrication cost, hindering their commercial use and the lack of portability and the existence of sophisticated and complex instruments limit the versatility. Thus, robust, sensitive, economically sustainable, and low-cost fabrication of glucose biosensors is required for on-site commercial applications.

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<주요 연구 분야>

- Digital health care/ Mobile health care/ Wearable device/ Opto-fluidics/ Biomedical image processing/ Machine learning