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Recent Development and Challenge of Glucose Sensing: a Review

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ABSTRACT. *As the number of diabetes patients escalates, glucose monitoring has been an emergent need for the diabetic people. Continuous glucose sensing (CGM) and self-monitoring of blood glucose were proposed to realize real-time management of blood glucose level. With the aid of these devices, it is possible that diabetes patients can modify their treatment and therapies accordingly. This paper reviews the constitute of typical CGM systems, the category of CGM and mechanism by analyzing experiment results and existing commercial products. SMBG, a point-sample blood glucose testing, is briefly discussed. Although glucose monitoring has convincible performance in laboratory, they are not applied widely due to some shortcomings. Several challenges are issued and their future trends are briefed. The review concludes that a user-friendly, painless products would be developed and is promising to benefit the diabetic patients.*

KEYWORDS: *Continuous glucose sensing (cgm), Self-monitoring of blood glucose (smbg), Diabetes*

1. Introduction

Diabetes were firstly discovered by ancient Egyptians in B.C 1500, which was considered as a rare body situation then in that age. Patients suffered from frequent urination and weight decline. Matthew Dobson detected and discovered the rise of glucose level in urine of patients until 1776. Since paper about diabetes were published in public until 1812, this disease was finally recognized completely by clinical practice. Although pathogenesis of diabetes is clearly understood and effective approaches are discovered in detection prevention and care area, cure methods are still under research.[1]

Diabetes, a saccharide-related disease, is the failure transportation of glucose in blood of cells in body. Consequently, insulin produced by pancreas is highly demanded to digest glucose to maintain metabolic blood glucose concentration. A significant rise of blood sugar level even the abnormal glucose level in urine would be detected as a result of inadequate insulin secretion. Diabetes can be classified into

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various types according to different causes but mostly they are relevant to insulin. Type I diabetes stands for the loss of function of body insulin production or limited exudation deficient for metabolic cycle. It's caused by immune fault attack to cells that produce insulin. Type II diabetes is caused by resistance of insulin and lack of insulin production. Insulin cannot work effectively since target organ fails to receive it due to some failure. Type II diabetes is the most common type which makes up around 80% to 90% of all patients.

In fact, the morbidity of diabetes has escalated in past two centuries especially in the last three and four decades. Therefore, in the view of public health and society, diabetes becomes one of the most common and tough epidemics. According to International Diabetes Federation (IDF) [2], 41.5 million adults suffer from diabetes half of which is not diagnosed. IDF's estimation also indicates that 5% -20% medical budgets in most countries would be applied on diabetes. As a chronic disease which can potentially give rise to comorbidities including renal illness, cardiovascular disease, cataract, and retinopathy, diabetes management is still a cutting-edge topic. [2]

2. Continue Glucose Sensing (Cgm)

American biochemist Leland C. Clark invented the first electrode to monitor oxygen in 1954. He used glucose as well as glucose enzyme (GoX) to eliminate oxygen. This simple device has been applied to measure oxygen, which gradually become a significant prototype of glucose sensor. [3] In 1982, Shichiri implanted a needle-based glucose sensor subcutaneously in human body. The sensor along with a small transmitter unit constructed the core of the first portable and wearable CGM. In 1990s, MiniMed (Northridge, CA, USA) developed the first CGM product for clinical use. The CGM was then approved by Food and Drug administration in US, indicating an important evolution of CGM.

Continuous glucose sensing (CGM), a useful approach of glucose level detection, can easily provide the trend of glucose levels. A sensor connected with transmitter is implanted subcutaneously to gain insight view of glucose level. Signal transmission and receiving, modified as receivers, are replaced by smartphones and smartwatches. Adjusting and calibration times are reduced that may improve the experience of patients. [4] MEMs-sensor technology as well as biocompatible materials have made great contribution to these developments. [5]. CGM systems can indicate the tendency, fluctuations and magnitude of glucose level. Patients may change their recipe or therapy with the aid of suggestions or alarm provided by CGM.

A typical CGM system is composed of fundamental parts. Glucose sensor is aimed to detect sugar level. Signal transmitter and monitor is for data interpretation and display. Suitable amount of insulin would be injected by the insulin pump. CGM glucose sensor can be embedded into epidermal skin as the sensor will detect the glucose level in interstitial fluid and send signal to CGM monitor simultaneously after processing. GOx is immobilized on glucose sensor and is applied to oxidize glucose in ISF. Instantaneous current generated by redox reaction travels through

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internal wires. Equipped with micro calculation part, monitor will predict glucose trends and order the insulin pump to inject hormones.

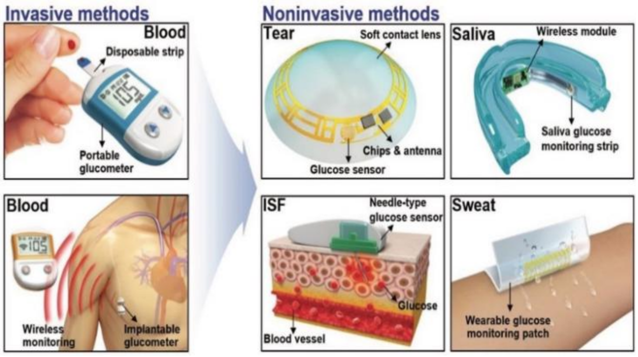

Fig. 1 Invasive and non-invasive glucose sensing [6]

2.1 Invasive glucose sensor

Detection of glucose in blood has been one of the most prevalent applications of enzyme-based sensors. A large number of portable devices have been developed for blood glucose monitoring. Equipped with strips and needles which collect blood, portable glucometers can investigate the sugar level in blood. Sensors which are transcutaneous or subcutaneous implanted are a typical symbol of invasive CGM. Due to a quick updating CGM technology, accuracy, sensitivity, power-supply and calibration have been developed in recent years. Gabriela et al. [7] constructed a needle-based self-powered glucose sensor with good distinction of glucose against interferences including ascorbic and uric acid. Jiang et al. [8] developed a low-invasive glucose sensor with less than 1mm implanted length, which displayed a similar trend as conventional sensors and excellent selectivity. Although the invasive sensor enjoys prestige of small-size and accuracy, diabetes patients are reluctant to applied the sensors due to pain and sense of uncomfortableness. Unpredictable shift and lag of sugar level has been discovered in these devices, requiring a frequent calibration. Few days lifetime restrict the long-term usage [9]. Experimental data may be less convincible when transfer to clinical use and there is still a gap between research and commercialized product in CGM.

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Fig. 2 Different technology for minimal-invasive and non-invasive glucose sensing [10]

2.2 Non-invasive glucose sensing

Another branch of the glucose monitoring, non-invasive glucose sensing, which can conduct many painless glucose sensing of diabetes patients. Such technologies employ other biofluid such as sweat, saliva, urine, tears and interstitial fluids (ISF) [11][12] but fail to provide a similar accuracy as invasive method [13]. Furthermore, the biofluids mentioned above are unlikely to become eligible analytic of CGM. Tissue sites such as oral mucosa, skin and tongue can be suitable testing places [9]. Figure-2 shows the technology employed by minimal-invasive and non-invasive sensing. Optical and transdermal are two main categories of non-invasive glucose monitoring.

(1) Optical Polarimetry (OP)

Glucose as a chiral molecule, which can rotate the plan of polarization, can be utilized in optical polarimetry. The rotation angle is proportional to the glucose concentration in tissue. Wavelength of the beam is typically in a region between lower region of optical band and upper of NIR. This approach is usually applied on aqueous humor in eye rather than skin because of the optical properties. Light coming from the source is polarized, reflected by the eye and finally received and analyzed. [10] This approach is still in experiment stage due to safety consideration. [14]

(2) Raman spectroscopy

When light emitted from the beam collide with the target, it is scattered to different directions. Small portion of the scattered light reveals a various wavelength,

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which is known as Raman scattering. Since different chemical bonds and structure would produce distinct wavelength difference, Raman spectroscopy can detect glucose by capturing the rotation and oscillation mode inside the molecule. In 2011, a Raman spectroscopy-based glucose sensor, C8 MediSensors (CA, USA) was approved. This device applied light on abdomen skin and analyzed the scattered light to indicate the concentration of glucose. However, this company was closed due to financial difficulties, implying a dilemma of Raman spectroscopy in glucose sensing.[15]

(3) Near-Infrared spectroscopy

Near-Infrared spectroscopy employs light within 750-2500 nm range to capture the absorption or emission of light interact with the tissue. Narkhede et al. have conducted a research about NIR glucose sensing system. It has been discovered that NIR can provide prediction about the tendency of glucose level in human body [16]. Shinde and Prasad [17] developed a blood-glucose testing method based on NIR spectroscopy. They applied Fast Fourier Transform to analyze the optical signal data. It has been observed that evident frequency variation in diabetic patients. Frequency change was disappeared when testing healthy persons. The violence of frequency variation is proportional to the sickness of patient.

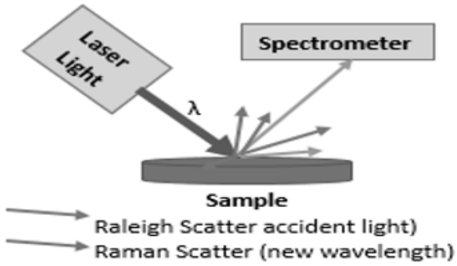

Fig. 3 Raman spectroscopy [14]

(4) Reverse iontophoresis

This technique is to generate current through small portion of interstitial fluid (ISF) beneath tissue by attaching two electrodes on the surface at skin. Once the skin is charged, molecules in ISF will move spontaneously to maintain neutrality. As shown in Figure 3 Migration of sodium ion gives rise to transfer of electro-osmotic flow with glucose to cathode [18], at which a Gox sensor is installed. *GlucoWatch* (Redwood, CA, USA), a reverse iontophoresis-based glucose sensor, was a wristwatch approved by FDA. It can provide real-time monitoring every 10 minutes. However, this device fails to satisfy the market due to its instability in sweating and temperature change as well as skin irritation. Sugar BEAT^{TM} (UK) is another arm ring glucose sensor which measures at 5-minute interval. This product is promising but has not been CE-approved [19].

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(5) Bio-impedance spectroscopy

Two electrodes are installed on the surface of the skin tissue to investigate the dielectric variation due to glucose concentration. Based on a finding that glucose concentration triggers the change of concentration of sodium and potassium ions [20], which would further change the conductivity of membrane in red blood cell, this technique can measure the current change to indicate glucose concentration. T. Raúl Sulla et al. [21] applied AFE4300 and found the relationship with glucose concentration and impedance. Generally, the positive bioimpedance indicates a decreasing glucose level. However, their results suffer from a deviation caused by temperature, suggesting potential demerits of this method. Pendra® is a wristwatch glucose sensor developed by endragon Medical Switzerland. The device failed to survive in market due to a poor accuracy [22]. This technique completes the proof-of-concept but struggle to win in market.

Although these methods are painless and more acceptable for diabetes patients, the accuracy and efficiency of the testing should be taken into consideration compared to the invasive devices. The relationship of sugar level between biofluids and blood is yet to be investigated, which is one of the unsolved barriers hindering the non-invasive glucose monitoring [6]. Detailed discussion will be in challenge part.

3. Self-Monitoring of blood glucose (SMBG)

SMBG devices are very similar to CGM systems in glucose detecting aspect. Both of them make use of the current generated by the reaction of glucose and GOx to indicate glucose level in blood. These two devices also share working environment which locates in epidermal skin. Differences occur in another working mode of SMBG devices that requires blood sample collecting. Essential wound is created and capillaries are applied to prepare blood sample. The reaction takes place in ribbon with GOx immobilized in advance. After electrochemical reactions, current would be detected by meter and transferred to other signal to display glucose level.

SMBG devices mainly constitute working electrode and reference electrode. The first electrode, coated with enzymes including GOx, may generate varying current due to redox reaction. The reference one is set as constant potential to support reaction. Enjoying the prestige of reasonable price, quick response and simple operation, SMBG devices has been popular in blood glucose monitoring. However, essential wound of blood sample also brings unavoidable pains as well as possible infection for diabetes patients. The testing data is instantaneous which fails to predict trend. This also gives rise to multiple pricking and may increase burden of patients. [23]

Allemann et al. [24]discovered that 1) SMBG has long-lasting controlling effect on diabetes; 2) SMBG leads to a more frequent recording of hypoglycaemia; 3) the positive effect of frequent SMBG is considerable comparing to less intensive SMBG.

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4. Challenges

4.1 Accuracy

A crucial fact that hinders the widespread use of CGM devices was the accuracy. Many ideas of glucose monitoring indeed obtained good results in experimental stage, but extremely small portion of them were implemented in products and survive in the market. At the early stage, physiological lag of glucose from blood and interstitial fluids led to sensor delays and calibration error. Delay is still a significant limitation of real-time CGM. Accuracy decreases when glucose level is low, indicating a hysteresis warning of impeding hypoglycaemia [25]. Thanks to the boost of technology, measuring lag decreases and preciseness is modified as CGM updates quickly. In 2017, *Freestyle Libre* with mean absolute relative difference (MARD) of 11.4% [26] was approved by FDA to provide diabetes treatments without pricking finger checks. Increasing accuracy of CGM is hopeful and promising.

4.2 Cost

Cost is another important consideration. Insurance and reimbursement cover partly of retrospective CGM rather than real-time CGM for type 1 diabetes patients in USA. As registrations, treatments, hospitalization are normalized as similar diseases, specific solutions including CGM seldom occurs in health plan. Facing with pricing issues, patients tend to choose cheaper one but may influence the treatment. As most study indicate, T1D patients would benefit from CGM if they wear the device in majority of time. Long-term cost should be considered.

4.3 User experience

For SMBG and invasive CGM devices, patients are reluctant to apply them because of pain. Many potential issues such as infection and contaminations are closely-related to wound of issue. Prior education about CGM system, including the installation and removal of sensors, interpretation of data should be taught to patients. This information is necessary but complex comparing to normal medical devices. Patients have to understand benefits and potential risks brought by CGM. Relative high learning requirements has been a barrier needs to be resolved between patients and technology. Fortunately, users can visualize and analyze their glucose level in smartphones and PCs. A lot of researches have been conducted on non-invasive sensing, suggesting the painful testing experience would gradually be a part of memory.

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4.4 Instability

The patterns of the glucose monitoring are not stable due to a closed-loop system. Nevertheless, control algorithm can exploit further information if the patterns are stable. Erratic measuring patterns can reveal the data indeed, but fail to allow a systematic analysis. Nowadays, users can store or read their measuring data in local or cloud with the intervention of smart CGM.

Calibration is a necessary process prior to applying the device. Pairs of invasive and non-invasive testing would be employed in this process, which is considered as an important reason for discomfort. Therefore, a good glucose sensing product is expected to require shorter calibration time and painless process. For instance, *Pendra* requires a 3-day calibration process while *Sugar BEAT* needs finger-prick reading every 24 hours. These examples also imply that calibration frequency is an issue to be resolved. Recent manufactures have managed to reduce the frequency of their products. *GlucoTrack* allows calibration every 6 month. Researchers and developers have been aware that users' appliance and acceptance are vulnerable to the duration and complexity of calibration. [15]

5. Conclusion

The paper briefs the tough situation of diabetes and illustrates the basic part and working mechanism of continuous glucose monitoring (CGM). Invasive sensor as well as the category of technologies applied in non-invasive sensor are introduced. Optical polarimetry has good performance and accuracy in experiment but suffer for safety risks. The paper also reviews the principle and mechanism of Raman and near-infrared spectroscopy. Although several challenges such as poor accuracy and complex calibration still persists, more recent devices show considerable modifications. More advanced products would be developed to benefit diabetes patients with rapid-evolving technology.

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