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Review on Glucose Biosensors

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Abstract: Glucose monitoring technology has been used for three decades in diabetes management. Current instruments use enzymatic methods to measure concentration of glucose and provide information on the point samples. Continuous glucose monitoring devices have become more recently available offering more detailed information on glucose excursions. The continuous glucose sensor may become a critical component of the closed loop insulin delivery system in future applications, and as such it must be sensitive, fast, reliable and appropriate for continuous use by patients. Blood glucose control is a valuable tool in diabetes management. A series of appropriate glucose biosensors have been developed since it is recommended to maintain normal blood glucose levels. The development of glucose biosensors including point-of-care applications, continuous glucose monitoring systems and non-invasive glucose monitoring systems has been significantly enhanced over the last 50 years. Nevertheless, the achievement of accurate and reliable glucose monitoring continues to pose many challenges. It needs more technical improvements in glucose biosensors, standardization of the analytical objectives for their efficiency, and continuous assessment and training of lay users. This article discusses the brief history, basic principles, analytical success and current status in clinical practice of glucose biosensors.

Keywords: Continuous glucose monitoring, Diabetes, Blood sugar, Glucose sensors, Sensor technology.

INTRODUCTION

It is a leading cause of morbidity and mortality in most developed societies worldwide, and a major health concern. Diabetes prevalence keeps on rising. In the United States (US), the approximate estimated prevalence of diabetes in adults was reported to be 9.6 percent (20.4 million) in 2003-2006. Furthermore, 48.3 million people in the US are expected to have diabetes by 2050. In 2000, the World Health Organization (WHO) put the number of people with diabetes around the world at about 171 million, and this is expected to rise to 366 million by 2030. A recent study reported that the worldwide prevalence of diabetes among adults (age 20–79) would be 6.4 percent in 2010, affecting 285 million individuals [1]. And it will increase to 7.7 per cent, which will affect 439 million adults by 2030. It is suspected that a sedentary lifestyle combined with

improvements in eating habits and the increasing frequency of obesity is the main causes of such increased rates. Diabetes mellitus is the most common Carbohydrate metabolism endocrine condition.

For the diagnosis and treatment of patients with diabetes numerous laboratory tests are used. The blood glucose concentration is the main diagnostic test in HbA1c-level diabetes and is a useful tool for tracking patients' Blood glucose self-monitoring (BGMV) has been developed as a valuable tool for diabetes management [2]. The aim of SMBG is to help the patient achieve and maintain normal

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concentrations of blood glucose to postpone or even avoid micro-vascular (retinopathy, nephropathy and neuropathy) and macro-vascular complications (stroke and coronary artery disease) progression. The results of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) clearly demonstrated rigorous control of high blood glucose levels in diabetes patients; decreases the incidence of complications such as nephropathy, neuropathy and retinopathy and may decrease the prevalence and severity of major diseases of the blood vessels[3]. It may also be useful for predicting hypoglycemia and providing real-time information to modify medicine, food regimens, and physical activity to meet glycemic objectives. Regular and frequent blood glucose measurements may provide data for improving and/or changing strategies for treating patients.

This article discusses the brief history of biosensors, basic operating principles, criteria for analytical succ ess and the present status of glucose biosensors. In ad dition, how to determine the reliability of results will be addressed in clinical practice.

BASIC PRINCIPLES OF GLUCOSE BIOSENSORS

A biosensor may be defined as a "compact analytical system or unit incorporating an integrated or associated biologically or biologically derived sensitive recognition feature" [4]. A biosensor has three main parts:

(i) The biological recognition elements that identify the target molecules in the presence of different chemicals;

(ii) A transducer that translates the bio-recognition event into an observable signal;

(iii) A signal processing device that converts the signal into a readable form.

The components of molecular recognition are receptors, proteins, antibodies, nucleic acids, micro-organisms, and lectins. The five main types of transducer are electrochemical, mechanical, thermometric, piezoelectric, and magnetic The majority of the current glucose biosensors are of an electrochemical form due to their increased sensitivity, reproducibility, easy maintenance and low cost. The electrochemical sensors may be subdivided into types of potentiometry, amperometry, or conductometry. Biosensors of enzymatic amperometric glucose are the most common devices available commercially, and have been widely studied over the last few decadesAmperometric sensors track the produced currents when electrons are exchanged between a biological system and an electrode either directly or indirectly.

Glucose tests are generally based on one of three enzyme interactions: hexokinase, glucose oxidase (GOx) or glucose-1-dehydrogenase (GDH). The hexokinase assay is the standard tool used in many clinical laboratories to measure glucose by spectrophotometry. Glucose biosensors for SMBG usually are based on the two families of enzymes, GOx and GDH. The basic concept of the glucose biosensor is based on the fact that the immobilized GOx catalyzes the oxidation of β-D-glucose by the gluconic acid and hydrogen peroxide producing molecular oxygen. GOx requires a redox cofactor-flavin adenine dinucleotide (FAD) to function as a catalyst. FAD serves as the initial electron acceptor and is reduced to FADH2. The cofactor is regenerated by oxygen reaction, leading to hydrogen peroxide formation. Hydrogen peroxide is oxidized in a classically platinum (Pt) anode which is catalytic. The electrode recognizes the number of electron transfers easily, and this flow of electron is proportional to the number of glucose molecules in the blood.

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For the electrochemical sensing of glucose, three general techniques are used; by measuring oxygen consumption, by measuring the amount of hydrogen peroxide released by the enzyme reaction, or by using a diffusable or immobilized mediator to move the electrons from the GOx to the e electrode. Recently, the number and types of amperometric biosensors based at GDH have increased. The GDH family includes the dinucleotides GDH-pyrroquinolinequinone (PQQ) and GDH-nicotinamide-adenine (NAD). The enzymatic GDH reaction is independent of the oxygen being dissolved. The identifying feature of the quino protein GDH uses PQQ as a cofactor. Neither oxygen nor NAD+ is required to this mechanism. GDH-PQQ is a particularly efficient enzyme system, with a rapid transfer rate of electrons, but it is relatively costly. GDH uses NAD as a cofactor, rather than H_2O_2. NAD is a major glucose oxidation electron acceptor during which the NAD+ nicotinamide ring accepts a hydrogen ion and two hydride ion corresponding electrons. The reduced form of this carrier that is produced in this reaction is called NADH which can be oxidized electrochemically.

HISTORICAL PERSPECTIVES OF GLUCOSE BIOSENSORS

Although there are a number of glucose sensors available, over several years the glucose biosensor has, in theory, changed little. Yet the first meter of blood glucose was not a biosensor. Based on a reflectometer developed in 1971, it was the Ames Reflectance Meter (ARM), and the Dextrostix. Dextrostix, the first blood glucose monitor, was available since 1965, and was initially designed to show color changes. After one minute, the blood sample was gently washed off, before inserting the strip into the meter. Although the ARM was costly and difficult to use, it replaced the glucose analyzer Ames Eyetone. Early versions of devices that detected glucose were based on the reflectometer.

First generation of Glucose Biosensors:

The first generation of glucose biosensors is based on the use of the natural oxygen substratum and the detection of the emitted hydrogen peroxide. Measurements of the formation of peroxides have the benefit of being simpler, especially when considering miniature devices. The main problem with the first-generation of glucose biosensors, however, was that the amperometric measurement of hydrogen peroxide demanded high selectivity operating potential.

Second generation of glucose Biosensors:

The shortcomings of the first-generation glucose biosensors described above have been overcome with the use of controlled glucose biosensors, i.e. glucose sensors of the second generation. The enhancements were made by replacing oxygen with non-physiological electron acceptors, referred to as redox mediators that could transfer electrons from the enzyme to the working electrode surface. Instead of hydrogen peroxide, a reduced mediator is formed and then reoxidized at the electrode, giving an amperometric signal and regenerating the mediator's oxidized shape. A number of mediators on electron, Sensor efficiency was improved with the use of ferrocene, ferricyanide, quinine, tetrathialfulvalene (TTF), tetracyanoquinodimethane (TCNQ), thionine, methylene violet, and methyl viologen. Ferrocenes meet every criterion for a good mediatorIncluding oxygen-free, soluble in both oxidized and reduced forms, independent of pH, reversible electron transfer kinetics and rapid reaction with the enzyme. Both GOx and GDH-PQQ and the electrodes were extensively studied as electron-shuttling mediators. In 1970 the first work on amperometric determination of blood glucose using a redox pair-mediated, GOx-catalyzed reaction was shown. This study did not,

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however, result in the rapid application of amperometry in SMBG in home setting.

Third generation of glucose biosensors:

The biosensors of the third generation glucose are reagent less and dependent on direct transfer without mediators between the enzyme and the electrode. Instead of highly toxic mediators; the electrode can carry out direct transfers of electrons using organic conductive materials[5] based on complex charges. Consequently, glucose biosensors of the third generation have led to implantable, needle-type devices for continuous in vivo monitoring of blood glucose. The electrochemistry of pyrrole-quinolinequinone enzymes (GDH-PQQ) and flavoproteins (GOx) is known to mediate organic salts, such as tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ), and the lack of mediators means superior selectivity for the biosensors. Nevertheless, it has been proved that only a few enzymes like peroxidases demonstrate direct electron transfer on typical electrode surfaces. Many studies have been reported for other direct electron transfer approaches on third-generation glucose biosensors, including TTF-TCNQ with a tree-like crystal structure, the GOx / polypyrrole method, and oxidized diamond-doped boron electrodes.

Continuous Glucose Monitoring Systems (CGMS):

There are currently two types of continuous glucose monitoring systems in use-a continuous subcutaneous glucose monitor, and a continuous blood glucose monitor. Nevertheless, most CGMSs do not directly measure blood glucose due to surface contamination of the electrode by protein and coagulation factors, and the possibility of thromboembolism[6]. Thus, subcutaneously implantable needle-type electrodes were developed that measure glucose concentrations in interstitial fluid, representing blood glucose levels.

Non-invasive Glucose Monitoring System:

The goal of glucose sensor technology is the non-invasive glucose analysis, and significant attempts were made to achieve this goal. The most common methods of non-invasive glucose sensing are optical or transdermal approaches. The optical glucose sensors use light's physical properties in the interstitial fluid or the eye's anterior chamber. Such methods include polarimetry, Raman spectroscopy, and spectroscopy of infrared absorption, photo acoustics, and tomography of optical coherence [7-9].

Glucose Biosensors for Pont-of-Care Testing (POCT):

While laboratory analysis is the most accurate method for determining glucose levels, POCT is commonly used to evaluate glucose levels in the inpatient (ER/ICU/ward) and outpatient (office / home) environment, due to cost and time delays [10]. Many POC glucose biosensors rely on disposable enzyme electrode test strips which are screen-printed. Such strips of plastic or paper have electrochemical cells and contain, together with a redox mediator, GDH-PQQ, GDH-NAD, GDH-FAD or GOx Next, a test strip is inserted into the meter, then a small drop of capillary blood is collected with a lancing device from the fingertip, and added to the test strip Finally, a conversion factor is added, and the results of the test are usually shown as plasma glucose equivalents as recommended by the IFCC.

Analytical Performance Validation of Glucose Biosensors:

The analytical output for most glucose monitoring devices has been verified by healthcare professionals according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). Nevertheless, in ISO 15197 guideline, the ISO Technical Committee ISO / TC 212 published a standard for validating the accuracy and repeatability of glucose monitoring devices at three to five different levels of glucose. These recommendations emphasize the need

to test biosensors for glucose in real-life situations. The guidelines also define criteria for in vitro glucose monitoring systems that measure glucose concentrations in capillary blood samples, and protocols for performance verification and evaluation by intended users.

CONCLUSION

Blood glucose levels are calculated using different glucose biosensors for the screening, diagnosis, and long-term treatment of diabetes patients. Given the increasing prevalence of diabetes, novel technologies for glucose biosensors, including POC devices, Over the past few decades, CGMS and non-invasive glucose monitoring systems have been developed. Recently, the importance of glucose biosensors has been widely accepted by medical professionals at the POCT and by patients at the SMBG. Rapid, successful correction of blood glucose levels is based on daily measurements of glucose using glucose biosensors. Glucose biosensors have developed to be more robust, quicker and more precise and are more lightweight and simpler to use as well. Development for advanced technologies, including electrodes, membrane, techniques for immobilization, and nano-materials, continues to be carried out. Given the remarkable developments in glucose biosensor technology, the achievement of accurate glucose monitoring continues to pose many challenges. The ADA recommends a blood glucose POC assay's precision to be < 5 per cent of the calculated amount However this condition is not met by many POC apps. Biosensor technology is less reliable and less precise than central laboratory methods.

To ensure reliable and accurate monitoring, it is recommended that the analytical efficiency of glucose biosensors be evaluated more systematically. Effective linearity include the analytical criteria for suitable hospital or home POC devices In comparison with a clinical laboratory reference system, precision and correlation as well as resistance to specific interference. System configuration and quality control should be carried out on a regular basis in compliance with the instructions of the manufacturer. Information quality can also be influenced by user-dependent variables and, by extension, care outcomes. Improper use of the test strip, lack of quality control protocol, fingers that are not clean and dirty tools are the most commonly cited issues. Different studies have shown that education and quality training can minimize mistakes caused by the aforementioned factors and increase measurement efficiency.

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