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A new generation of sensors for non-invasive blood glucose monitoring

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Abstract

In recent years, the incidence of diabetes mellitus has grown exponentially worldwide. It is well-established that blood glucose monitoring is crucial to evaluate pancreatic islet function and determine the optimal medication regimen. However, most current blood glucose meters use invasive techniques, which can cause pain and infection. Non-invasive blood glucose monitoring techniques have gained significant attention as a potential solution to overcome the limitations of current monitoring methods. This review compares the progress and challenges of electrochemical, optical, and electromagnetic/microwave non-invasive blood glucose monitoring techniques to discuss future research trends. Due to the rapid development of wearable devices and transdermal biosensors, which provide efficient, stable, and cost-effective monitoring without the need for invasive blood samples, the market for non-invasive blood glucose monitoring is predicted to become more competitive.

Keywords: New sensor, blood glucose monitoring, non-invasive detection technology

Introduction

Diabetes Mellitus is a disease caused by abnormal islet function and can be divided into type 1 (T1D, absolute insulin deficiency) and type 2 (T2D, relative insulin deficiency). According to the data published by the World Health Organization (WHO), there are about 450 million cases in the world at present and more than 150 million in China, which has the world's largest diabetes epidemic [1]. The United Kingdom Prospective Diabetes Study (UKPDS) revealed that patients with type 2 diabetes mellitus may only have 50% of their islet function remaining at the time of diagnosis, yet pancreatic endocrine function can continue to deteriorate over time. As a result, many patients develop brittle diabetes, characterized by erratic fluctuations in blood glucose levels and challenges in maintaining stable blood glucose levels through conventional endocrine therapy [2].

Continuous blood glucose monitoring has important clinical significance for diabetes patients, especially in cases with brittle diabetes. It is well-established that recurrent hypoglycemia can cause sudden confusion or inability to move, resulting in secondary disasters (such as traffic accidents and falls). Hyperglycemia causes acute ketoacidosis and increases the risk of long-term complications. By monitoring blood sugar and accurately adjusting insulin dosage, blood sugar control can be effectively improved, and severe hypoglycemia can be prevented. Currently, available blood glucose monitoring techniques mainly harness electrochemical methods that require a small amount of blood to be extracted from the body through finger puncture or subcutaneous implantation of a thin needle. The former method is known as a Self-Monitoring Blood Glucose (SMBG) sensor, as it only provides glucose level readings at a specific moment in time and can be used by individuals without the assistance of a medical professional. In contrast, the latter method is called a Continuous Glucose Monitoring (CGM) sensor and offers continuous monitoring of glucose levels. However, invasive testing can cause discomfort and pain in patients, increase the risk of infection and allergies, and lead to poor compliance with blood glucose monitoring. Therefore, since the end of the 20th century, significant efforts have been undertaken to develop non-invasive (NI) and minimally invasive (MI) devices, namely blood glucose monitoring devices that do not require blood collection, aiming at overcoming the problems related to traditional blood glucose monitoring methods. Marjan Gusev et al. conducted a review of recent research advancements and key challenges in noninvasive glucose measurement techniques [3]. Accuracy, usability, and compatibility for home use were identified as the primary obstacles in this area. It was suggested that only devices capable of addressing these challenges could significantly impact the lives of millions of individuals with diabetes. The review also proposed future trends, such as integrating artificial intelligence algorithms and incorporating additional physiological and psychological parameters (e.g., heart rate variability to detect autonomic dysfunction), as well as using nanotechnology and other innovative techniques.

Nowadays, most non-invasive blood glucose monitoring techniques rely on the quantification of glucose molecules that exhibit distinct characteristics in different light frequencies, such as ultrasonic waves, near-infrared (NIR), and visible light. While these methods enable real-time quantitative monitoring, they do not offer the same level of accuracy as traditional electrochemical blood glucose meters in clinical settings [4]. As a result, improving the accuracy and precision of non-invasive monitoring devices remains a critical technical challenge in the field of diabetes treatment.

Over the past few years, many renowned scholars have reviewed several NI glucose monitoring techniques and devices. In this respect, Chen et al. comprehensively described the status quo of MI and NI technology of CGM analysis [5]. Van Enter and Von Hauff reviewed the physical and chemical properties of glucose molecules and analyzed their impact on the accuracy and effectiveness of NI technology [6]. Uwadaira and Ikehata provided a comprehensive overview of the technical parameters of non-invasive glucose monitoring technology and summarized its main technical advantages and limitations. Khalil provided an excellent description of the characteristics of glucose molecules and tissues under different light wavelengths and then compared and analyzed the accuracy and sensitivity of glucose measurement for *in vitro* and *in vivo* samples [7]. This review will cover a variety of innovative technologies for non-invasive blood glucose monitoring that have emerged in recent years, including electrochemical, optical, and microwave dielectric spectroscopy techniques. These sensors' principles, benefits, and limitations are examined, substantiating that electrochemical non-invasive blood glucose monitoring holds significant potential due to its high sensitivity and low cost.

Electrochemical technology

Numerous studies have confirmed a high correlation between glucose concentrations in blood and exudate [8,9]. Electrochemical techniques can indirectly reflect blood glucose concentration by measuring exudate (sweat [10,11], saliva [12,13], tears [14]). However, this technology is limited by the sensor's low penetration into the epidermis and the influence of other components in the exudate on measurement accuracy. A feasible alternative is to use an electric field to stimulate the skin, enabling glucose molecules to pass through the skin and collect around the electrode, and then measure them using biochemical methods.

Flexible biosensors based on electrochemical methods

Gold nanostructure-programmed flexible electrochemical biosensor Mengke et al. [15] developed a flexible chip with gold electrode arrays, which used gold nanopine needles (AuNNs) to amplify the input signal. They applied the electrochemical sedimentary method to deposit AuNNs on the working electrode, increasing the surface area ratio and allowing more enzymes to be fixed, thus increasing sensitivity. The catalytic mechanism on the electrode surface caused glucose to oxidize and produce hydrogen peroxide when a certain potential was applied. The decomposition of hydrogen peroxide produced hydrogen ions and electrons, which caused alterations in current that could be quantified (Figure 1A). Interestingly, to determine the concentration of glucose in sweat [16], cyclic voltammetry (CV) has been employed to examine current changes resulting from hydrogen peroxide decomposition [17].

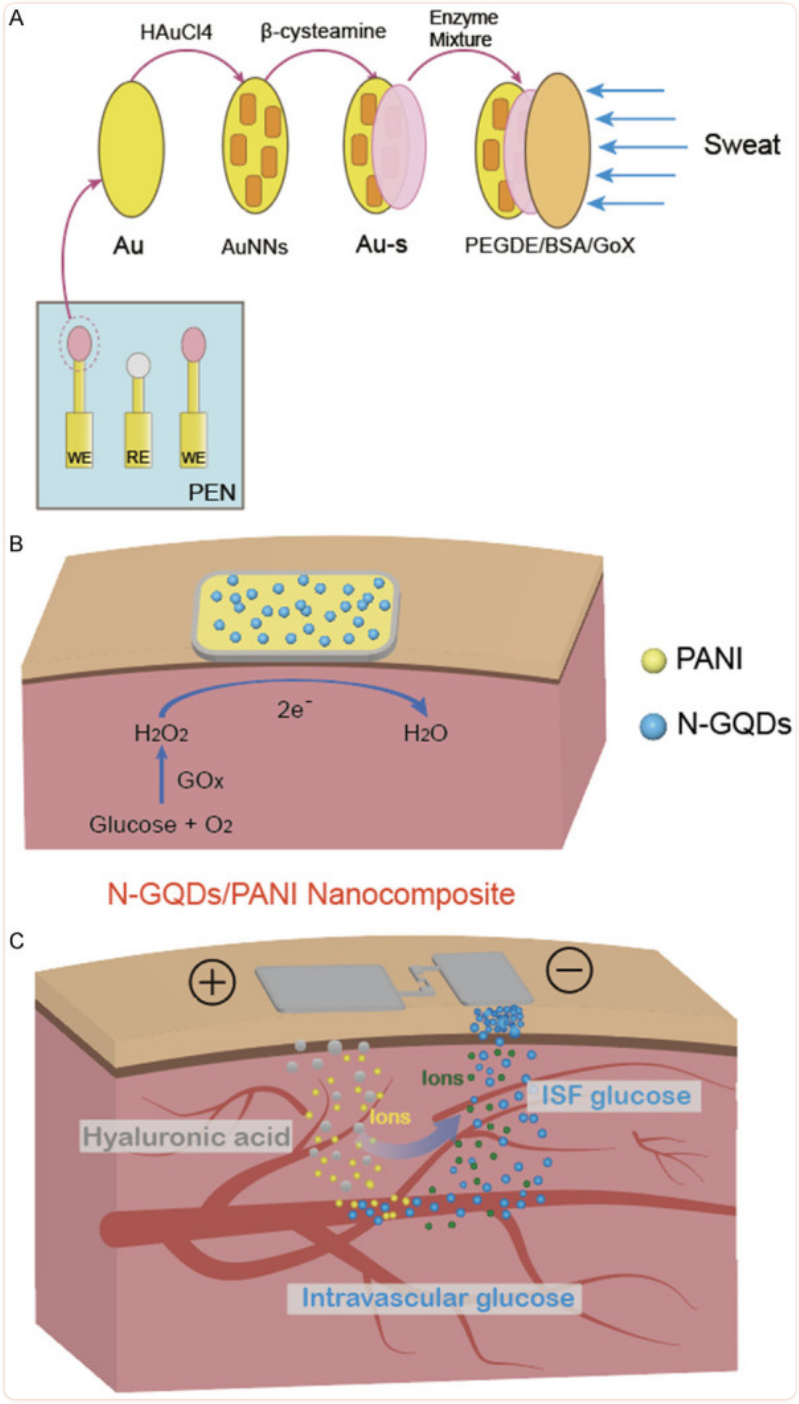

Figure 1

A. The biosensor consists of a flexible chip with an array of gold electrodes and gold nanoneedles (AuNNs) deposited on the working electrode using electrochemical deposition. When glucose or lactate in the sweat reacts with enzymes on the electrodes, an electrical signal is generated. This electrical signal is amplified by gold nano-pine needles (AuNNs) for better detection. A feature of this sensor is that AuNNs achieve signal amplification by increasing the surface-to-volume ratio, which allows more enzymes to be immobilized on the electrode, thereby improving detection sensitivity. B. The detection principle of a non-invasive wearable sweat biosensor with a flexible N-GQDs/PANI nanocomposite layer. The biosensor utilizes a flexible N-GQDs/PANI nanocomposite layer that is immobilized with glucose oxidase (GOx) to detect glucose in artificial sweat. When glucose in the sweat reacts with GOx, it produces hydrogen peroxide (H_2O_2), which is then detected by the biosensor. The detection process involves the reduction of H_2O_2 at the working electrode, which generates an electrical signal that can be measured and quantified. C. Schematic of the ETCs, which perform HA penetration, glucose refiltration, and glucose outward transportation. The ETCs (enzyme-based

transdermal patches) consist of a microneedle array that penetrates the stratum corneum and delivers hyaluronidase (HA) to enhance skin permeability. The HA allows glucose to pass through the skin and into the ETCs, where it is filtered by a glucose oxidase (GOx) membrane. The filtered glucose is then transported out of the ETCs through a diffusion layer and detected by an electrochemical sensor.

It has been demonstrated that the flexibility of Polyethylene Naphthalate (PEN) film enables electrochemical sweat sensors to adhere easily to human skin. The sensors were subjected to bending tests, and it was found that after 1000 bends, the sensor generated a signal with the same initial level. The cyclic voltammetry curve nearly overlapped, indicating that bending did not significantly affect the sensor's performance. These findings demonstrate the good flexibility of the sensors, making them suitable for clinical use, and hold great promise for application in future wearable real-time medical monitoring devices.

Flexible nanocomposite layer non-invasive biosensor Yuchi Lin et al. [18] developed a novel biosensor based on a nanocomposite layer of Nitrogen-doped Graphene Quantum Dots/Polyaniline nanocomposite (N-GQDs/PANI) (Figure 1B). With glucose oxidase (Gox) immobilized onto the electrode, the biosensor demonstrated excellent performance detecting glucose in artificial sweat. Wearable devices face a challenge in maintaining their electrochemical performance when subjected to significant deformation, which can cause cracks and damage to the electrodes. However, the design of Gox/N-GQDs/PANI has been successful in reducing charge-transfer resistance and maintaining its sensitivity during continuous bending testing. Compared to Gox/Pt, this design was associated with a 21.9% increase in sensitivity for glucose detection. Additionally, Gox/N-GQDs/PANI exhibited high selectivity and good stability and repeatability for glucose detection. These properties enable it to effectively overcome biomarker chemical signal fluctuations, which is crucial for continuous biomarker monitoring and disease diagnosis.

The authors used cyclic voltammetry to study the catalytic activity of N-GQDs/PANI nanocomposites to detect H_2O_2, electrochemical impedance spectroscopy (EIS) to measure charge-transfer resistance (Rct), and ammeter method to measure the response of Gox/N-GQDs/PANI based SPCEs to different glucose concentrations.

NiO (nickel oxide) nanosheets using graphene oxide film

Haiyan et al. [19] used a graphene oxide (GO) film as a template to prepare novel nanoparticle-assembled NiO nanosheets that could be utilized to develop non-enzymatic electrochemical glucose sensors. An electrochemical analyzer was utilized for electrochemical measurements, with a three-electrode battery consisting of a glass carbon electrode (GCE) as the working electrode, an Ag/AgCl (saturated KCl) electrode as the reference electrode, and a platinum foil as the counter electrode. NiO-based glucose sensors exhibited a low detection limit, wide detection range, and good selectivity compared to traditional electrochemical detection methods. The nanosheet NiO/GCE could respond quickly to glucose substrates, with a sharp increase in current to reach a stable value. When a potential of +0.60 V was applied, the current at the anode of the sensor sharply increased and reached 95% of the steadystate current within 2 seconds, exhibiting a fast ampere response. These findings present new strategies and opportunities for synthesizing NiO-based sensing materials and manufacturing high-performance glucose sensors.

Electrochemical twin channels (ETC) high sensitivity biosensor

Yihao Chen et al. [20] presented a novel strategy to design and manufacture a skin-like biosensor for non-invasive and high-precision blood glucose monitoring by integrating an ultra-thin skin-like biosensor with electrochemical twin channels powered by paper batteries. The designed subcutaneous ETC could extract blood glucose from the blood vessels and transport it to the skin's surface. The ultrathin nanostructured biosensor was highly sensitive (130.4 μA/mM) and could fully absorb and measure glucose. The results of subsequent *in vivo* clinical trials showed a high correlation (>0.9) between non-invasive measurements and clinically measured blood glucose levels.

The system consisted of a flexible biocompatible paper battery and an ultra-thin skin-like biosensor. The paper battery was attached to the skin to generate subcutaneous ETC (Figure 1C). The ISF (Interstitial Fluid) was penetrated by the ETC via hyaluronic acid (HA), while glucose escaped from the blood vessels and reached the skin surface, where glucose reverse ion electroosmosis therapy was applied. The anode of the paper battery repelled high-density positively charged hyaluronic acid (HA), causing it to penetrate transdermally into the ISF. The additional HA increased ISF osmotic pressure and disrupted the balance between ISF filtration and reabsorption, thus promoting intravascular glucose refiltration at the end of the artery and reducing reabsorption at the end of the vein. Under low current conditions, the higher molar glucose concentration in ISF also increased the flux of reverse ion electroosmotic therapy. The findings suggest that more glucose in the intravascular space was transported from the blood vessels to the skin surface, leading to the measurement of "actual" blood glucose levels. The principle of the continuous blood glucose monitoring system (CGM) is to monitor the glucose concentration in the subcutaneous interstitial fluid through the glucose sensor, thereby reflecting the monitoring technology of the blood glucose level. Compared with traditional blood sugar monitoring methods, CGM can provide continuous and comprehensive blood sugar information, understand the trend of blood sugar fluctuations, and thus discover high and low blood sugar signals that are not easily detected by traditional monitoring methods, and provide more comprehensive clinical data. In this technology, under normal working conditions, the sensor will use the electrochemical dual channel (ETC) to detect and output blood glucose measurement results. Since blood glucose is measured from the skin surface, it will not affect the human body (such as sleep), so it is suitable for continuous blood glucose monitoring.

A flexible dual-analyte electrochemical biosensor for the simultaneous detection of lactate and glucose in saliva was developed by researchers from Tsinghua University [21]. This biosensor was based on a flexible screen-printed electrode with two working electrodes. By sharing the reference and counter electrodes, multi-channel detection of different analytes in a single electrolytic cell could be achieved. A timing modulation data acquisition method was adopted to detect response signals of multiple analytes. The glucose and lactate channels of this sensor exhibited sensitivities of 18.7 μA/(mM·cm^2) and 21.8 μA/(mM·cm^2), respectively. The dual-channel biosensor exhibited wide linear ranges of 0-1500 μM for the glucose channel and 0-2000 μM for the lactate channel, suggesting it could accurately measure the glucose and lactate levels within this range. This broad detection range enabled the detection of low-level saliva metabolites, suggesting it has great potential. Given that large amounts of blood constituents can penetrate saliva through intracellular or paracellular pathways, and saliva is easy to obtain [11], it is very suitable for non-invasive monitoring.

Optical technology

Near-infrared spectroscopy

It is now understood that to measure glucose levels using near-infrared light, the light must be absorbed and scattered by chemicals in the tested tissue. Near-infrared spectroscopy generally selects areas with rich blood vessels and thin skin, such as the tongue, lips, and earlobes, for measurement. A feasibility study was conducted to assess the relationship between tissue reduced Scattering Coefficient to changes in blood glucose levels in diabetes volunteers. A significant correlation was found among 30 of 41 subjects [22]. This study demonstrated that unabsorbed light could be reflected from or transmitted through tissues before being received by optical detectors. When light propagates through organs with higher glucose concentrations, it becomes stronger due to less scattering, which results in shorter light paths and reduced light absorption (Figure 2) [23].

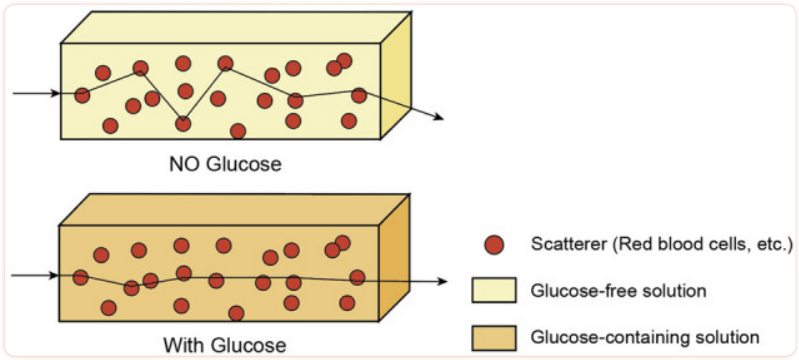

Figure 2

Schematic description of the influence of glucose on light propagation. Near-infrared light can effectively penetrate body fluids and soft tissues, enabling the detection of tissue conditions. The figure shows how glucose affects light propagation by absorbing and scattering near-infrared light. The absorption and scattering properties of glucose can be used to detect glucose levels in biological samples using near-infrared spectroscopy.

It is well-established that near-infrared spectroscopy is primarily focused on the visible and near-infrared ranges, including wavelengths ranging from 0.59-0.95 μm [24], 1.21-1.85 μm [25], and 2.12-2.38 μm [26]. Near-infrared light can effectively penetrate body fluids and soft tissues, enabling the detection of tissue conditions. This approach harnesses the frequency doubling and combined absorption of the fundamental frequency vibration of compounds that contain X-H bond groups (X can be C, O, N, etc.) in the mid & infrared region. The spectral absorption characteristics changed as the contents of organic compounds containing X-H bond groups and inorganic compound samples combined with them varied. It has been shown that glucose and other tissues have specific absorption bands in the near-infrared range. When near-infrared light penetrates human tissue, it is partially absorbed. The concentration of blood sugar can be calculated by detecting and calibrating the near-infrared spectrum absorption value [15]. Near-infrared light is a highly promising method for detecting glucose levels as it can provide real-time, non-invasive, fast, and chemical reagent-free glucose monitoring without risk of pain or infection. Accordingly, it is considered a promising detection method.

A typical near-infrared spectral sensing instrument mainly includes thermal and light detectors. The thermal detector functions by using crystals of certain thermoelectric materials positioned between two metal plates. When light shines on the crystals, the surface charge distribution changes, thereby measuring the power of infrared radiation (Figure 3A). A light detector generates signals due to the absorption of light by the materials in the detector, which leads to the release of electrons and induces a current output (Figure 3B).

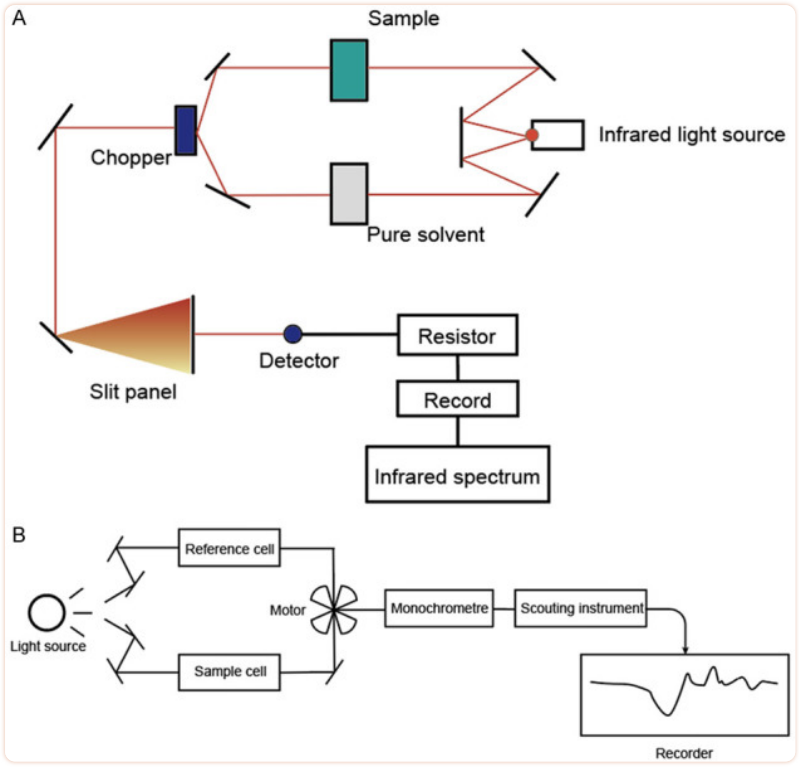

Figure 3

A. Near-infrared spectroscopy technology is a non-invasive blood sugar monitoring technology, which determines the content of glucose in the tissue by analyzing the spectral signal of a beam of infrared light passing through or reflected by human tissue. B. Near-infrared thermal detector principle. When near-infrared radiation is absorbed by a material, it causes a temperature increase, which generates a voltage output in the thermopile. The voltage output is proportional to the intensity of the absorbed radiation and can be used to measure the concentration of glucose in biological samples. Both infrared light detectors and infrared heat detectors can be used as measuring instruments, and further research can be carried out to produce non-invasive detectors with higher sensitivity and stability.

At present, four major technical bottlenecks hinder the application of near-infrared spectroscopy for blood glucose monitoring: (1) The device can only detect a weak signal, and therefore effective signal amplification methods need to be developed; (2) Measurement accuracy is impacted by individual differences in the human body and dynamic changes in body components; (3) Effective measurement sites need to be identified (such as fingers, tongue tips, etc.), and supporting facilities must be developed for dynamic monitoring of blood sugar; (4) Overlapping spectra make it challenging to accurately extract glucose component information, thus effective extraction methods need to be developed.

Optical rotation method

The “Optical Rotation Method” uses a visible light source for measurement, with the main measurement sites being the aqueous humor and cornea of the human eye. The principle of the optical rotation method is that optical active substances cause the polarization plane of polarized light to rotate, and the angle generated is related to the optical path, wavelength, temperature, and concentration of the solution in which polarized light propagates. When a beam of polarized light shines into a solution containing glucose, its transmitted light is also linearly polarized, and it forms an angle with the polarization direction of the original light, which is the optical rotation caused by glucose [27,28]. The detection of glucose molecules can be achieved using a fiber optic sensor based on the principle of optical rotation. This involves sending a light beam from a light source through the fiber optic and into the modulator. The interaction between the light in the modulator and the external measured parameters causes changes in the optical properties of light, such as intensity, wavelength, frequency, phase, and polarization state, resulting in a modulated optical signal. After the signal is sent through the fiber optic to the optoelectronic device and demodulated, the measured parameters are obtained (Figure 4).

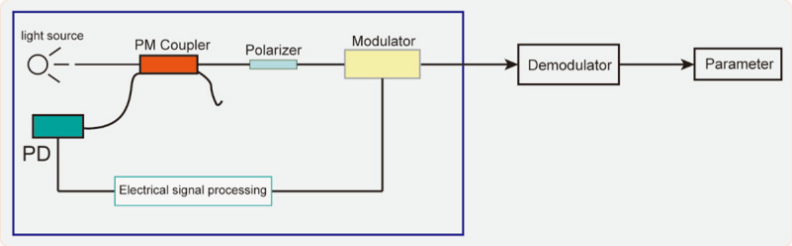

Figure 4

The principle of fiber optic sensors. This method harnessed the optical rotation properties of glucose molecules to quantitatively detect blood glucose by measuring the optical rotation angle. This instrument can be used for non-invasive blood glucose monitoring.

Brent D. Cameron et al. [29] developed a non-invasive blood glucose monitoring method based on optical polarization technology. This method harnessed the optical rotation properties of glucose molecules to quantitatively detect blood glucose by measuring the optical rotation angle. A new type of optical polarimeter was designed and manufactured to monitor blood glucose *in vivo*. This instrument leverages a new type of optical polarization element to achieve high-precision measurement of the optical rotation angle. A new type of optical probe has also been designed to achieve non-invasive detection of skin tissue. The experimental results showed that this method could monitor blood sugar accurately with good stability and repeatability.

One key factor limiting optical polarization as a non-invasive blood glucose measurement method is the sample noise caused by corneal birefringence in the presence of motion. Casey W. Pirnstill et al. [30] used dual-wavelength polarimetry to measure the glucose concentration in the anterior chamber and determine the blood glucose level. The author provided hitherto undocumented evidence that dual-wavelength polarimetry can accurately detect glucose concentration in rabbits. The experimental results showed that the overall average relative differ-

ence was 4.49% (11.66 mg/dL), and the Clarke error grid had a 100% Zone A+B hit rate, with 100% falling on Zone A, indicating the high accuracy of dual-wavelength polarimetry. It was concluded that dual-wavelength polarimetry could effectively reduce the noise caused by corneal birefringence, thereby accurately measuring the glucose concentration in aqueous humor and correlating it with blood sugar. Overall, this study provided a new method for non-invasive blood glucose monitoring.

It has been established that the high scattering coefficient of human skin tissue results in the complete depolarization of the light beam [31]. Accordingly, the aqueous humor has been subject to extensive research in recent years [32,33]. In 2014, the Google X Lab announced the development of contact lenses for non-invasive blood sugar measurement [34], which comprised two layers of soft lens material with a wireless chip and a micro glucose sensor implanted in the middle. The lens can measure the glucose concentration in tears. Notwithstanding that significant inroads have been made, products utilizing near-infrared spectroscopy for glucose monitoring have not yet been widely adopted. In an interview, Steve Pacelli, Executive Vice President of Dexcom, expressed his lack of optimism about the Google contact lens and noted that it is still just a scientific project.

Electromagnetic and microwave technology

Dielectric properties of glucose

The dielectric constant is used to measure the ability of a medium to store charge. Current evidence suggests that the dielectric properties of materials affect the behavior of electromagnetic waves in the medium. Therefore, the dielectric properties of different materials are one of the main design parameters for microwave sensor structures. Interestingly, the dielectric properties of glucose can be used to measure its various parameters using microwave sensors. The assessment of dielectric characteristics is crucial for the success of microwave diagnosis and therapeutic applications since it depends on the differences between normal and abnormal tissues [35].

Non-invasive blood glucose monitoring requires microwave sensors to detect glucose levels in epidermal tissue. A study found that the unipolar Cole-Cole equation could accurately simulate the dielectric behavior of biological tissue over a wide range of frequencies. The unipolar equation is as follows [36]:

$$\hat{\varepsilon}(\omega) = \varepsilon_{\infty} + \frac{\varepsilon\xi - \varepsilon_{\infty}}{1 + (j\omega\tau)(1-\alpha)} + \frac{\sigma_i}{j\omega\sigma_0}$$

Where, ε_{∞} -Relative dielectric constant at a field frequency; $\varepsilon\xi$-Static dielectric constant; *the* τ-Relaxation time of dispersion area; α-Wide distribution of relaxation time constant; σ_i -Ionic conductivity.

The blood sugar levels of healthy individuals are typically maintained within the range of 72 mg/dL to 216 mg/dL. It has been reported that the relative dielectric constant and conductivity decreased when the glucose concentration increased from 72 mg/dL to 600 mg/dL [37]. Dielectric properties typically exhibit limited sensitivity to changes in blood glucose concentration, with a relative dielectric constant of about 0.2 units and a conductivity of about 0.1 S/m. The relative dielectric constant decreased slightly more than conductivity with increased blood glucose levels.

Electromagnetic sensor system

Jessica Hanna et al. [38] proposed a wearable multi-sensor system for high-sensitive, non-invasive continuous blood glucose monitoring, which comprised a multi-band slot antenna, a multi-band band stop filter, a skin temperature sensor, a skin conductance response (SCR) sensor [39], an environmental temperature and humidity sensor [40] and motion sensor [41], etc. Each sensor could perform non-invasive and continuous monitoring of these different disturbance factors, forming an integrated glucose sensing system.

These sensors were designed to simulate the anatomical structures of the vascular system in the human body to improve sensitivity to changes in blood glucose. Additionally, these sensors were designed to be wearable, allowing them to align with body curves and adapt to small movements. The sensors included in the system have been fully validated in serum, animal tissues, diabetic animal models, and clinical settings. The non-invasive measurement results of a human trial reported a high correlation (>0.9) between the physical parameters of the system and blood glucose levels, with no time lag observed. The sensor adopted an adjustable electromagnetic topology structure based on vascular anatomy, which simulated the anatomical structure of the vascular system in the human body to improve sensitivity to blood sugar changes, thus achieving accurate and real-time monitoring functions. Importantly, these wearable devices could wirelessly sense the changes from hypoglycemia to hyperglycemia with high accuracy. This sensor system aims to target multiple body positions simultaneously, opening the door for the development of a closed-loop artificial pancreas [42].

Microwave sensors

The principle of microwave sensors is to measure blood sugar levels by utilizing the reflection and absorption of microwave signals when they pass through human tissues. These sensors determine blood glucose levels by measuring the complex dielectric constant in the blood. Non-invasive microwave sensors can monitor blood sugar levels in real time with high sensitivity and compact size [43]. However, the disadvantage of these sensors is their susceptibility to interference from other substances, such as fats and proteins, leading to measurement errors. In addition, these sensors require more testing and validation to ensure their accuracy and reliability.

A recent study [44] revealed that the resonance frequency of monitoring antennas was associated with the dielectric constant and the conductivity of the blood, both of which are related to the glucose level. Therefore, the resonance frequency of microwaves is correlated with glucose levels, providing a feasibility basis for measuring blood sugar noninvasively with “microwave sensors”. The study used blood samples from 10 patients with glucose levels from normal (87 mg/dl) to hyperglycemia (330 mg/dl) to establish a real database of blood dielectric proper-

ties. Using Agilent 85070E dielectric probe and Agilent 8720B network analyzer [45], the dielectric constant and conductivity of blood samples were measured in the frequency range of 1 GHz-10 GHz. The resonant frequency of the broadband antenna tied to the patient's body was monitored when the patient ingested fast-acting glucose tablets. These experimental results substantiated that the resonance frequency of the antenna increased as the glucose level increased.

Tuba Yilmaz et al. [46] reviewed research on the interaction between electromagnetic waves and glucose molecules and proposed methods to increase measurement sensitivity and selectivity, such as using a narrow belt resonant with a high Q factor (a dimensionless parameter used to describe the underdamped condition of an oscillator or resonator) to improve accuracy and sensitivity. To more accurately measure glucose levels using the dielectric constant, Carlos G. Juan et al. [47] used microwave sensors to measure the glucose level in human plasma solutions. These sensors are microstrip open-loop half-wave resonators that track glucose concentration by detecting changes in the dielectric constant of plasma solutions. To compare the impact of resonant frequencies on the experimental results, the authors set the sensors to three different frequencies of 2 GHz, 5.7 GHz, and 8 GHz (denoted as R1, R2, and R3). To characterize the solutions, plasma was mixed with glucose, lactate, and ascorbic acid to create 25 solutions, each group containing five solutions, with glucose concentrations of 0%, 2.5%, 5%, 7.5%, and 10%. All solutions were characterized using three microwave sensors (R1 to R3), and 90 measurements were conducted. The frequency response (S parameter) of the sensor was measured by a vector network analyzer (VNA) and evaluated as a glucose tracker in a background close to real human blood. The experimental results indicated that variations in other components could affect sensitivity, but the microwave sensor detected glucose levels accurately and exhibited a linear response. The sensitivity of R2 and R3 was better than R1 (Figure 5), indicating that higher frequencies are necessary for future designs. It was concluded that before the application of microwave sensors, it is essential to comprehensively model the actual application environment and conduct a large number of experiments using different frequencies and measurement parameters to improve sensitivity while ensuring the accuracy of the results.

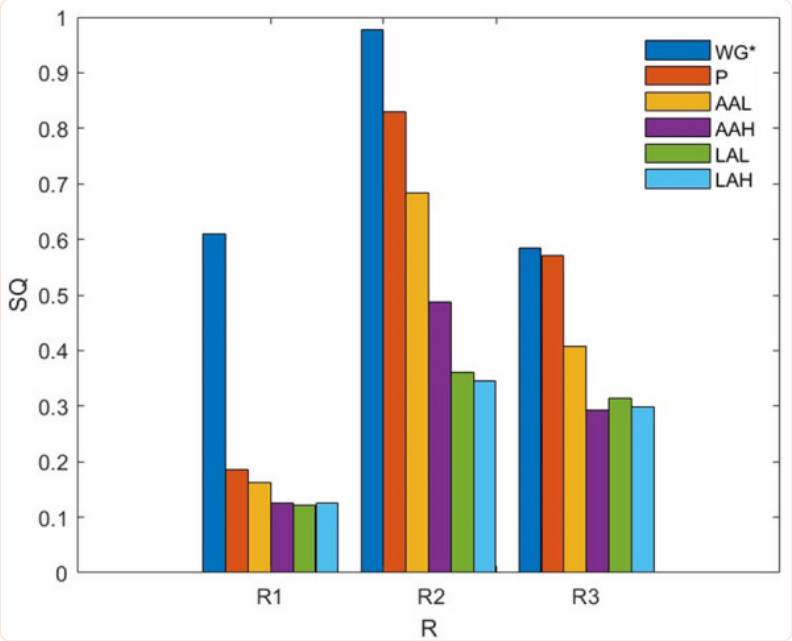

Figure 5

Comparison of the sensitivity (SQ) of the sensors at different resonant frequencies. The figure provides information on the sensitivity of the sensors in detecting glucose levels in different experimental conditions. WG, P, AAL, AAH, LAL, and LAH refer to different plasma solution groups. Among them: WG* - Water glucose solution; P - Plasma solution; AAL - plasma solution with a low concentration of ascorbic acid added; AAH - plasma solution with a high concentration of ascorbic acid added; LAL - plasma solution with a low concentration of lactic acid added; LAH - plasma solution with a high concentration of lactic acid added.

Conclusions and outlook

We summarize the advantages, disadvantages, and detection sites of the non-invasive blood glucose detection sensors (Table 1). Over the past few decades, significant efforts have been undertaken to explore various non-invasive methods for detecting blood sugar levels. Although many novel detection methods have demonstrated high accuracy in laboratory settings, these technologies have not yet been put into clinical practice and still need to be further improved and meet market regulations. The non-invasive blood glucose detection technology mentioned above shows great potential for development, but some challenges remain.

Table 1

Summary of the sensors mentioned in this article

Sensor	Advantages	Disadvantages	Detection site
Gold nanostructured flexible sensor	Good flexibility, excellent selectivity, repeatability, and stability.	The activity of various enzymes must be ensured, and the requirements for storage and use are high.	Sweat
Flexible N-GQD/PANI nanocomposite layer sensor	Has high sensitivity and repeatability, and stability, and can effectively overcome the fluctuations of biological signals.	The requirements for the materials are high, and the manufacturing cost is high.	Sweat
Electrochemical dual-channel sensor	Suitable for continuous monitoring during sleep, high blood glucose correlation.	Low flexibility.	Subcutaneous blood
Near-infrared spectrometer	No risk of infection, strong penetration, low cost.	Easily affected by environmental changes (such as temperature, humidity, pressure).	Oral mucosa, tongue, fingers
Polarimeter	No risk of infection, and low cost.	Long detection time, may cause harm to the human eye.	Aqueous humor, the cornea
Electromagnetic sensor	Personalized detection, high accuracy.	High detection cost.	Subcutaneous blood
Microwave sensor	Good real-time performance, small size.	Easily interfered with, low accuracy.	Fingers

The difficulty in signal detection and quantification

Biological tissues contain large quantities of water, which strongly absorbs light, leading to severe light attenuation. The glucose content in tissue fluid and blood is relatively low, making it challenging to detect small changes (the density of glucose is only 1% to 10% of the density of glucose in the blood). Body fluid glucose measurement accuracy may be reduced due to water evaporation, seasonal changes in liquid volume, and other internal components, making it unsuitable for continuous, long-term, and sleep monitoring. In addition, the absorption coefficient of glucose is much smaller than water's, which will weaken the signal triggered by changes in blood sugar concentration. Accurately and reliably detecting these values requires instruments with a high signal-to-noise ratio, which is currently not achievable with non-invasive blood glucose detection technology. As a result, it still cannot meet the rigorous requirements of clinical detection.

Changes in measurement conditions

Specificity remains one of the most important challenges in non-invasive blood glucose measurement. It is widely acknowledged that the tissue structure varies significantly across different parts of the human body, and this heterogeneity is also unique to each individual. If the probe cannot be accurately positioned at the same position during measurement, it will inevitably affect the propagation path of light. In addition, changes in measurement conditions such as temperature, area, and angle of light at the measurement site will directly affect the propagation of light, and the light intensity changes caused by them are much greater than those triggered by changes in blood glucose concentration. Therefore, accurate detection of blood glucose concentration is not feasible without stable measurement conditions.

Testing safety

Safety is a priority for this detection technology since it involves direct contact with the human body. Certain sensors contain potentially hazardous components such as enzymes, strong light sources, etc., which must be carefully evaluated to avoid possible bodily harm.

The past few years have witnessed significant progress in non-invasive blood glucose detection technology. However, their accuracy is still far from mainstream methods [48], hindering the widespread implementation of non-invasive blood glucose measurement technology. Therefore, the following four aspects need to be studied and improved in the future.

Continuous glucose monitoring

Some technologies that can continuously monitor blood glucose are mentioned in the article, such as electrochemical sensors, electromagnetic sensors, microwave sensors, etc. It should be noted that human activities may cause large detection errors. To build a sensor system, various influencing factors need to be considered to ensure the accuracy of the results as much as possible. In addition, the feasibility of continuous monitoring must be ensured. For example, the measurement of blood sugar in the cornea by polarimetry cannot be continuously monitored while the patient is resting.

1. It is necessary to consider the significant impact of measurement location, accuracy of experimental equipment, and experimental methods (in vitro and in vivo) on the detection results. Indeed, *in vitro*, experiments can better control experimental conditions but cannot simulate the real biological environment. In contrast, in vivo, experiments can better simulate the real biological environment but are subject to more interference factors. Therefore, in the future, it will be necessary to improve the experimental environment, ensure the universality of experimental results as much as possible, and provide sufficient theoretical support for future clinical trials.

2. It is necessary to ensure that non-invasive measurement equipment is feasible, including ease of operation, repeatability, and low noise levels.

(1) To achieve ease of operation, a system with automated measurement functions can be developed.

(2) To ensure repeatability, flexible materials can be developed and verified through numerous experiments. One example is the “Flexible N-GQD/PANI Nanocomposite Layer Non-invasive Biosensor” mentioned earlier.

(3) Regarding “low noise”, improving experimental methods and signal processing techniques or optimizing the structure and materials of sensors to reduce noise.

3. Further research on nanomaterials is necessary for the development of biosensors, which have a wide range of applications in the medical field. These applications include disease control, clinical care, preventive treatment, patient health information, and disease review [49]. Since biosensors come into direct contact with the human body, it is crucial to ensure that nanomaterials do not cause harm while improving flexibility and durability to ensure normal operation. Biosensors can be used in personalized medicine, providing patients with new treatment and diagnostic options and significantly impacting healthcare.

4. The sensor’s detection capability can be extended to simultaneously detect multiple biological indicators. Indeed, it is well-established that metabolic disorders usually cause systemic dysfunction and may lead to abnormal levels of various metabolites [50]. For example, patients with diabetes often present with elevated blood sugar, lipids, and lipoproteins levels due to metabolic disorders. Higher hemoglobin A1c levels in diabetic patie nts can also increase the likelihood of lactic acid disorder by strengthening the anaerobic fermentation process [51]. Future research should focus on developing three-channel or multi-channel biosensors, which can provide actionable information on multiple metabolites and generate comprehensive personal health information for more comprehensive medical testing.

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Disclosure of conflict of interest

None.

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