NON-INVASIVE BLOOD GLUCOSE MONITORING: A NEW APPROACH FOR DIABETIC PATIENTS

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INTRODUCTION

Description: What is Diabetes?

Currently, four main non-communicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes) are becoming global public health concern. The probability of dying from any one of four of them between the ages of 30 and 70 decreased by 22% globally 2000 and 2019 (World Health Organization [WHO] (2023).

Briefly, diabetes is a chronic (long lasting) health condition that affects how our bodies turn food we have eaten into energy (Center for Disease Control [CDC] (2023). The World Health Organization describes it is a chronic condition, which is diagnosed and monitored with blood glucose testing. Ordinarily, our bodies break down the food we eat into sugar (glucose) which is released into our blood stream. When the blood sugar rises, it signals one's pancreas to release insulin (hormones that regulates blood glucose) which acts like a key to let the blood sugar into our body's cells for use as energy.

On the other hand, diabetes disease occurs when one's body does not make enough insulin or can't even use the insulin released as it should. When there isn't enough insulin or the cells have stopped responding, too much blood sugar remain in one's bloodstream. That is, diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. The common effect of uncontrolled diabetes is hyperglycemia which is also called raised blood or raised blood sugar (CDC & WHO, 2023).

Over time, this abnormal blood glucose sugar level leads to serious damage to many body's systems-heart, blood vessels, eyes, kidneys and nerves with associating health problems (WHO, CDC, 2023). Diabetes can cause permanent vision loss by damaging blood vessels in the eyes. A number of persons with diabetes develop problems with their feet due to nerve damage and poor blood flow with consequential foot ulcers that may lead to amputation. Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar). Its chronicity means there is no cure yet for diabetes rather one can strive and live usually through instituting control measures- losing weight, eating healthy food, and being active (exercise) (CDC. 2023). Other precautions are; taking his medicine as prescribed, checking the blood glucose level, getting diabetes self –management education and support, and making and keeping health care appointment.

Diabetic patients must regularly check their blood glucose levels for medication and fluctuating levels as an integral control measure. Most of the current glucose monitoring methods are invasive, painful, time-consuming, and a constant burden for the household budget. Graciously, the so long desired non-invasive glucose monitoring devices are available as convenient, simple, 'minimally-in World Health Organization [WHO] (2023) invasive' or ''truly non-invasive glucose monitoring'' device.

Nutrition therapy is also commendable as a diabetic control measure for this chronic condition. The U.S Department of Agriculture (USDA) described several eating pattern designed to assist people to follow the recommendations enshrined in its dietary guidelines. Three specific food patterns developed by USDA: the healthy U.S. Style Pattern, the healthy Vegetarian, and the Healthy Mediterranean-Style Pattern. The American Diabetes Association's position statement in 2013 ''Nutrition Therapy Recommendations for Management of Adult with Diabetes,'' equally promotes the use of variety of eating patterns to help with the management of diabetes (American Diabetes Association, 2023). DASH (Dietary Approaches to Stop Hypertension) plan is one of the several eating pattern recommended. DASH plan is equally recommended for diabetic patients, as a dietary approach that is nutritious, balanced, and sustainable eating plan which could improve a number of health parameter- hypertension, insulin resistance, hyperlipidemia (high lipid blood level), overweight/obesity. This realization is, persons with diabetes are at higher risk of developing hypertension than persons without diabetes. Additionally, studies found the percentage of adult with diabetes ≥18 years of age who have hypertension was 57.1% in 2009 compared to 46.2% in 1995 (WHO, 2023). This suggests that the conceiting effort being put to help prevent and manage hypertension must also apply especially in diabetes population. DASH eating pattern is recommended for these patients because it is practicable; it does not require special foods or supplements, and it is an approach that is appropriate for patients' entire family to follow. In Nigeria, DASHDIET Africa (dashdietafrica@gmail.com), is being packaged by a Nigerian ''Culinary Wellness Expert & DASH DIET COACH, 'with amazing testimonies from both diabetic and hypertensive patients.

Globally diabetic people are cheered and encouraged annually. ''World Diabetes Day 2023: Need for equitable access to care for people with TB and diabetes''. Annually, 14 November celebrates person living with diabetes, 2023 theme highlighted the need for equitable access to essential care for people affected by diabetes and tuberculosis (TB).

Prevalence of Diabetes

Diabetes Mellitus is a disease caused by abnormal islet function and can be divided into type 1 (T1D, absolute insulin deficiency) and type 2 (T2D, relative insulin deficiency). According to the data published by the World Health Organization (WHO), there are about 450 million cases in the world at present and more than 150 million in China, which has the world's largest diabetes epidemic (Wang, Gao, Zhang, Huang & Zhang et al., 2013). The United Kingdom Prospective Diabetes Study (UKPDS) revealed that patients with type 2 diabetes mellitus may only have 50% of their islet function remaining at the time of diagnosis, yet pancreatic endocrine function can continue to deteriorate over time. As a result, many patients develop brittle diabetes, characterized by erratic fluctuations in blood glucose levels and challenges in maintaining stable blood glucose levels through conventional endocrine therapy (Holman, Paul, Bethel, Mattews and Neil (2008).

In 2014, literatures reported that 8.5% of adults age 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% from diabetes occurred before age of 70 years. Another 460 000 kidney disease deaths resulted from diabetes, and raised blood glucose caused around 20% of cardiovascular deaths (American Diabetic Association, 2020; WHO, 2023). And between 2000 and 2019, there was a 3 % increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increase 13%. According to WHO, 422 million people worldwide are having diabetes and, the majority of them are living in low-and middle-come countries and 1.5 million deaths are directly attributed to diabetes each year. About 38 million US adults have diabetes, and surprisingly, 1 in 5 of the do not know they have it (American Diabetic Association, 2023). Both the number of cases and prevalence of diabetes have been steadily increased over the past few decades (WHO, 2023). Diabetes is the eighth leading cause of death in the United States. Diabetes is the **No. 1** cause of kidney failure, lower-limb amputations, and adult blindness. In the last 20 years, the number of adults diagnosed with diabetes has more than doubled (CDC, 2023).

Global report on diabetes of June 22, 2023 did state that more than half of a billion people are living with diabetes worldwide, and it is affecting men, women, and children of all ages in every country, with every country seeing an increase (Lancet Diabetes Endocrinal, 2023).

Nigeria being of the 48 countries of the International Federation of Diabetes [IFD] African region, and being houses 537 million people with diabetes in the world and 24 million people in African Region being projected to rise to 55 million by 2045. In 2021, there were 96,812,400 total adult population, 3.7% prevalence and, 3,623, 500 total cases of diabetes in adults (IFD, 2023).

Types of Diabetes and dangers associated with them

There are **three major types of diabetes: type 1, type 2, and gestational (diabetes in pregnancy)**. The most common is type 2 diabetes referred as adult onset, usually occurs in adults when the body becomes resistant to insulin or not produce enough insulin. In the past 3 decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, (previously called juvenile or childhood, insulin-dependent diabetes), is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival. Previously, there is a globally agreed target to halt the rise in diabetes and obesity by 2025 (WHO 2023; CDC & Prevention, 2023).

According to the WHO, type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake). This reaction stops your body from making insulin. Approximately 5-10% of the people who have diabetes have type 1 and can be diagnosed at any age, and symptoms often develop quickly. This group patients take insulin every day to survive. Currently, there is breakthrough on how to prevent type 1 diabetes.

Patients with type 2 diabetes, do not use insulin well and can't keep blood sugar at normal levels. About 90-95% of people with diabetes have type 2, and develops over many years and is usually diagnosed in adults (but more and more in children, teens, and young adults). Early diagnosis is important to prevent the worst effects of type 2 diabetes, and the best way to detect diabetes early is to get regular check-ups and blood tests healthcare providers. Type 2 symptoms may not be readily noticed especially among persons who are at risk. Type 2 diabetes can be prevented or delayed with healthy lifestyle changes, such as: losing weight, eating healthy food and being active.

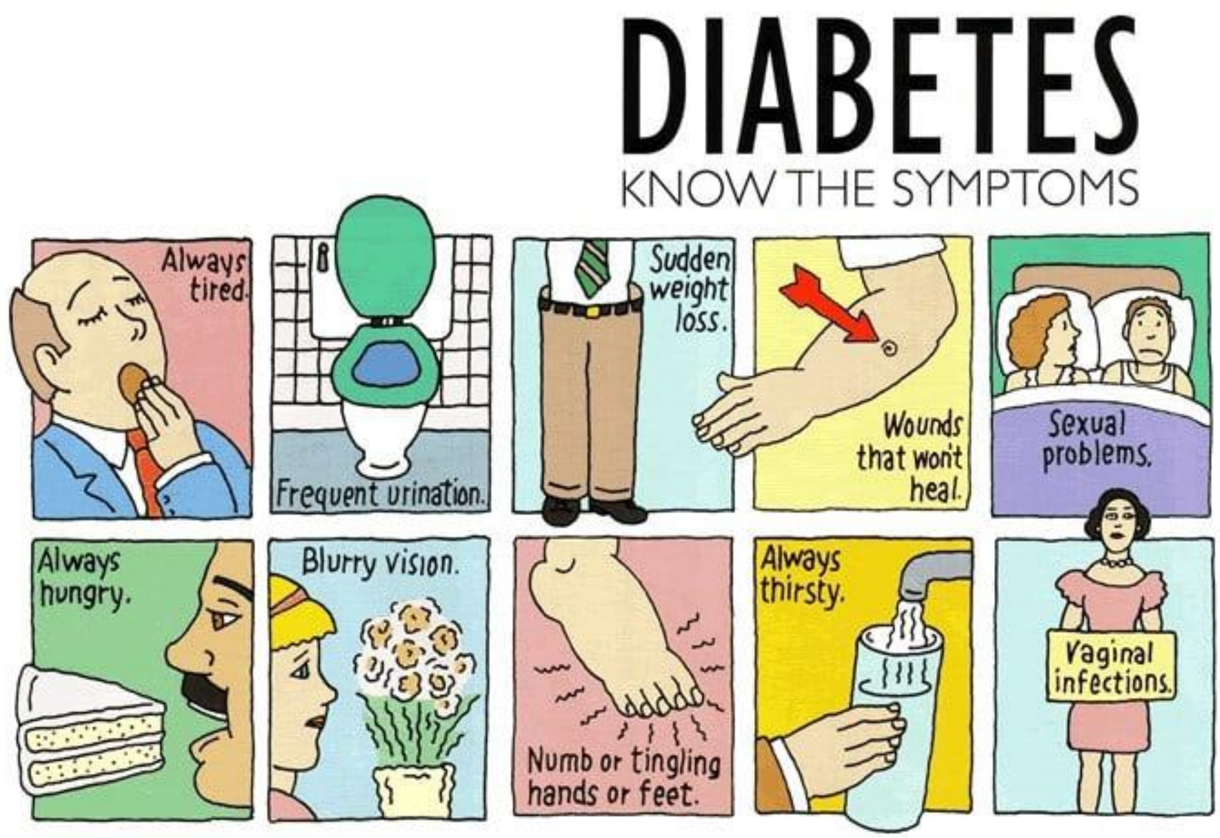
Gestational diabetes develops in pregnant women who have never had diabetes. The baby of gestational diabetic woman could be at higher risk for health problems. Gestational diabetes usually goes away after the baby is born. However, it increases her risk for type 2 diabetes later in life. Her baby is more likely to have obesity as a child or teen and develop type 2 diabetes later in life (CDC & Prevention, 2023).

Prediabetes

It's reported that in the United States, about 98 million adults—more than 1 in 3—have prediabetes. More than 8 in 10 of them are not aware they have it. In prediabetes, the blood sugar levels are higher than normal, but not high enough for a type 2 diabetes diagnosis. Prediabetes predisposes to type 2 diabetes, heart disease, and stroke (CDC & Prevention, 2023). Lifestyle changes is the ultimate.

Symptoms of Diabetes

The symptom of diabetes may occur suddenly. Symptoms of type 2 can be mild may take many years to be noticed. These symptoms include: feeling very thirsty (Polydipsia), needing to urinate more often than usual (Polyuria), excessive hunger (polyphagia), and feeling tired, losing weight unintentionally, wounds that never heal, sexual problem, blurry vision.



Management of Diabetes through monitoring (pricking of fingers with needle, etc)

Pharmacologic Therapy

Exogenous insulin. In type 1 diabetes, exogenous insulin must be administered for life because the body loses the ability to produce insulin.
Insulin in type 2 diabetes. In type 2 diabetes, insulin may be necessary on a long-term basis to control glucose levels if meal planning and oral agents are ineffective.

Monitoring Blood Glucose

Glucose levels must be determined daily to monitor the interactions and effect of diet, exercise, and medication on an individual diabetic regimen. Detection of extreme or episodic hyperglycemia is necessary to avoid diabetic acidosis (DKA) and diabetic coma, which is caused by too little insulin accompanied by increased caloric intake, physical or emotional stress, or underdiagnosed diabetes. DKA is most likely to occur in type 1 diabetes but may be seen in type 2 in conditions of severe illness or stress when extra demand for insulin cannot be met by the pancreas.

Traditionally, monitoring has been accomplished by checking for the presence and degree of glycosuria (sugar in urine). This technique provides only gross, semiquantitative information. Many factors do affect urine test results, such as age, medications, disease, and the individual renal threshold. Urine testing also cannot measure the presence or degree of hypoglycemia. Urine testing for ketourine (ketone in urine), however, is a valuable aid in determining the advent of DKA and is recommended for every patient with type 1 diabetes when the patient is experiencing hyperglycemia or acute illness (Lewis, Heitkemper &Dirksen, 2000)

Self-Monitoring. Self- monitoring of blood glucose using capillary blood glucose monitoring (CBGM) technology is a more reliable technique for measuring blood glucose. . Commercially available glucose-testing products, including disposable lancets and lancets holders, are widely available. Its approach involves that a small drop of capillary blood (usually from a finger stick) is dropped onto a reagent strip. After a specified time, the strip is read either visually or by a machine. The machines are either reflectance meters or sensors. Reflectance meters work by measuring the amount of light reflected onto a strip that has reacted with a color change in response to the reaction of glucose with the reagent strip. Sensors use the measurement of conductivity of electricity of electricity as it is affected by the glucose in the blood. The technology of CBGM is a rapidly changing field with newer and more convenient systems being introduced every year . Blood glucose monitoring technology uses a noninvasive spectroscopy, or the use of laser light on a skin surface (Lewis, Heitkemper &Dirksen, 2000). Implantable sensors for continuous glucose monitoring are also being considered in research trials (Shichiri et al, 1998). Many meters are computerized and are becoming increasingly sophisticated. Some models are capable of storing results of previous blood glucose tests. These test can be retrieved to provide a more complete picture of blood glucose fluctuations over time and to guide adjustment to the regimen.

The blood glucose level reported by laboratory is often higher than the patient's home glucose monitoring or the hospital's capillary whole blood sample rather than a plasma sample so it may be approximately 10% to 155 lower. Plasma or serum gives a higher glucose reading (Davidson (1998). To further complicate the process, some monitors are calibrated to give whole blood results while other meters are calibrated to give values equivalent to plasma concentrations. This must be determined by reading the literature accompanying the particular monitor and strips being used by the patient. Finally, home monitoring equipment must be cleaned and calibrated regularly to maintain its accuracy. The technique for using a blood glucose-monitoring product accompanies each product. Because errors in monitoring technique can cause errors in clinical management strategies that may be based on erroneous CBGM information, patient training should be emphasized not only at the initial session but a follow-up visits with any of the health care team. Patient technique reassessed at30 to 180 days after training and yearly thereafter (The National Steering Committee for Quality Assurance in Capillary Blood Glucose Monitoring (1993).

Steps of Capillary Blood Glucose Monitoring

Capillary blood glucose monitoring has specific steps that the patient should follow when performing it. Hands are washed in warm water. Cleaning the site with alcohol is not necessary and may even interfere with test results; If it is difficult to obtain an adequate drop of blood for testing, the patient should warm the hands in warm water or let arms hang dependently for a few minutes before the finger puncture is made; The puncture is made on the side of the finger pad rather near the center. Fewer nerve endings are along the side of the finger pad; The puncture should be only deep enough to obtain a sufficiently large drop of blood. Unnecessarily deep punctures may cause pain and bruising (Lewis, Heitkemper &Dirksen, 2000).

Advantages of Capillary Blood Glucose Monitoring

Immediate information: Capillary blood glucose monitoring (CBGM) ensures immediate information about blood glucose levels and produces accurate records with daily glucose fluctuations and trends (Position Statement of American Diabetes Association, 1998). CBGM is preferred
glucose monitoring- method for patient with type 1 diabetes. The type 2 diabetic patient may also benefit from CBGM by seeing the correlation between dietary choices and blood levels. As weight is lost and blood glucose levels are lowered, the obese type 2 patient may also gain reinforcement from CBGM.

The frequency of monitoring depends on the glycemic goals the patient and healthcare provider set and the intensity of the treatment regimen. The patient receiving two or more injections per day may want to test before meals every day. If the glycemic control is relatively stable, the patient may elect to test two or more times a day on certain days of the week. Testing is most done before meals but can be done any time the patient needs to know a factor, such as exercise or stress affecting the blood glucose level. The frequency of recording CBGM results to guide therapy decisions should be mutually determined by the health care provider and the patient.

Ideally, a patient should be motivated to learn not only CBGM technique but also how to interpret the results. Most patients find that CBGM brings about physiologic and motional benefits, as well as a willingness to be an active partner in the treatment. Achieving the desired level of patient participation also requires time and effort from the healthcare professional. The nurse involved in this aspect of management should anticipate a close working relationship with the patient for a period of 3 to 6 months as the patient learns refinements of the technique and appropriate decision making regarding changes in diet, medication, and exercise. A patient who is visually careful impaired, color blind, or limited in manual dexterity needs careful evaluation of the glucose-monitoring method most appropriate for the that patient's needs. Glucose monitors are now commercially available for the visually impaired (Lewis, Heitkemper, and Dirksen (2000)

Electrochemical Technology

Numerous studies have confirmed a high correlation between glucose concentrations in blood and exudate (Moyer, Wilson, Finkelshtein, and Wong, 2012; Amer, Yousuf, Siddqiui and Alam, 201). Electrochemical techniques can indirectly reflect blood glucose concentration by measuring exudate (sweat [Heikenfeld, 2016, Coyle, Curto, Benito-Lopez and, Florea], saliva [Liu, Sheng, Sun, Feng, Wang, Zhang, Xu, Jiang, 2015; Gupta, Sandhu, Bansal and Sharma, 2015], tears [Bandodkar and Wang]). However, this technology is limited by the sensor's low penetration into the epidermis and the influence of other components in the exudate on measurement accuracy. A feasible alternative is to use an electric field to stimulate the skin, enabling glucose molecules to pass through the skin and collect around the electrode, and then measure them using biochemical methods.

A New Generation of Sensors for Non-invasive Blood Glucose Monitoring

What is a noninvasive glucose monitoring?

An image of a non-invasive blood monitoring Device

A noninvasive glucose monitoring (NIGM) is the measurement of blood glucose levels, required by people with diabetes to prevent both chronic and acute complications from the disease, without drawing blood, puncturing the skin, or causing pain or trauma.

While non-invasive blood glucose monitoring devices offer great conveniences to individuals with diabetes, their results can be less precise than other methods, hence researchers are working out producing new models that increase accuracy, newer, better models are currently being developed (Health news, 2023).

Self-monitoring of blood glucose levels provides diabetic patients with a prompt method of measuring their blood glucose concentration, as opposed to conventional laboratory measurements. Frequent testing aids patients in the prevention and detection of hyper or hypoglycemia events. Only invasive and minimally invasive glucose sensors are currently commercially available. However, during the last couple of decades, work towards the development of a non-invasive glucose monitor has increased significantly among research groups with motivating results. Many techniques have been studied and implemented, each with their particular advantages and challenges. Ongoing technologic advancement on the most promising approaches towards the development of a truly non-invasive and clinically accurate glucose sensor are being discussed (Losoyal-Leal, Camacho-Leon, Dieck-Assad & Martinez-Chapa (2012).

The New Approach

Researchers in the recent years are aggressively responding to the incidence of diabetes mellitus which has grown exponentially worldwide. It is well-established that blood glucose monitoring is crucial to evaluate pancreatic islet function and determine the optimal medication regimen. However, most current blood glucose meters use invasive techniques, which can cause pain and infection. Non-invasive blood glucose monitoring techniques have gained significant attention as a potential solution to overcome the limitations of current monitoring methods. Due to the rapid development of wearable devices and transdermal biosensors, which provide efficient, stable, and cost-effective monitoring without the need for invasive blood samples, the market for non-invasive blood glucose monitoring is predicted to become more competitive (Juncen, Yuging, Hao & Meng, 2023).

Summarized advantages, disadvantages, and detection sites of the non-invasive blood glucose detection sensors (Table 1) - (Juncen, Yuging, Hao & Meng, 2023).

Sensor	Advantages	Disadvantages	Detection site
Gold nanostructured flexible sensor	Good flexibility, excellent selectivity, repeatability, and stability.	The activity of various enzymes must be ensured, and the requirements for storage and use are high.	Sweat
Flexible N-GQD/PANI nanocomposite layer sensor	Has high sensitivity and repeatability, and stability, and can effectively overcome the fluctuations of biological signals.	The requirements for the materials are high, and the manufacturing cost is high.	Sweat
Electrochemical dual-channel sensor	Suitable for continuous monitoring during sleep, high blood glucose correlation.	Low flexibility.	Subcutaneous blood

Sensor	Advantages	Disadvantages	Detection site
Near-infrared spectrometer	No risk of infection, strong penetration, low cost.	Easily affected by environmental changes (such as temperature, humidity, pressure).	Oral mucosa, tongue, fingers
Polarimeter	No risk of infection, and low cost.	Long detection time, may cause harm to the human eye.	Aqueous humor, the cornea
Electromagnetic sensor	Personalized detection, high accuracy.	High detection cost.	Subcutaneous blood
Microwave sensor	Good real-time performance, small size.	Easily interfered with, low accuracy.	Fingers

Juncen, Yuging, Hao & Meng (2023) in their summary of the sensors mentioned herein, the highlighted that over the past few decades, significant efforts have been undertaken to explore various non-invasive methods for detecting blood sugar levels. Although many novel detection methods have demonstrated high accuracy in laboratory settings, these technologies have not yet been put into clinical practice and still need to be further improved and meet market regulations. The non-invasive blood glucose detection technology mentioned above shows great potential for development, but some challenges remain.

Discussing the approach and Significance of Continuous blood glucose monitoring Sensor: Do they have advantages over the previous Self-monitoring blood glucose Sensor method?

Continuous blood glucose monitoring (CGM) has important clinical significance for diabetes patients, especially in cases with brittle diabetes. It is well-established that recurrent hypoglycemia can cause sudden confusion or inability to move, resulting in secondary disasters (such as traffic accidents and falls). Hyperglycemia causes acute ketoacidosis and increases the risk of long-term complications. By monitoring blood sugar and accurately adjusting insulin dosage, blood sugar control can be effectively improved, and severe hypoglycemia can be prevented. Currently, available blood glucose monitoring techniques mainly harness electrochemical methods that require a small amount of blood to be extracted from the body through finger puncture or subcutaneous implantation of a thin needle. The former method is known as a **Self-Monitoring Blood Glucose (SMBG) sensor**, as it only provides glucose level readings at a specific moment in time and can be used by individuals without the assistance of a medical professional. In contrast, the latter method is called a Continuous Glucose Monitoring (CGM) sensor and offers continuous monitoring of glucose levels. However, invasive testing can cause discomfort and pain in patients, increase the risk of infection and allergies, and lead to poor compliance with blood glucose monitoring. Therefore, since the end of the 20th century, significant efforts have been undertaken to develop non-invasive (NI) and minimally invasive (MI) devices, namely blood glucose monitoring devices that do not require blood collection, aiming at overcoming the problems related to traditional blood glucose monitoring methods. Marjan Gusev et al. conducted a review of recent research advancements and key challenges in noninvasive glucose measurement techniques (Gusey, Spasevski, Kosevski, Koteska, Simjanoska, Ackoyska, Stojmenski and Trontel, 2020).

Accuracy, usability, and compatibility for home use were identified as the primary obstacles in this area. It was suggested that only devices capable of addressing these challenges could significantly impact the lives of millions of individuals with diabetes. The review also proposed future trends, such as integrating artificial intelligence algorithms and incorporating additional physiological and psychological parameters (e.g., heart rate variability to detect autonomic dysfunction), as well as using nanotechnology and other innovative techniques.

Nowadays, most non-invasive blood glucose monitoring techniques rely on the quantification of glucose molecules that exhibit distinct characteristics in different light frequencies, such as ultrasonic waves, near-infrared (NIR), and visible light. While these methods enable real-time quantitative monitoring, they do not offer the same level of accuracy as traditional electrochemical blood glucose meters in clinical setting (Tonyushkina and Nicholas, 2009). As a result, improving the accuracy and precision of non-invasive monitoring devices remains a critical technical challenge in the field of diabetes treatment.

Over the past few years, many renowned scholars have reviewed several non-invasive (NI) glucose monitoring techniques and devices. In this respect, Chen et al. comprehensively described the status quo of minimally invasive (MI) and non-invasive (NI) technology of CGM analysis (Chen, Zhao, Li, Zhu, Qian, and Flewitt, 2017). Van Enter and Von Hauff reviewed the physical and chemical properties of glucose molecules and analyzed their impact on the accuracy and effectiveness of NI technology (van Enter and vonHauff, 2018). Uwadaira and Ikehata provided a comprehensive overview of the technical parameters of non-invasive glucose monitoring technology and summarized its main technical advantages and limitations. Khalil provided an excellent description of the characteristics of glucose molecules and tissues under different light wavelengths and then compared and analyzed the accuracy and sensitivity of glucose measurement for *in vitro* and *in vivo* sample (Khalil, 1999).

In this review, a variety of innovative technologies for non-invasive blood glucose monitoring were reported to have emerged in recent years, including electrochemical, optical, and microwave dielectric spectroscopy techniques. These sensors' principles, benefits, and limitations were examined, substantiating that electrochemical non-invasive blood glucose monitoring holds significant potential due to its high sensitivity and low cost (Juncen, Yuging, Hao and Guo, 2023).

Any Short Coming (s) of the Continuous Blood Glucose Monitoring in Diabetes management.

While tremendous advancement are being in the electrochemical technological, there are however observable apparent shortcomings. The shortcoming are:

The difficulty in signal detection and quantification. Biological tissues contain large quantities of water, which strongly absorbs light, leading to severe light attenuation. The glucose content in tissue fluid and blood is relatively low, making it challenging to detect small changes (the density of glucose is only 1% to 10% of the density of glucose in the blood). Body fluid glucose measurement accuracy may be reduced due to water evaporation, seasonal changes in liquid volume, and other internal components, making it unsuitable for continuous, long-term, and sleep monitoring. In addition, the absorption coefficient of glucose is much smaller than water's, which will weaken the signal triggered by changes in blood sugar concentration. Accurately and reliably detecting these values requires instruments with a high signal-to-noise ratio, which is currently not achievable with non-invasive blood glucose detection technology. As a result, it still cannot meet the rigorous requirements of clinical detection (Juncen, Yuging, Hao and Guo, 2023).

Changes in measurement conditions. Specificity remains one of the most important challenges in non-invasive blood glucose measurement. It is widely acknowledged that the tissue structure varies significantly across different parts of the human body, and this heterogeneity is also unique to each individual. If the probe cannot be accurately positioned at the same position during measurement, it will inevitably affect the propagation path of light. In addition, changes in measurement conditions such as temperature, area, and angle of light at the measurement site will directly affect the propagation of light, and the light intensity changes caused by them are much greater than those triggered by changes in blood glucose concentration. Therefore, accurate detection of blood glucose concentration is not feasible without stable measurement conditions.

Testing Safety. This is a priority for this detection technology since it involves direct contact with the human body. Certain sensors contain potentially hazardous components such as enzymes, strong light sources, etc., which must be carefully evaluated to avoid possible bodily harm. The past few years have witnessed significant progress in non-invasive blood glucose detection technology. However, their accuracy is still far from mainstream methods (Kalatehjary, Shrabi, Khosravi and Zolfaghari, 2008), hindering the widespread implementation of non-invasive blood glucose measurement technology. Therefore, the following four aspects need to be studied and improved in the future.

Continuous glucose monitoring. Some technologies that can continuously monitor blood glucose include electrochemical sensors, electromagnetic sensors, microwave sensors, etc. It should be noted that human activities may cause large detection errors. To build a sensor system, various influencing factors need to be considered to ensure the accuracy of the results as much as possible. In addition, the feasibility of continuous monitoring must be ensured. For example, the measurement of blood sugar in the cornea by polarimetry cannot be continuously monitored while the patient is resting.

1. It is necessary to consider the significant impact of measurement location, accuracy of experimental equipment, and experimental methods (in vitro and in vivo) on the detection results. Indeed, *in vitro*, experiments can better control experimental conditions but cannot simulate the real biological environment. In contrast, in vivo, experiments can better simulate the real biological environment but are subject to more interference factors. Therefore, in the future, it will be necessary to improve the experimental environment, ensure the universality of experimental results as much as possible, and provide sufficient theoretical support for future clinical trials.

2. It is necessary to ensure that non-invasive measurement equipment is feasible, including ease of operation, repeatability, and low noise levels.

(1) To achieve ease of operation, a system with automated measurement functions can be developed.

(2) To ensure repeatability, flexible materials can be developed and verified through numerous experiments. One example is the “Flexible N-GQD/PANI Nanocomposite Layer Non-invasive Biosensor” mentioned earlier.

(3) Regarding “low noise”, improving experimental methods and signal processing techniques or optimizing the structure and materials of sensors to reduce noise.

3. Further research on nanomaterials is necessary for the development of biosensors, which have a wide range of applications in the medical field. These applications include disease control, clinical care, preventive treatment, patient health information, and disease review (Haleem, Javaid

, Singh, Suman and Rab, 2021). Since biosensors come into direct contact with the human body, it is crucial to ensure that nanomaterials do not cause harm while improving flexibility and durability to ensure normal operation. Biosensors can be used in personalized medicine, providing patients with new treatment and diagnostic options and significantly impacting healthcare.

4. The sensor's detection capability can be extended to simultaneously detect multiple biological indicators. Indeed, it is well-established that metabolic disorders usually cause systemic dysfunction and may lead to abnormal levels of various metabolites (Fuentes-Antras, Pictostic, Ramirez, Egido, Tunon and Lorenzo, 2015). For example, patients with diabetes often present with elevated blood sugar, lipids, and lipoproteins levels due to metabolic disorders. Higher hemoglobin A1C levels in diabetic patients can also increase the likelihood of lactic acid disorder by strengthening the anaerobic fermentation process (English and Williams, 2004). Future research should focus on developing three-channel or multi-channel biosensors, which can provide actionable information on multiple metabolites and generate comprehensive personal health information for more comprehensive medical testing.

Implication

Usage of non-invasive continuous glucose monitoring (CGM) sensor is a breaking news in the present management of diabetes in in contrast to the setbacks of self-monitoring blood glucose (SMBG) sensor.

Researches yet to develop multi-channel biosensors which can provide actionable information on multiple metabolites and generate comprehensive personal health information for more comprehensive medical testing is not ascertain.

This will imply that diabetes who must monitor their blood glucose level would still utilizing the former self-monitoring blood glucose sense despite its inconveniences and trauma encountered.

Conclusion

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin (hormone) it produces in order to regulate the blood glucose. Diabetes as a metabolic disorder usually cause systemic dysfunction that may lead to abnormal levels of various metabolites in the human body.

It is well-established that blood glucose monitoring is crucial to evaluate pancreatic islet function and determine the optimal medication regimen. However, most current blood glucose meters use invasive techniques, which can cause pain and infection. Non-invasive blood glucose monitoring techniques have gained significant attention as a potential solution to overcome the limitations of current monitoring methods. Yet there are apparent shortcomings that call for immediate action.

It is hoped that future researches would focus on developing three-channel or multi-channel biosensors, which can provide actionable information on multiple metabolites and generate comprehensive personal health information for more comprehensive medical testing. And these non-invasive blood glucose monitoring devices be human friendly, accessible and affordable.

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