Recent Advances in Salivary Glucose Monitoring

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Abstract. Diabetes is a worldwide public healthcare issue that poses a significant threat to human health. Currently, diabetic patients rely primarily on invasive blood glucose monitoring, which causes tremendous suffering. In recent years, noninvasive glucose monitoring has been the focus of research, especially with saliva sensors. This review systematically illustrates the latest research progress of electrochemical glucose sensors, and the principles of saliva monitoring of blood glucose, and presents the relevant challenges faced and strategies to cope with them. In addition, material design and practical applications for salivary glucose monitoring such as mouth guards, pacifiers, etc. are presented. This review aims to promote the development and possible future commercialization of salivary glucose monitoring to improve the management of diabetes.

Keywords: glucose sensor, diabetes mellitus, saliva, non-invasive glucose monitoring.

1. Introduction

Diabetes is a metabolic disease characterized by chronically elevated blood glucose, which eventually causes serious damage to the heart, eyes, blood vessels, nerves, kidneys, and other organs. As an important part of the "Five Horsemen" proposed by the International Diabetes Federation, blood glucose monitoring has always been the focus of research and a hot spot. Continuous blood glucose monitoring is a barometer of diabetes control, and strict blood glucose control can greatly reduce the risk of diabetic complications while avoiding the treatment of expensive and difficult late-stage diabetic complications. Due to the limitations of invasive and discontinuous blood sampling and the increasing market demand for continuous glucose monitoring, a new generation of wearable non-invasive glucose monitoring devices based on novel sensing principles, minimally invasive, advanced nano and polymer materials have sprung up and made great progress in the past 20 years. Saliva, as a body fluid with high secretion volume, easy access, simple composition and a close relationship with blood glucose has high research value and broad commercial prospects. Therefore, this review focuses on the basic principles of continuous salivary glucose monitoring, the principles and progress of enzymatic and non-enzymatic reaction-based sensors, the application of novel polymeric materials and nanotechnology to salivary sensors, and the commercial value of salivary glucose sensors.

2. The principle of the electrochemical glucose sensor

2.1. Enzymatic glucose sensor

2.1.1. First generation enzymatic glucose sensor

In 1967, Updike and Hicks developed the first generation enzymatic glucose sensor that measured glucose levels in terms of the amount of hydrogen peroxide or the reduction of oxygen produced by glucose and oxygen catalyzed by enzymes [1]. This generation of sensors is simple in design and miniaturized. However, due to its dependence on oxygen and high potential, the limited oxygen in biological fluids and the redox of electrochemically active substances such as uric acid and ascorbic acid can affect the sensor. The use of oxygen-rich carbon dextrose electrodes with high oxygen solubility can solve the problem of oxygen deficiency. The potential can be reduced by modifying the electrode with Prussian blue or precious metals. In addition, the addition of Nafion, cellulose

acetate layer or polyurethane on the electrode surface as selective permeation membranes minimizes the remaining of the remaining substances [2].

2.1.2. Second generation enzymatic glucose sensor

In the 1970s, the second generation enzymatic glucose sensor used electron transfer mediators. Such mediators are soluble, low molecular weight redox-active materials, for example ,ferrocene derivatives and ferricyanides. The mediators promote the transfer of the electron from the redox center of the enzyme to the electrode surface, significantly increasing the rate of the enzymatic reaction [3]. This second-generation enzyme glucose sensor does not require the involvement of oxygen and reduces the redox potential. However, the medium is small and has potential leaching and long-term instability, which can affect the examination results detection results. Nowadays, carbon nanostructures, graphene, and CNT are widely introduced to immobilize media to reduce their leaching, accelerate electron transfer and improve sensitivity [2].

2.1.3. Third generation enzymatic glucose sensor

The third generation enzymatic glucose sensor does not require oxygen molecules or electron transfer mediators as electron acceptors and transmits electrons generated by the enzyme redox center directly to the electrode through nanomaterials, which has the advantages of high selectivity and sensitivity, short reaction time, and low working potential [2]. The active center of the glucose oxidase of the third generation enzymatic glucose sensor is buried in a thick insulating protein, which prevents direct electron transfer and is potentially toxic [3]. For a comparison of the three generations of enzymatic glucose sensors see specifically Table 1.

2.2. Fourth-generation glucose electrochemical sensor

2.2.1. Principle

Fourth-generation glucose electrochemical sensors use atoms on the electrode surface itself to act as electrocatalysts for glucose oxidation [4]. Easy to prepare, low environmental impact, and long storage time, it can fundamentally solve the problem of enzyme instability. Two models explain this principle, namely the model of actived chemisorption [5] and that of initial hydrated oxygen adsorbed atomic medium [6].

Table 1. Comparison of three generations of enzymatic glucose sensors

Sensors	Advantages	Disadvantages	Solution	Product	Ref.
First Generation	Simple and economic	1) Hypoxia 2)High Potential	1) H_2O_2electrocatalys 2) Anti-interference film	Dekang	[2]
Second Generation	1) Oxygen-independent 2) low potential	1) Intermediate leachability 2) Instability	Wired Enzyme Technology	Abbott	[2]
Third Generation	1) No electronic media required 2) High sensitivity	1) No direct transfer of electrons 2) Potential Toxicity	To be studied	Not yet available	[3]

2.2.2. Metal Synergy with other materials

The fourth generation of sensors, non-enzymatic sensors, use metals as electrocatalysts. Precious metals e.g. Au, Pt and transition metals e.g. Ni,Co have been widely used for glucose non-enzymatic sensors and each has its characteristics as shown in Table 2.

The role of single metal is limited, and the synergistic effect of multi-material combinations based on metals is the main research trend now. Fengchao Sun et al. prepared Fe3O4@Au@CoFe-LDH using a self-generated substitution reaction. The sandwich structure confined the highly sensitive and low oxidation potential Au between Fe3O4 and CoFe-LDH, and the synergistic effect of the three extends the linear detection scope with low detection limitation, high stability and selection[7].

2.2.3. Electrolyte pH

Normal human plasma pH is 7.35-7.45, and plasma pH below 6.9 or above 7.8 will be life-threatening. Disturbances in sugar, fat, and protein metabolism in diabetic patients make the body's acid base unstable, and in severe illness or stress, ketone bodies increase leading to diabetic ketoacidosis [8]. This all suggests that non-enzymatic glucose electrochemical studies should focus on the detection of neutral or weakly acidic solutions.

However, most current non-enzymatic glucose sensors require an alkaline environment and are difficult to use in humans, so the development of highly selective glucose oxidation catalysts for use at physiological pH remains a challenge [9]. Au, Pt has good prospects for development due to its excellent electrochemical properties, stability, and reproducibility. Shih-Sin Wang et al. synthesized different Pt shell structures on the surface of Pd nano-cubes by varying the Pt precursor concentration, which can be used in the neutral environment of human blood [10]. Based on the high biocompatible, catalytic activity of platinum black, Somasekhar et al. reported a three- and two-electrode structure of a non-enzymatic glucose sensor with Au/Pt black/Nf microneedles enabling a low detection potential and high selectivity in the physiological range for improved glucose detection [11].

Table 2. Metal-based electrochemical enzyme-free glucose sensors

Metal	Advantages	Drawbacks	Outlook	Ref.
Au	1)High biocompatibility, selectivity 2)Low potential	1)Low catalytic capacity 2)High cost 3)Toxic effect	1)Alloy & MIP Synergy 2)Au nanostructures	[12]
Pt	Neutral environment	1)Poor selectivity 2)Toxic effect 3)Slow electron transfer	1)Coarsened porous nanostructured Pt 2)Combining organic polymer 3)A suitable carrier	[13]
Ni	1)Low detection limit 2)High sensitivity,stability	1)Poor electrical conductivity 2)Easy to be affected 3)Easy Reunion	1)Highly stable NiO 2)Porous structure in Ni-MOF 3)Bimetallic materials such as CuNi	[14]
Co	1)Good catalytic ability, electrical conductivity 2)Low cost	Poor stability	Multi-metal composites	[15]
Cu	1)Low cost 2)Non-toxic 3)Highly active 4)Multi-chemical form	Poor conductivity and selectivity of CuO and Cu2O	1)Multiphase composites 2)Copper nanowires 3)Bimetallic materials such as CuNi	[16]

Future research remains focused on the developing non-enzymatic glucose sensors for neutral or weakly acidic environments (e.g., patients with ketoacidosis) on the basis of non-toxicity, high conductivity, selectivity, stability, and biocompatibility.

3. Principle of saliva glucose monitoring

3.1. Physiological characteristics of saliva

Saliva is secreted mainly by the three main glands (parotid, submandibular, and sublingual) and consists of water (99.5%), inorganic salts and enzymes (0.2%), and protein (0.3%), with each gland secreting a slightly different composition of saliva, in addition to a mixture of some gingival furrow fluid and debris. Salivary secretion is regulated by sympathetic and parasympathetic nerves and the composition of saliva produced by the two types of nerve stimulation varies [17]. Normal average daily salivary secretion can reach 500-1000 ml, 90% of which is produced by taste or smell stimulation, with a large variation in flow rate. The basal rate of salivary secretion in the unstimulated state is about 0.5 ml per minute [18]. The salivary flow rate is at its highest level in the morning and

gradually decreases. Almost no saliva is produced at night. In general, saliva is characterized by a relatively simple composition and easy variation in the quality, quantity, and speed of secretion.

3.2. Correlation between salivary glucose and blood glucose

Saliva is an ultrafiltrate of blood and can be a good substitute for blood. Glucose, as a hydrophilic small molecule, enters saliva from the blood through the paracellular pathway via salivary glandular vesicle cells. Zhang et al. demonstrated a linear relationship between salivary glucose and blood glucose in a fasting state (R2=0.92) with their developed disposable nano-biochip [19]. However, experiments have shown that glucose and insulin levels in the saliva of domestic dogs fluctuate with a lag of roughly 30 minutes compared to blood, which may be due to the slower process of substance dispersion in saliva [20]. This lag limits the clinical application of the Point-of-Care test.

3.3. Saliva collection and processing

Since saliva glucose concentration is 0.5-1.0 mg/dl, which is more than 1000 times lower than blood, and most saliva-based diagnostic techniques rely on homogeneous saliva in a non-stimulated state, high demands are placed on the collection method and sample standardization. One study found that unstimulated parotid saliva had the highest correlation with blood glucose (R2=0.707) by collecting saliva from 80 healthy individuals by various methods depending on the collection site and whether it was stimulated or not [21]. Enduardo team developed a simplex cotton-paper-syringe filtration system for simple, rapid, and low-cost pretreatment of saliva samples, which significantly reduced the lower limit of detection of glucose in saliva (2.60 × 10-6 mol/L) [22]. Chin et al. reported a sensor based on glucose dehydrogenase flavine-adenine dinucleotide (GDH-FAD), which is promising for clinical development because the signal-to-noise ratio and enzymatic activity of GDH-FAD are several and tens of times higher than those of GOx without the need for professional saliva sample pretreatment [23].

4. Material design for salivary glucose monitoring

4.1. Nanomaterials

The glucose concentration in saliva is much lower than that in plasma, and nanomaterials' unique advantage of being enhanced surface area, high electrical conductivity, and substitutable enzymes are used for saliva electrochemical sensors, with alloys and bimetals, transition metal oxides, and carbon nanomaterials being prevalent.

4.1.1. Metals

Salivary glucose sensor based on alloy and bimetallic complexes with high selectivity due to intermetallic synergy. Eva Vargas+ et al. designed a dual G/I sensor chip based on a three-electrode system consisting of a thin-film sputtered Ag and Au electrode on a recycled plastic PETG substrate, two Au-operated electrodes and an Ag/AgCl reference/counting electrode for the detection of pmol I and mmol G concentrations in one microliter of saliva in 30 min [24]. However, the above salivary glucose sensor is costly, so the use of high catalytic activity and surface area, low-cost transition metal oxide nanostructured electrodes has become a hot research topic. Pinak Chakraborty et al. used the chemical deposition method to grow porous NiO nanostructured films on FTO-coated glass substrates to fabricate electrodes based on porous NiO nanostructures for saliva sample detection showing extremely sensitivity and verifying the close association between salivary glucose levels and blood glucose levels [14].

4.1.2. Carbon materials

Carbon nanomaterials as carbon nanotubes and graphene have already been used for glucose sensors and displayed biocompatibility, higher sensitivity, selectivity and lower limits [24].Omotayo Adeniyi et al. prepared GCE-SWCNT/CoPc/rGO using salivary glucose determination by promoting

electron transfer through the synergism among SWCNT, CoPc and rGO to improve the sensitivity of the sensor with high selectivity, fast response, good stability and reusability, which provides a non-invasive and rapid salivary glucose assay new idea [25].

4.2. Polymers

Polymers and their derivatives have the advantages of biocompatibility, degradability, and flexibility, and their doping into mesogels can overcome problems such as mesogel instability.

4.2.1. Conductive polymers

Conductive polymer (CP) can be used to immobilize enzymes in saliva glucose sensors. Eloïse Bihar et al. reported a paper-based sensor including a conductive polymer, biofilm, and dielectric and encapsulation layers for daily monitoring of salivary glucose with good sensitivity [26]. Alternatively, An organic conducting polymer enzymatic sensor comprising poly 3,4-ethylene dioxythiophene, polystyrene sulfonate, and Pt electrodes can be used to monitor micro-molar levels of glucose in saliva with good applicability [27].

4.2.2. Hydrogel

Conventional hydrogel membranes are widely used for salivary glucose detection because of their fast response and wide detection range, but the adsorption of non-specific proteins on the sensor can affect the accuracy of the results. The interconnection polymer network hydrogel converts PBA into an amphoteric polymer brush matrix with high sensitivity without thick antifouling coating, but it requires saliva pretreatment to remove contaminants such as proteins [28]. Zhang et alreported a novel hydrogel with a sandwich structure consisting of a substrate medium, amphoteric ionomer, and phenylboronic acid with a weak physical barrier and high antifouling properties without saliva pretreatment [29].

4.2.3. Molecularly imprinted polymers

Molecularly imprinted polymers (MIP) have high affinity, sensitivity, and low-cost advantages. However, either the MIP is too thick or too thin reduces sensitivity and response time. Dong-Ming Kim et al. reported a sensor in which a conductive polymer was doped into the MIP layer to capture glucose and monitor changes in the potential signal [30]. This sensor can also be used to monitor glucose at micromolar levels in saliva. Alassane Diouf et al. proposed a sensor made by polymerizing acrylamide on MIP-based AuSPE with glucose as a template. The sensor avoids interference from similarly structured substances such as lactose within the saliva [31].

Although polymers have many advantages, there are still many limitations. For example, CPs are time-consuming and have low sensitivity, and MIPs are environmentally sensitive and costly. We expect to develop more new materials and processing technologies for polymers in the future to improve their disadvantages.

5. Commercial value of saliva glucose sensors

5.1. Mouthguards

Mouthguards are mainly used in strong confrontation sports such as boxing to protect the oral cavity or for dentistry, using them for saliva monitoring has the advantages of being real-time, non-invasive, stable, and long-term, and has a good market prospect. Its use for monitoring oral flora, salivary uric acid, lactate, sodium, and nitrite has been explored [32], and monitoring of salivary glucose metabolism is also a hot research topic. In 2015, Takahiro's team developed a removable "Cavitas sensor" mouthguard for real-time non-invasive monitoring of salivary glucose, achieving stable and long-term (more than 5 hours) real-time monitoring through a remote sensing system [33]. In 2020, the team improved it by developing a cellulose acetate (CA) film on the mouthguard [34], which will exclude the effect of vitamin A and uric acid components of saliva on salivary glucose concentration. A wireless measurement environment for Android system terminals was also

developed. Lucas et al. integrated microfluidic paper-based devices (μPADs) onto silicone mouth guards via 3D printing, enabling noninvasive monitoring while greatly reducing costs ($0.01 for disposable test strips and $10 for recycled mouth guards) and avoiding direct oral contact with the test strips affecting oral health [35].

5.2. Pacifiers

After being removed from the maternal hyperglycemic environment, newborns of diabetic mothers are prone to hypoglycemia if they are not supplemented with sugar promptly. In addition, the prevalence of hyperglycemia is higher in newborns because of their immature blood glucose regulation function or family history of diabetes. And at present, blood glucose measurement in newborns mainly relies on the invasive taking of blood specimens for monitoring, which has risks such as infection. Due to all of the above, it is necessary to develop pacifiers for the noninvasive monitoring of saliva glucose. Garca-Carmona et al. innovatively developed a pacifier that combines saliva sampling with miniature wireless electronics and electrochemical sensing. This sensor is a first-generation enzymatic glucose sensor on the basis of Prussian blue-modified electrodes. The infant's sucking allows a unidirectional flow of saliva to the outside of the pacifier for detection, which safeguards the infant and addresses the risks that conventional infant sensors can pose to the infant. But this pacifier has limitations, such as susceptibility to interference from other substances within saliva and limited lifetime, and research is needed to obtain sensor materials and technologies with higher stability, safety, and lifetime [36].

6. Conclusion and Future Outlook

Saliva composition is simple and variable, and glucose in fasting saliva is linearly related to blood glucose. Nanomaterials for salivary glucose sensors, require an alkaline environment and do not meet the physiological pH of saliva. Future research can focus on combining new polymeric materials and nanomaterials suitable for physiological environments to play a synergistic effect. The practical application of salivary glucose sensors is embodied in mouth guards and pacifiers. Mouth guards are effective in detecting non-irritating saliva, but are difficult to wear for long periods to achieve CGM. Meanwhile, the development of a pacifier saliva glucose sensor offers a non-invasive way for neonatal glucose testing.

However, saliva testing is still challenging: 1) The hydration state and saliva flow rate of the body may lead to the concentration or dilution of saliva glucose. 2) Glucose may be consumed by resident flora in the oral cavity. 3) Food residues and oral cavity contamination like blood may be a disturbance. 4) Salivary composition is not constant and is affected by sampling points, making preprocessing and calibration a tricky task. 5) Salivary glucose concentration is low and hysteretic. 6) Oral diseases such as periodontitis, ulcers, and caries are common long-term complications of diabetes patients, whose impact should be taken into consideration.

In conclusion, salivary glucose sensor applications are promising. In the future, miniaturized and intelligent saliva monitoring devices should be developed using composite materials to increase selectivity, sensitivity, and comfort based on stability. Through the multidisciplinary cooperation of clinical medicine, preventive medicine, and biomedicine, many devices are now in phase III clinical trials and will be applied to reduce diabetics' pain in CGM.

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