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Glucose Screening Measurements and Noninvasive Glucose Monitor Methods

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Abstract

Diabetes alone does not affect the health, but its complications always bring danger to people's health. To avoid the development of diabetes and posterior to discover diabetes, checking blood glucose level is an effective way. The development of glucose screening measurements is introduced. Non-invasive glucose monitor methods, as accurate, safe, convenient and comfortable methods, are also illustrated and compared in this paper. Also, an Intelligent dynamic health inspection is designed with a proposed non-invasion glucose monitor measurement.

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1. Introduction

Diabetes mellitus, as a common disease worldwide, the early symptom of which is not apparent. In the real-world application, people with diabetes are often discovered with diabetes complications, such as hypoglycemia, hyperglycemia, diabetic coma and nonketotic hyperosmolar coma, which may cause significant health issues [1, 2]. To reduce the incidence of diabetes complications and diabetes-related health problems, maintaining blood glucose in a relatively normal range, e.g., the range of glucose for a healthy person should be 4.4 to 6.1 mmol/L, while the glucose of a well-glucose-control diabetic patient may be just below 7 mmol/L, is an effective way [3].

In the procedure of managerial diabetes, blood glucose monitoring is of great value. From the perspective of short-term benefits, monitoring blood glucose can master blood glucose fluctuations, guide medication and diet schedule, monitor the events of high and low blood glucose and prevent ketoacidosis [4, 5, 6]; From the perspective of long-term benefits, controlling blood glucose can improve glycated hemoglobin levels, reduce the incidence of microvascular and macrovascular diseases and decrease the incidence of mortality [7, 8, 9].

Furthermore, the condition of self-monitoring glucose level in diabetic patients is not adequate. Observing over 5953 diabetic patients from 50 medical institutions in 29 provinces, as Fig. 1 shows, only 18.98 percentages of them screen their blood glucose and only 7.27 percentages of them check their glucose level at least once a day [10].

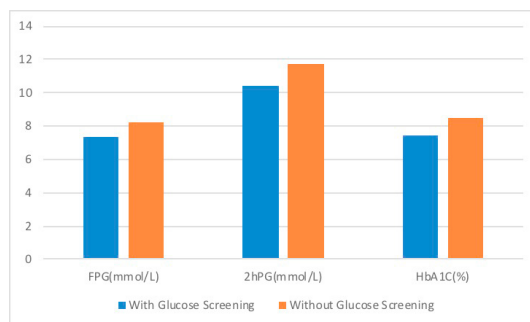


Fig. 1. The condition of self-monitoring glucose level in diabetic patients.

Additionally, monitoring glucose is necessary for Non-hyperglycemia, e.g., potential hyperglycemia, gestational hyperglycemia and in-hospital hyperglycemia. People of pre-hyperglycemia can control their habits and diets to prevent the risk of developing diabetes; During the period of gestation or hospitalisation, stress, recreation, drugs and other causes can cause a transient increase in blood glucose, as shown in Fig. 2, a cross-sectional survey conducted by the University of Tennessee Medical Center shows that 38 percentages of hospitalised patients have hyperglycemia. However, one-third of them have no history of diabetes (Non-hyperglycemia) [11]. Therefore, blood glucose management should not be limited to diabetic patients. Measuring blood glucose should be part of a daily health record to maintain blood glucose as well as measuring weight to keep fit.

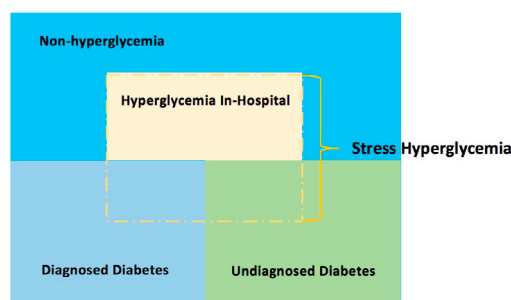


Fig. 2. The condition of Hyperglycemia In-Hospital.

The organisation of this paper is shown below: Section 2 illustrates and compares the different glucose monitoring types of equipment and their testing measurements. Then, this paper concludes seven non-invasive technology and compare them with merits and demerits in section 3. Section 4 illustrates two possible research directions and proposes a non-invasion measurement to monitor the blood glucose. Section 5 summarises this paper.

2. The development of blood glucose monitoring measurements

2.1. Equipment

In the processing of maintaining the blood glucose level in a stable range, the screening glucose is one of the essential equipment to monitor blood glucose and control it in a relatively normal range.

- **Ames Reflectance Meter:** The first blood glucose meter is the Ames Reflectance Meter, which was developed by Tom Clemens in 1969 [12]. The Ames Reflectance Meter allowed diabetic patients to monitor blood sugar levels themselves. Indicating the intensity of blue light with a needle, which was reflected from a named Dextrostix paper strip [13, 14]. There are quantitative numbers of glucose levels according to different exposure performances of the Dextrostix [15].
- **Reflomat:** Boehringer Mannheim released the first portable blood glucose meter in the world which was designed for healthcare professionals office in 1974. It only requires a small number of blood [16].
- **MediSense:** In 1987, the first biosensor system to screen blood glucose named as the ExacTech, which was launched by MediSense. An enzyme electrode strip was applied and developed at Cranford University and Oxford University in the United Kingdom [17].
- **Four generations of glucose meter:** It was produced in the 1990s. It made sample sizes vary from 30 to $0.3\mu\text{l}$, and then the testing consuming time would be varying from 5 seconds to 2 minutes, while that of current meters typically require less than 15 seconds.

All of the equipment mentioned above requires the blood sample extraction, and the processing of blood extraction relates with pricking fingertip, pricking ear, exsanguinating and so on [18, 19, 20]. As monitoring blood glucose needs long-term values of blood glucose, including more than 4 times every day [21]. Therefore, persistently extract blood and record glucose level are the most reliable ways of screening glucose level for people with diabetes or pre-diabetes. However, frequently pricking skin is not only uncomfortable but also inconvenient. In fact, puncturing skin may irritate skin, and it may be inaccurate if there are any changes in the condition of the body or the temperature of surroundings. Extracting blood samples by pricking skin is the risk of incorrect, infection, inconvenient and uncomfortable for people. Therefore, accurate, safe, convenient and comfortable measurements to check the blood glucose level are required.

Another equipment, continuous glucose monitoring is, therefore, proposed. Continuous Glucose Monitoring (CGM) can measure blood glucose continuously, which makes it very easy to study the pattern and trend over the whole day. A sensor of CGM is usually inserted under the skin to monitor the glucose at any time [22].

2.2. Testing measurements

There are three types of testing blood glucose, including Glycated haemoglobin (HbA1c), Self-monitoring of blood glucose (SMBG) [23] and ambulatory glucose profile (AGP) [24] as shown in Table 1.

- **HbA1c** can reflect the average of plasma glucose level over the previous two to three months [25]. The measurement of HbA1c does not need special preparation to test the glucose value at any time of the day. Therefore, Recently, the HbA1c measurement is applied to screening potential diabetic patients [26].
- **SMBG** can collect the value of blood glucose at any time points conveniently, it is, therefore, recommended to diabetic patients to randomly check their blood glucose level. Besides, the results are always accurate. However, the SMBG measurements involve the blood sample extraction, which is inaccurate, infection, inconvenient and

uncomfortable. Moreover, the results are discrete rather than continuous. Some important points of glucose values are often missing [27].

- AGP can interpret the daily glucose pattern for people [28]. The AGP measurement can obtain adequate data of the blood glucose to analyse the highest and the lowest points [29]. However, it is difficult to interpret the result, and the calibration is still required [30]. Noninvasive technology develops from AGP, and it is becoming more popular because of its convenience and its characteristics of pain-free.

Measurements	Merits	Demerits
HbA1c	Reflect the average blood sugar level of 2-3 months, which is a good standard for the long-term blood sugar control level	Unable to reflect high blood sugar and low blood sugar; Unable to reflect the diurnal fluctuations of blood sugar
SMBG	Provide only blood glucose information at the current time point	Even if test 6 times a day, people often miss high blood sugar and low blood sugar; With pain; Unable to get continuous blood glucose data at night; It is very time consuming to interpret the blood sugar fluctuation pattern through blood glucose records
AGP	Provide large amounts of glucose data	Report is more difficult to interpret; Blood calibration is still required

Table 1. The comparison of current glucose measurements.

3. Non-invasive technology

The challenge of blood glucose monitor is painful and inconvenient, the non-invasive method is, therefore, a feasible solution.

The technology of Polarization change is the first proposed noninvasive methods. Paper [31] described a non-invasive sensing of optical polarimetric blood glucose. Laser light of helium-neon was coupled according to a linear polariser, and the phase was related with the rotation vector proportionally. Paper [32] proposed a sensor design, based on the different body impedances according to different blood sugar levels. Paper [33] provided blood glucose and accounted for the mismatch of the index. The proposed method disclosed eye-coupling designs with no or minimal contacting. As shown in Table 2, it applies visible light, but it is sensitive to eyes [34, 32].

Raman spectroscopy [35] can observe low-frequency modes. Paper [36] proposed a Raman spectroscopy sensor of surface-enhanced, which is short for SERS. The SERS based sensor facilitated interactions between the surface and the glucose molecule. Paper [37] used a laser light and induced rotation and oscillation through molecule vibration. The vibration could be different with a different glucose molecule. In Table 2, the Raman spectroscopy technology display as fixed wavelength lasers, and it is not stable for the wavelength and intensity.

Paper reviewed various methods of the fluorescent spectroscopy [38] is an electromagnetic spectroscopy technique, which can analyse fluorescence of a sample. Paper [39] indicated a slight increase in the people with concomitant diabetes. Because it is related with a more poor prognosis, the increased number of white blood cells is insofar important index. Paper [40] reviewed various methods of the fluorescence-based blood glucose sensing and their current status. Paper [40] evaluated an IV-CGM system with a sensor. The accuracy of the IV-CGM system is high. From Table 2, fluorescent spectroscopy can use the visible light spectrum, but lead to the phenomena of scattering.

Near-infrared spectroscopy [41, 42] applies near-infrared light of 780-2500nm. Glucose level can be estimated according to variations of light intensity. Paper [43] investigated non-invasive measures for healthy subjects and solved the restriction of instability. Paper [44] established matched references and removed the systematic errors. Table 2 implies that NIS technology owns high energy, but it is not clearly delineated [45, 46].

Mid-infrared spectroscopy [47] was developed from NIR principles by using the light of 2500-10,000 nm spectrums. Paper [48] combined the radiation and photo-acoustic detection, and then a specific non-invasive measurement was built. Paper [49] used a transducer and computed the distance of the sample surface and the first generated node to evaluate the blood glucose. In the fifth line of the Table 2, mid-infrared spectroscopy is sharper and having a poor condition of penetration [50].

Bioimpedance spectroscopy is painless measurement and can be applied to estimate the number of fluids and the body composition [51]. Paper [52] was developed from the impedance of tissue with the known intensity. From Table 2, we can observe that the battery is long lasting and it is difficult to calibrate [53]. Thermal emission spectroscopy is a measurement of the Mars Global Surveyor [54]. Paper [52] monitor specific wavelengths of glucose, such as $9.8\mu\text{m}$, $10.9\mu\text{m}$. Paper [55] demonstrated the reproducibility of monitoring glucose, which showed acceptable accuracy without the processing of calibration. Table 2 identifies the good performance of reproducibility and is easy to be interfered with the temperature and the body condition [56].

Technology employed	Author, year	Target site	Merits	Demerits
Polarization change	B.D. Cameron, 2001 [32]	Eye	The first proposed technology; uses visible light, easy	sensitive to eye
Raman spectroscopy	Lyandres, 2008 [36]	Skin	Fixed wavelength lasers can be used at a relatively low cost	Instability (the wavelength and intensity for the laser), long consuming times of the spectral acquisition
Fluorescent spectroscopy	Romey, 2012 [40]	Intravascular	The visible light spectrum is used, adequate for studying fluorescence of tissues	Lead to strong scattering phenomena
Near infrared spectroscopy	Acosta, 2006 [57]	Many regions or volumes of the body	High accuracy; High energy signal	relatively weak, not clearly delineated, quite laborious, not transferable.
Mid-infrared spectroscopy	von Lilienfeld-Toal H, 2005 [48]	Skin	Sharper than NIR, which is broad and weak	Poor penetration
Bioimpedance spectroscopy	Caduff, 2009 [58]	Skin	long lasting battery, remind of rapid changes of glucose	vary towards different individuals, difficulty in calibration, it is not suitable for all skin types
Thermal emission spectroscopy	O.S. Khalil, 2004 [59]	Skin of the forearm, fingertip or ear	Good reproducibility for detecting glucose concentrations	strongly interfered by the temperature and the body movement

Table 2. The comparison of current glucose measurement technology.

All of the aforementioned noninvasive methods are pain-free and convenient to monitor glucose levels. By this way, potential diabetes or diabetes can control their lifestyles to prevent or reduce the harm of hyperglycemia.

4. The Intelligent dynamic health inspection and our non-invasion glucose monitor measurement

4.1. Possible research interests

The common technology is invasive methods, including both of invasive and minimally invasive measures. As invasive methods may cause the pain, long consumed time, expensiveness and high risk of infectious diseases, e.g. the transmission of hepatitis and HIV, it is an annoying and patience-consuming task to measure blood glucose four times a day. It is, therefore, impossible to screen glucose continuously. Additionally, the service life of an invasive device is limited, generally only around 3 to 14 days.

Currently, the application of electrical and electronic equipment in the medical field for the purposes of clinical diagnosis and academic research has increased dramatically. Biomedical devices, i.e., wearable instruments, play a more significant role in solving medical issues and improving the quality of life than that of before. It is, therefore, highly desirable to develop a reliable, continuous (including instantaneous and cumulative blood glucose concentration), low prime cost, effective and comfortable measurement system to detect blood glucose concentrations. There are two research interests as follows:

- Minimally invasive and implantable device: The anti-infection mechanism, e.g., safe needle design and waterproof treatment, as well as the the communication chip design, e.g., directly uploaded to the diabetes management cloud platform, no additional scanning, are improved directions for the minimally invasive device; Another research direction for the minimally invasive and implantable device is that the operational life span should be longer than 15 days.

- Non-invasive wearable blood glucose measuring equipment: Optical signals: A fingertip measuring instrument and electromagnetic field technology: a smart watch, are improved directions for non-invasive device.

The development of the above two devices can achieve a hypoglycaemia risk prediction 30 minutes in advance; Moreover, the result of the device should be consist with that of the regular fingertip blood as more as possible and the accuracy should be higher than 90 %. Non-invasive blood glucose measuring device is a recommended method between the mentioned two research directions to monitor an individual's blood glucose level continuously. In the next subsection, a feasible non-invasion method is, therefore, proposed.

4.2. A feasible non-invasion monitor measurement

With the analysis of the technique and equipment described in section 2 and section 3, a new glucose monitor measurement without pain is proposed in this subsection. Specifically, the application architecture of NB-IoT (Narrow Band Internet of Things) [60] is employed in our non-invasion blood glucose equipment. Also, an active sensor collects and studies the body temperature, heart rate, pulse, and walking status as well as the blood glucose of people and their corresponding NB-IoT architectures. Then, our measurement can screen the whole condition of an individual and check the measured value of blood glucose with the other physiological features. The proposed non-invasion measurement, therefore, calibrates individual's level of blood glucose without a blood sample. In this way, the proposed method enhances the accuracy of measuring blood glucose. Fig. 3 shows the three processes of our non-invasion glucose monitor as below.

- Power and Device module: The design of power provision is illustrated in Fig. 3. This module provides the energy for the equipment, and the button indicator light is also included.
- Feature acquisition module: This is the most primary part of our measurement. The multifunctional sensor collects physiological features with different dimensions including the blood glucose. Currently, the main issue of non-invasion methods is the low accuracy. The proposed measurement employs the other dimensions and the previous diabetes-related model to calibrate the observed value of blood glucose for an individual. Then, the accuracy could be greatly improved to meet expectations.
- NB-IoT communication module: According to the NB-IoT application architecture, IP address and the IMSI number can distinguish the terminal of the device in communication. The IP address and IMSI number of the destination terminal are added to the transmitted data packet, which ensures that the data packet arrives at the destination terminal and could be able to have appropriate reactions.

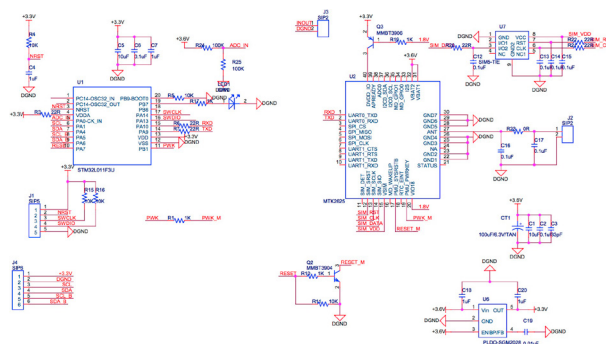


Fig. 3. IC Design for Our Glucose Monitor Measurement.

4.3. An application of the proposed measurement

There is an application of our measurement of blood glucose in Fig. 4, which is named as the intelligent dynamic health inspection (IDHI) model. Combined the calibrated blood glucose with the measured values of body tempera-

ture, heart rate, pulse, blood glucose, and walking status, the IDHI model can evaluate and predict the physical status of an individual. Besides, the NB-IoT function could transmit and receive signals and send out appropriate reactions [61]. Moreover, the device manager is the part between the user and the equipment. This part can also maintain registration and user accounts.

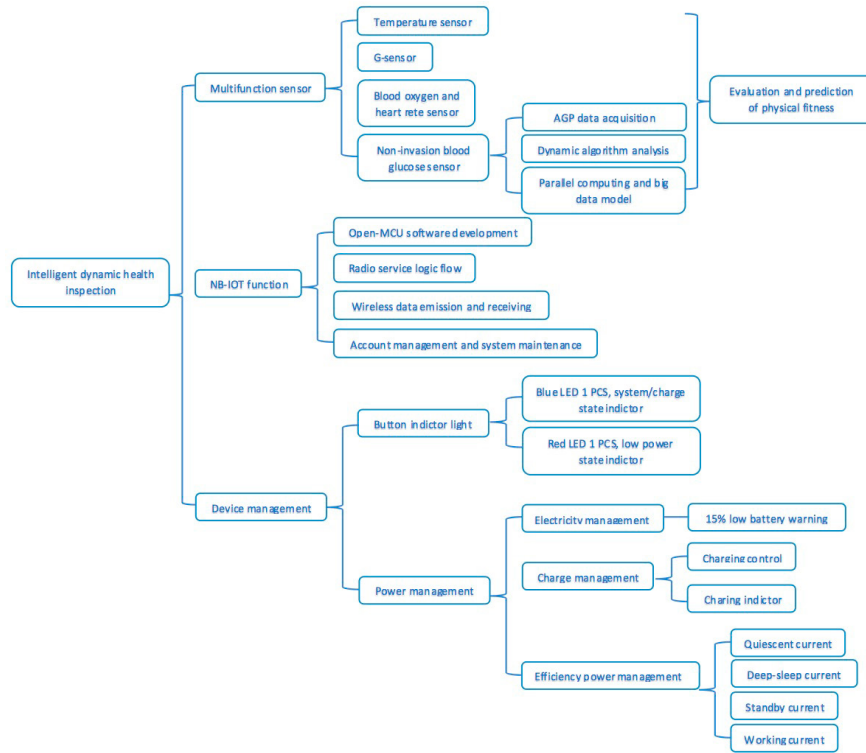


Fig. 4. The intelligent dynamic health inspection.

5. Conclusion

This paper describes and compares five types of equipment, three testing measurements, seven noninvasive methods of the blood glucose level monitoring. CGM equipment with AGP is one measurement that fits for the real-world application. Mid-infrared spectroscopy and near-infrared spectroscopy are two of the most useful technology to screen blood glucose non-invasively. Finally, a non-invasion glucose monitor measurement is proposed, and an application of the Intelligent dynamic health inspection is described to demonstrate the significance of our non-invasion measurement.

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