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Review Article

Sensor Technology Developments in Diabetes Monitoring

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Abstract

In this mini-review, the historical development of glucose monitoring systems and its applications as implantable and non-implantable devices are discussed, as well as its use in different body fluids at different sites. In addition, the concept and development of the feedback-loop sensing delivery systems and their clinical use are evaluated.

Introduction

An analytical device which functions to analyze a sample for the presence of a specific compound is known as a sensor. A sensor which utelizes biological material to specifically interact with an analyte is known as a biosensor. An analyte refers to the compound which has to be "sensed" or the presence of which has to be determined. The interaction of analyte and biosensor is measured and converted to signals, which are again amplified and displayed. A biosensor thus involves converting a chemical flow of information into electrical signals. The biological materials used in biosensors are mostly enzymes, antibodies, nucleic acids, lectins, a cell as a whole etc [1].

Seven million people develop diabetes annually. According to the World Health Organization (WHO) and the International Diabetes Federation, its worldwide prevalence is projected to double over the next decades, from 347 million people in 2005 to 700 million people in 2030. Notably, more than 80% of diabetic patients live in low-and middle income countries [2,3].

Symptoms have been alleviated and treament improved by appropriate medication and blood sugar monitoring to improve treatment decisions and glucose control. Glucose sensor systems are classified into two groups based on duration of measurement method and time: the point sample test and the continuous glucose monitoring systems (CGMs). Most glucose sensors are enzyme -based whereas others are enzyme free [4].

A plethora of biosensors have been developed to provide diagnostic information regarding a patient's health status. Many different types of sensors have been investigated over the past decade, such as enzymatic and non-enzymatic glucose sensing [5]. Spectroscopic methods for non-invasive glucose detection have also been growing in popularity [6-10]. However, the real challenge that remains is the creation of biosensors for daily use by patients in personalized monitoring [10]. Technical advances on wearable and or implantable devices have several shortcomings. They trigger the foreign body reaction which results in loss of functionality in a few days and they typically record only single analytes. When a device that is implanted in a peripheral tissue such as subcutaneous tissue is used to monitor analyte changes in the blood, loss of sensitivity and lag times are observed [11].

Technical advances and 50 years of research integrating sensors in wearable platforms have initiated the transition to real time, continuous monitoring [12-16]. Despite the impressive progress in the development of glucose biosensors, the promise of tight diabetes management has not been fulfilled and there are still many challenges related to the achievement of a highly stable and reliable continuous glycemic monitoring process. Technology themes will be center stage at the 2018 Annual Meeting of the American Diabetes Association (ADA) in Orlando. In this mini-review the historical development of glucose monitoring systems and its applications as implantable and non-implantable devices will be discussed as well as its use in different body fluids at different sites. In addition the concept and development of the feedback loop sensing delivery systems, and its clinical use are evaluated.

History of glucose monitoring

Clark and Lyons at the Children's Hospital in Cincinnatti proposed in 1962 the first- generation of glucose biosensors [17]. These sensors were initially based on an electrochemical approach, which used the enzyme glucose oxidase (GOx)-(9). Electrochemical sensors were chosen for blood glucose measurements due to their high sensitivity, on the order of umol to mmol, good reproducibility, and ease of fabrication at relatively low costs [18]. GOx was employed as the enzymatic basis for the sensor, owed to its high selectivity for glucose. Less common enzymes, such as hexokinase and glucose-1 dehydrogenase were also used for glucose measurements [19,20], but GOx can tolerate extreme changes in pH, temperature and ionic strength in comparison with other enzymes. Withstanding these conditions can be important during any manufacturing process, making it a prime candidate for glucose monitoring devices [21,22].

GOx catalyzes the oxidation of glucose to gluconolactone in the presence of oxygen, while producing hydrogen peroxide (H2O2) and water as by-products. Gluconolactone further undergoes a reaction with water to produce the carboxylic acid product, gluconic acid. GOx requires a redox cofactor to carry out this oxidation process, where flavin adenine dinucleotide (FAD+) is employed. FAD+ is an electron acceptor which becomes reduced to FADH2 during the redox reaction. Subsequent reaction with oxygen to produce H2O2 regenerates the FAD+ cofactor. This reaction occurs at the anode where the number of transferred electrons can be correlated to the amount of H2O2 produced and hence the concentration of glucose [23].

In this sensor design presented by Clark and Lyons, indirect quantification of glucose concentrations was achieved by placing a layer of the GOx enzyme on a platinum electrode via a semipermeable dialysis membrane. This sensor measured the decrease in oxygen concentration and the liberation of hydrogen peroxide, which was proportinial to the glucose concentration [17]. The main obstacle to overcome with this approach was the interference of other electroactive species present in blood such as ascorbic acid and urea [9,24]. This approach was further developed in 1975, when the first commercial sensor based on GOx was made available [9]. This sensor directly measured glucose concentration by amperometric detection of hydrogen peroxide. The electrochemical signal required a high operating potential and the platinum electrode used was too expensive. This led to the second generation of glucose biosensors in the 1980s [24].

Second generation biosensors

In the design of the first generation sensors, oxygen was employed as the electron-acceptor, which can result in errors from variations in oxygen tension and limitations, known as the oxygen deficit [25]. This deficit is caused by oxygen concentrations. In order to overcome these challenges, oxygen was replaced with a synthetic electron redox mediator in second generation sensors [24]. The evolution of this sensing approach also led to the development of disposable enzyme electrode strips, which were accompanied by a pocket-size blood glucose meter [26,27]. Each strip housed miniaturized screen-printed working and reference electrodes, where the working electrode was coupled with the required sensing components: glucose oxidase, an electron shuttle redox mediator, stabilizer and linking agent. These revolutionary second generation glucose sensors directly resulted in the advent of self-monitored glucose management, known as the finger-pricking approach. This method is enzyme-based and involves sampling blood from a finger via pricking to be analysed by *in vitro* methods using test strips and a glucometer [28].

Artificial pancreas and third generation biosensors

In the early 1970s Albisser *et al.* and Shiori *et al.* at first introduced in vivo continuous glucose monitoring using an artificial pancreas [29,30]. The artificial pancreas design was based on continuous glucose monitoring, where the device would remove blood from the body to an external benchtop analyzer that was connected to an insulin pump. As this suggests, the device was not implanted and therefore not portable, although it was named "the artificial pancreas". This led to the development of the third -generation of glucose biosensor, which was implanted subcutaneously. It wasn't until the late 1990s that the first commercially available personalized in vivo glucose monitor was launched by Medtronic, Inc.Sylmar, CA, USA [24].

Unfortunately, the device could not provide real-time information, with data assessed by a physician every 3 days [9]. Although implantable glucose monitoring systems offer regular glucose level readings, this approach isn't recommended for all diabetics, due to its invasive nature [18]., and some continuous glucose monitoring (CGM) methods have been shown inaccuracies up to 21% [31]. These inaccuracies are often attributed to sensor drift, caused by changes in the catalyst performance of the enzyme. This requires the device to be periodically recalibrated via the finger-pricking method [32]. Despite current commercially available glucometers, such as the Freestyle -Navigator by Abbott (Abbott Park, IL, USA), providing real-time measurements every 1-5 minutes, the longest working model without calibration is approximately two weeks. Consequently, there is a high consumer demand for a CGM system which can quantify glucose concentrations without frequent calibration. For that reason, often more accessible biological fluids such as interstitial fluid, ocular fluid, sweat, breath, saliva or urine have been investigated as alternative sample media for non-invasive CGM [18,33-35]. It is likely that the development of a device for glucose sensing with a working model of more than two weeks may target on of these more accessible fluids [28]. New developments in feedback loop systems might offer other opportunities to solve this problem [36].

Feedback Loop Systems and fourth generation biosensors

Artificial pancreas systems, also referred to as closed loop systems rely on CGM readings to automatically calculate at every sampling time the necessary insulin dose to keep patients' blood glucose in safe ranges [37]. In 2017, the first artificial pancreas system hit the market in the United States, although still requiring patient intervention at mealtimes [38]. CGM is associated with improvement of glycemic control in patients with type 1 diabetes, reducing glycated hemoglobin (HbA1C) percentage without increasing the occurence of hypoglycemic episodes [39-41].

Physical exercise has been identified as one of the major challenges facing artificial pancreas systems [42]. Physical exercise is also a hurdle to CGM accuracy due to changes in subcutaneous tissue circulation, variations in oxygen concentration of blood, increase in body temperature, mechanical forces where the sensor is placed, and rapid changes in glucose concentrations caused by exercise. Nevertheless, if CGM accuracy is poor, the closed loop performance may be detoriated [44] and thus increase the intrinsic risk of hypo-and hyperglycemic episodes caused by physical exercise. Several studies have reported the impact of physical exercise in the accuracy of current CGM systems [43,45-47].

Biagi *et al.* studied the accuracy of a CMG system (Paradigm Veo Insulin Pump and two Enlite-2 sensors, Medtronics) before, during and after aerobic and anaerobic exercise sessions in 6 type 1 diabetes patients [36]. They concluded that CGM might present lower accuracy during aerobic exercise, but return to regular operation after exercise cessation. No significant impact for anaerobic exercise was found [36].

As more groups have demonstrated safety and improved glycemic control with closed- loop systems [39-41], device development has been rapid [48]. Notably, Backingham *et al.* recently published data on the safety and feasibility of an HCL (hybrid-closed loop) system with OmniPad, DexCom G4 CGM, and a model predictive algorithm [49]. The tslim insulin pump (Tandem Diabetes Inc. was previously shown to improve TIR (Time in Range) with the Diabetes Assistant USS algorithm and DexCom G4 by Ly *et al.* [50]. Currently, Tandem and Type Zero are collaborating on a trial using the tslim pump, DexCom CGM

and the control IQ algorithm. Bigfoot Biomedical has completed the recruitment for a study (Clinicaltrials.gov.NCT02849288) evaluating the performance and safety of a closed loop system. Finally, Beta Bionics has demonstrated safety and effectiveness of the "iLet" bionic pancreas in several recent trials [51,52]. A study is ongoing to evaluate two different types of stable glucagon in the bihormonal "iLet" bionic pancreas (Clinicaltrials.gov.NCT02971228).

It is widely agreed that success of a closed-loop system is based equally on the quality and efficacy of the infusion algorithm and accuracy of the sensor. CGM quality, as measured with mean absolute relative difference (MARD), has evolved since initial release of glucose sensors. The MARD is the difference between laboratory (or occasionally fingerstick) glucose and sensor glucose. The lower the MARD, the more accurate the sensor. Medtronic has released several sensors over the years: the Guardian Real Time, The Sof-Sensor, The Enlite Sensor and the Guardian3 Sensor, also known as the Enlite3, which is currently part of the 670G HCL system.

MARD data reported are highly variable and differ where the study is conducted, especially when comparing the clinical research unit versus the ambulatory setting [53]. The reported values also may be influenced by the reporter and funder of the study. For example, Calhoun *et al.* reported the MARDs for the Medtronic Sof-sensor and the Enlite to be 16% and 18%, respectively [54]. However, in 2012, a group from Medtronic wrote that the MARD was 9,9% [55]. Similarly, a Medtronic funded study published in 2014 reported the MARD for the Enlite sensor to be 13,6% [56]. In 2017, another group reported the MARD for the Enlite sensor to be 19% [57]. The new Guardian 3 sensor, which is used in the new HCL insulin delivery system, is less well studied. In 2017, Christiansen *et al.* evaluated the accuracy and performance of the Guardian 3 CGM and reported a MARD of 10, 3%, when calibrating every 12 h and 9, 6% when calibrating 3-4 times per day (58). The MARD reported in promotional materials by Medtronic is 9, 6% for the Guardian 3 sensor.

Despite the advances in technology, the current artificial delivery system requires significant patient and provider involvement in addition to high-resource utilization on initialization. The novelty of this system demands ongoing involvement from device representatives to help users and providers learn the new system. Despite the terminology of "auto mode" and the non-modifiable blood glucose targets of 120 and 150 mg/dl people have found ways to consistently decrease blood glucose levels below the target This is achieved by the administration of "phantom carbohydrates", where the users inform the insulin pump that they are going to eat carbohydrates, when they are not going to eat anything. It are these patients who are hypoglycemic on the HCL system.

Very recently, the FDA approved the first long-term implantable CGM, as the maker Senseonics annonced at June 21th 2018. The Eversense CGM system features an implantable glucose sensor that can remain in place for up to three months, beating out the usual wear time of 3-10 days for many of the other CGMs currently available. The small cylindrical device, measuring 3, 5x18, 3mm is made of a fluorescence-based glucose sensor implanted s.c. under local anaesthesia in the patient's upperarm. The glucose data is then transmitted via Bluetooth to the user's mobile application and stored in a HIPAA-compliant cloud. The approval was largely based upon positive findings from the multicenter PRECISE 2 trial which tested the system in 90 patients with type1 and type 2 diabetes. Although the accuracy of the device was questioned

in the first 30 days of wear in the trial, the overall accuracy of the device throughout the 90 day studu was high, with a MARD of 8,5% (95% CI;8,0%-9,1%) from 15,735 unique readings. The device was able to alert the user to 98% of hyperglycemic events and 95% of hypoglycemic events; however, 17% and 16% of these were false positives. Much of this latest research will be presented at the upcoming ADA meeting in Orlando, USA [79].

Monitoring Glucose in Alternative Physiological Fluids

Interstitial Fluid

Blood and the surrounding vascularised tissue readily exchanges biological analytes and small molecules by diffusion with the interstitial fluid [10,59]. Methods for monitoring glucose via the skin have become very popular in recent years, where these approaches have been developed to counteract the challenges with patient compliance and invasive monitoring [59]. Some of these approaches include sensing by optical detection such as light absorption or fluorescence detection, ultrasound or sonopheresis, polarimetry, heat or thermal emission, electromagnetic techniques, photoacoustic detection, Raman or bio-impedance spectroscopy, electrochemical methods and reverse iontophoresis-based electrochemical sensing, among others [35,59-62]. A limitation of reverse iontophoresis is that typically stable measurements can only be recorded for a period of 24 h before calibration is required. The Glucowatch used this technique. Although this device was a considerable advancement towards non-invasive CGM the method was hampered by the frequent calibration resulting in exceeding costs for testing equipment. Other drawbacks included long warm up times, sweating and skin rash with irritation [9,50,59,63].

Sode *et al.* have developed a self-powered implantable CGM device called the Bio Radio Transmitter for use in an artificial pancreas [64]. This device was composed of a capicitor, radiotransmitter, and receiver. In the presence of glucose, the capcitor of the Bio Radio Transmitter device discharges a radiosignal, which is recieved and amplified by the radioreciever. The change in transmission frequency is then related to the glucose concentration [64].

Microneedles and microneedle arrays have also garnered a lot of interest over recent years for interstitial fluid sensing, since this approach can offer minimally invasive methods for bio-sensing. This concept was used in the development of a glucose-sensing path by Jina *et al.* [61]. The device was designed in two comparments: the first containing the microneedle array and glucose biosensor with the second containing the electronics. Tests have shown that this device can operate successfully for up to 72 hours with only a 17-minute lag time caused by the passive dffusion of analytes from blood into the interstitial fluid matrix [61]. The device must be recalibrated daily. Potential clogging of the microneedles and the distortion of their shape upon the skin are other shortcomings [61].

Russell *et al.* where the first to introduce a tatoo sensing technology using hydrogel microspheres [65]. Zhi *et al.* further developed the technology by encapsulating the sensors in a thin film, which offered the advantage of fast analyte transport through the device [62]. These fluorescent mcrospheres however are subject to early destruction or rejection from the innate host immune systems upon transplantation in the dermis. Other methods for interstitial fluid sensing which are currently under development include sensors based on impedance spectroscopy (Pendra by Pendragon Ltd., Zürich, Switzerland) and optical transducers (C8 Medisensors Optical, Inc. San Jose, CA, USA).

Urine

Due to the intermittent nature of this fluid, where collection is required for sampling, it cannot be incorporated into a continuous glucose monitoring device.

Sweat

Although sweat sensing for diagnostic data might be very promising, there are also some concerns with this sensing fluid [66]. Among these are limited knowledge about the sensing fluid, and sampling issues associated with sweat production by exercising and contamination by the skin surface. The pH of sweat fluctuates over a wide range from pH 4,0-6,8 which can interfere with sensing. Moreover, the rate of sweat production can be very low or absent.

Breath analysis

Nanomaterials can be incorporated into sensing elements for monitoring acetone concentrations in breath, as an alternative to glucose monitoring for diabetes [67]. Ethanol and methylnitrite have also been identified as biomarker for diabetes [68]. Acetone levels in blood are approximately 330 times higher than in breath, at 0,1-2 p.p.m. for healthy induviduals' post-glucose loading and reaching to up to 103,7 p.p.m. in critically ill diabetic patients [69]. Therefore, the sensing units must have a high sensitivity to detect volatile organic coumpounds (VOCs). Jiang *et al.* have reported a breath acetone analyzer, which can detect acetone levels in diabetic patients [69]. Unfortunately, the device requires a controlled external atmosphere in order to diagnose diabetes accurately, where the reported diagnostic accuracy is estimated at 74%. However, other factors can affect acetone levels, including fasting, exercising, dieting and intra-individual variation, thereby limiting the use of acetone as a specific biomarker for diagnosing and monitoring diabetes [70].

Saliva

Saliva is a complex fluid containing many analytes that permeate in blood [59,71]. As a result, saliva has been investigated as an alternative fluid for non-invasive glucose sensing, with glucose levels for a healthy ndividual ranging from 0,23 mmol/l to 0,38 mmol/l and between 0,55 and 1,77 mnol/l for diabetics [59,72]. Although a relationship between glucose levels in blood and saliva obviously exists, it is not well understood, and relating saliva concentrations to therapeutic intervention is therefore more challenging. However, saliva offers many advantages for diagnostics, the main benefit being that saliva can be collected in a non-invasive fashion. As a result, there have been many emerging technologies reported for continuous and non-invasive glucose detection in saliva, using everyday platforms including mouth guards and dentures, as well a novel device, such as dental tatoos [59,73].

Kim *et al.* developed a lactate sensor for saliva [10,73]. This sensing approach has the potential to be used for glucose biosensing, by replacing the lactate sensor with a glucose sensor. Intraoral dental sensors have been of interest for non-invasive CGM. A tooth has the potential to act as a CGM device as it is in contact with the patient's saliva. Mannoor *et al.* developed a bacterial detection approach whereby a graphene-based nanosensor was printed on to water-soluble silk and transferred on to tooth enamel. This device operates by

the self-assembly of antimicrobial peptides on to the single sheet of graphene, where the bio-selective analysis can be performed at a single cellular level. This sensor could be replaced by a glucose sensor in the future [74].

Ocular fluid

The fluid surrounding the eye and ocular tissue, also known as the aquous humour, contains many analytes present in blood. This fluid can be excreted in the form of tears. Analytes in this fluid, such as glucose, ascorbic acid, lactate, proteins, peptides, hormones, carbohydrates, electrolytes, lipids and chloride can offer great insight in an individual's health status [59,71]. Recently, the Google X Lab and Novartis have collaborated on the development of glucose sensing techniques in the aquous humour. In 2014 they announced a smart contact lens to overcome CGM obstacles associated with current methods, which are either invasive in the case implanted wearable devices or non-continuous in the case of the finger=pricking approach. This novel technology incorporates an electrochemical battery-operated enzymatic glucose sensor, utilizing the enzyme glucose oxidase (GOx), in a microchip sandwiched between two layers of a soft contact lens. A tiny sensor relays data to a mobile device, from which the patient or physician can read the corresponding glucoe level in the ocular fluid [76].

However, there are disadvantages to an electrochemical sensing approach, which can be related to the use of enzymes leading to the production of corrosive hydrogen peroxide as a by-product or interference from electroactive species in the ocular fluid, such as ascorbic acid, lactate or urea [77]. Blinking may also stimulate a movement artefact in the wireless sensor signal. In addition to the battery source embedded in the lens, an external power source must be provided for enablng efficient sensor function and to facilitate wireless communication of the data. This is a very active area of research investigating the production of a safe biocompatible battery device [78,79].

Conclusion

Wearable sensors have the potential to play a major role in the coninuous and non-invasive monitoring of biomarkers for diabetes and other diseases. The majority of sensors still require further evaluation for clinical use. A key enabling step will be to create a better understanding of the relationship between blood glucose concentrations compared to glucose concentrations in other physiologically fluids. Existing wearable devices such as fitness bands and smartwatches are not accurate enough to be integrated in clinical practice. Currently FDA approved CGM systems generate 228 glucose measurements a day creating a flood of previously unavailable data and creating a new headache for physicians to review these data in order to determine the best course of treatment for their patients.

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