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Advanced Bioscience and Biosystems for Detection and Management of Diabetes

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Preface

Diabetes is a serious public health issue that affects people all over the world. As the world population ages, the prevalence of this chronic complicated metabolic illness increases at an alarming rate. It will have the greatest influence in underdeveloped countries. Because diabetes is a chronic, complicated metabolic condition, a multidisciplinary team of health professionals with experience in diabetes management should offer diabetes care in conjunction with the patient and family. Despite the fact that diabetes mellitus was recently given priority status by the WHO, many public health planners are still uninformed of its scope and its consequences. The rising incidence of the condition and the long-term expense of therapy for both patients and the health sector, as well as the economic cost to nations, are all factors to consider. Adult prevalence rates ranging from 7% to 25% have been observed in studies done in diverse communities throughout the region. Furthermore, a growing number of nations are reporting the emergence of type 2 diabetes mellitus at a young age. The goal of incorporating diabetes mellitus into primary health care is to develop routine screening methods to identify, monitor, and manage diabetes's frequent complications. Treatment should just focus not only on decreasing blood glucose levels, but also on addressing other noncommunicable disease risk factors including smoking, dyslipidemia, obesity, inactivity, and hypertension. Not only is diabetes care in shambles, but so is our knowledge of the processes that underpin clinical problems associated with the illness. The major goals in caring for diabetic patients are to prevent or at least slow the development of clinical complications such as micro-vascular (eye and kidney disease) achieved through blood sugar and blood pressure control, and macro-vascular (coronary, cerebrovascular, and peripheral vascular) achieved through lipids, hypertension, and smoking control. However, we do not understand how increased blood glucose, circulating insulin, and changed blood pressure affect the pathophysiology of blood arteries and cause serious organ failure.

As a result, in the lack of such a knowledge foundation, current treatment techniques focus on risk management. If we want to control this condition properly, we need to start monitoring diabetes early and keep it up to date. The early detection of variations in blood glucose levels is the foundation of diabetic care. Effective treatment, especially for undetected hypoglycemia, requires careful and timely

monitoring. Blood glucose levels are usually checked before a meal, two hours after, and before bedtime. Although the development of blood glucose self-monitoring in recent decades has encouraged diabetes treatment in the quest for euglycemia, its cumbersome use may result in insufficient data collection of blood glucose. The pattern, frequency, level, and timing of blood glucose changes have been tracked using continuous glucose monitoring. Diabetes diagnosis and management need precise, sensitive, consistent, quick, and attentive glucose monitoring frequently. Diabetes can create various vascular and neurological issues that impact multiple organ systems in the short and long term if not treated properly. Regular community-based screening and prompt diagnosis in undiagnosed patients, sufficient patient education and support, continuous medical treatment, psychological counseling, and societal support are all required to avoid acute consequences. Accurate blood glucose monitoring while enhancing glycaemic control and patient quality of life is one of the most difficult elements of diabetes mellitus treatment. Regular monitoring by the doctor or the patient is necessary to keep the diabetes patient's health from worsening. These recommendations are intended to aid in the standardization of diabetes treatment at the elementary, secondary, and tertiary levels and advise policymakers as part of efforts to enhance health care. Above all, we must all endeavor to improve diabetes mellitus prevention to reduce this increasing burden.

This book intends to offer recent work carried on the leading technologies for noninvasive (NI) and minimally invasive (MI) glucose monitoring sensors, devices presently found in the field of medicine sciences. The type of framework used for accuracy determination and new approaches undertaken by scientists have been discussed. This book also mentions the upcoming trends to be seen in diabetic diagnosis and management by using the machine learning and artificial intelligence. We hope you enjoy reading the book and find it useful whether this is helping patients or health professionals to manage diabetics and its complications using the current innovative technologies. The book will summarize that the invention and replacement of use of new technologies with the existing ones for glucose detection are the future for diabetic patients.

Doha, Qatar

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Contents

Introduction

Kishor Kumar Sadasivuni and Mithra Geetha

Abstract Effective diabetes management begins with blood glucose monitoring. Diabetic care goes beyond monitoring blood glucose levels. This includes overall health, including blood pressure, weight, cholesterol levels, sleep, mood, medications, and eye, kidney, and foot health. Monitoring blood sugar is fundamental to managing diabetes. Micro and macrovascular complications are reduced with regular glucose testing. Despite the recent development of minimally invasive glucose monitoring techniques, most glucose monitoring methods are invasive, painful, time-consuming, and expensive in the long run. In order to improve the quality of life for patients with diabetes, non-invasive, needle-free, and CGM approaches are needed. The purpose of this chapter is to provide an overview of different chapters covering various devices and sensors for invasive, minimally-invasive, and non-invasive glucose monitoring currently available on the market or in development, as well as their accurate real-time response and sensitivity.

Keywords Diabetes mellitus · Glucose · Monitoring · Medications · Blood pressure

Diabetes mellitus, often known as diabetes, is a set of metabolic diseases characterized by elevated blood sugar levels in the human body over an extended time. Several different pathogenic mechanisms cause diabetes. These can range from autoimmune destruction of β-cells of the pancreas, resulting in insulin insufficiency, to anomalies that result in insulin resistance. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency), type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance), and gestational diabetes mellitus (GDM-any degree of glucose intolerance with onset during pregnancy) are the most common types. The global prevalence of diabetes was projected to be 463 million people in 2019 [1]. Data indicates that diabetes patients have surged worldwide, with India being

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second only to China regarding the number of people with diabetes. According to the International Diabetes Foundation, the number of individuals diagnosed with diabetes would rise to 628.6 million in 2045, accounting for 6–7% of the global population [2]. Diabetes rates grow as the population, obesity, physical inactivity, and unhealthy diet all rise. The World Health Organization and the International Diabetes Federation have identified diabetes as a serious global problem [3].

The conventional view of diabetes mellitus pathophysiology remains that hereditary predisposition underpins disease progression, with genetic mutations affecting the stages of beta-cell activity, insulin secretion, contact with tissue cells, insulin receptor synthesis, and insulin action inside cells. The immune system targets and kills the insulin-producing beta cells in the pancreas in patients with diabetes type 1. As a result, the body's insulin synthesis halts. Type-2 diabetes mellitus can cause antibodies against islet beta-cell antigens to be elicited directly in certain people. In all diabetes mellitus, diabetes type 2 accounts for 80% of all cases. Because of beta-cell malfunction, this form of diabetes is caused by a relative insulin deficit. These individuals have a very gradual progression of insulin insufficiency, and they are classified as having latent autoimmune diabetes (LADA) with a delayed onset. Gestational diabetes (Type 3) has become a major public health concern during a woman's pregnancy. Placenta produces placental growth hormone (PGH) and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-) during a healthy pregnancy. Insulin sensitivity is reduced in adipose tissue, liver, and skeletal muscle due to these variables. This disease does not affect all pregnant women, but it does raise the dangers associated with pregnancy. It can occasionally cause difficulties for babies and can also obstruct the normal birthing process. However, after the delivery of a child, this syndrome largely subsides.

Chronic hyperglycemia can cause serious issues in a person's body, including damage to and even failure of organs like the kidneys and heart [4]. Diabetic complications might include blindness, renal illness, neurological and circulatory disease, limb amputations, stroke, and cardiovascular disease [5]. Patients may have polydipsia, polyuria, and polyphagia due to persistent hyperglycemia. Diabetic complications might also include cardiovascular disease and mortality [6]. Other comorbidities associated with diabetes include diabetic foot, diabetes retinopathy, ketoacidosis, and neuropathy. Recent research has discovered a strong link between glucose levels and heart rate variability (HRV). This strategy focuses on diabetes patients and alleviates their financial and health-related problems [7]. For patients, a technology that might give an early identification of such problems could be life-changing.

In 2017, the total cost of diabetes-related health care in the United States was predicted to be over $327 billion. According to the Mayo Clinic, quitting smoking and keeping the blood pressure and cholesterol under control are two of the top ten strategies to avoid diabetic problems. Regular exercise and drinking water as the primary beverage are not on this list, but they are equally vital. Diabetes can be managed with a balanced diet and, eventually, insulin injections [8]. Sleep disruption appears to have a role in diabetes, just as diabetes can create issues with sleep. Sleep deprivation raises hunger hormone ghrelin and lowers satiety hormone leptin levels [9]. People who suffer from sleep problems are more likely to seek consolation in high-sugar

meals Chapter "Review of Emerging Approaches Utilizing Alternative Physiological Human Body Fluids in Non- or Minimally Invasive Glucose Monitoring". Optimizing glycemic control by reducing blood glucose levels has been shown to reduce the risk of microvascular complications and long-term macrovascular disease [10]. Because Type 1 DM patients' insulin production by beta cells is reduced, pharmacological stimulation of insulin secretion or insulin absorption is no longer enough to keep them in a euglycemic state, and external insulin supplementation is the only way to keep them there.

The basis of diabetes management is timely recognition of the variation of blood glucose levels. Effective therapy, especially for undiagnosed hypoglycemia, is only feasible with good and early monitoring. Normally, blood glucose levels are tested before a meal, two hours after a meal, and before going to bed [11]. Although the introduction of self-monitoring of blood glucose (SMBG) has inspired diabetes care in recent decades in the pursuit of euglycemia, its inconvenient usage may result in inadequate blood glucose data collecting. Continuous glucose monitoring (CGM) has monitored the pattern, frequency, level, and time of blood glucose level fluctuations. Diagnosis and management of diabetes need regular glucose monitoring that is accurate, sensitive, dependable, fast, and attentive. Without adequate care, diabetes can cause a range of vascular and neurological problems affecting various organ systems in the short and long term. To avoid acute effects, regular community-based screening and timely diagnosis in undiagnosed individuals, adequate patient education and support, ongoing medical treatment, as well as psychological therapy, and societal support are all necessary. One of the most difficult aspects of diabetes mellitus therapy is correctly monitoring blood glucose while increasing glycaemic control and patient quality of life. To prevent the diabetic patient's health from deteriorating, regular monitoring should be performed by either the doctor or the patient Chapter "Current Status of Non-invasive Diabetes Monitoring".

Self-monitoring blood glucose levels give a consistent, trustworthy, and reliable method of detecting blood glucose levels. It's critical to monitor glucose levels in diabetic patients frequently [12]. The current standard of care for DM diagnosis is venous plasma glucose testing. Currently, all home blood glucose monitoring techniques need piercing the skin to get a blood sample. Because the treatments are invasive, this technique inhibits patient's cooperation and has severe disadvantages [13]. This invasive procedure aids patients in identifying and avoiding hypoglycemia and hyperglycemia. Various methods have been developed to assess glucose levels, including capacitive, coulometric, optical, enzymatic-electrochemical, and non-enzymatic electrochemical methods [14]. The major goal of these investigations is to create a less painful method and reduce infection risk [15].

The non-invasive method, which is a relatively new technology, relies on the body's glucose signals. It eliminates the need for "finger pricking" and allows for continuous blood glucose monitoring. A novel method for measuring glucose levels using an ECG monitor has been devised. The ECG is transmitted to a smartphone where it is temporarily stored and calculated heart rate variability characteristics. The algorithm then estimates a human's capacity to regulate glucose levels using advanced machine learning approaches. This strategy focuses on diabetes patients

and alleviates their financial and health-related problems Chapter "A New Solution for Non-invasive Glucose Measurement Based on Heart Rate Variability".

Procedures involving the application of fluorescent light to the body in a specific place and techniques involving the implantation of a sensor in the subcutaneous tissue cause interference with the process from surrounding signals such as ultraviolet and visible light. The primary recognition elements utilized in the construction of sensors include receptors, antibodies, enzymes, nucleic acids, lectins, and microbes [16] Chapter "Commercial Non-invasive Glucose Sensor Devices for Monitoring Diabetes". A biosensor is a transducer that converts a bimolecular binding event captured on the surface of a bio-receptor into a readable physical quantity [17]. The interaction of the optical field with an analyte as a detecting element completes the optical-based biosensor [18]. A label and an optical signal enhancer, such as gold nanoparticles, fluorescent or luminous labels, are used in a label-based sensing technique. The newest manufacturing processes and the major problems associated with the use of SPR, LSPR, SPR imaging, and PC biosensors to detect diabetes biomarkers are reviewed in Chapter "Optic Based Techniques for Monitoring Diabetics".

In 2017, over 51 million individuals globally used glucometers, with roughly 12% having type 1 diabetes, implying they are forced to take insulin therapy and use glucometers to monitor that medication by default. Diabetic patients must pay for constant or frequent self-monitoring and blood glucose testing strips (as much as $1 per strip) or continuous glucose monitoring sensors ($350 per month), glucagon, and other medications. Cardiovascular disease accounts for more than a quarter of the expenditures associated with diabetes patients. Regular finger pricking or continuous glucose meters and frequent trips to cardiologists are the most common treatments for these problems. A recently proposed approach addresses these issues with a single system. Simultaneously, the solution provides a gadget for continuous cardiac arrhythmia and assesses a person's capacity to regulate blood glucose levels.

The first indicators seen in children with diabetes are pro-insulin autoantibodies or insulin (PAA/IAA). High affinited IAA against pro-insulin was also linked to high IAA levels with HLA DPB1 * 04. HbA1c isn't the primary method for diagnosing diabetes, but it does offer enough information to do so. These diseases may be easily diagnosed using a boron-based probe produced using a targeted approach and aids in recognizing sugar on the cell surface. Because of their great stability and strong selection rate towards glucose, most glucose sensors use glucose oxidase (GOx). Mulyanti et al. developed software that was semi-numerical and used the transfer matrix approach. They also discovered that the concentration of glucose has a significant impact on the resonant wavelength shift. Jamil et al. [19] showed that the K-SPR technique with nano-laminated Au–Cr is extremely effective in detecting creatinine and urea Chapter "SPR Assisted Diabetes Detection". Acoustic spectroscopy is another method for detecting glucose signals using optical beams; however, it suffers from scattering effects, resulting in insensitivity. Multi-modal spectrography IC, which combines impedance and near-infrared methods, may also be used to assess glucose levels. In order to remove diverse systemic noises, new practices exploit indirect dielectric characteristics of the tissue surrounding the blood. The application of the Gabor filter for the analysis of facial contour data is a new approach for detecting

diabetes [20]. The concentration of acetone in human bodies is extremely low (0.1–0.8 ppm), however in diabetes mellitus, this amount rises to 1.8–5.0 ppm [21]. Due to ketonic species, notably acetone and aceto-acetic acid, which are generated when fatty acids are broken down, people with diabetes mellitus have insulin problem hormones in their bodies [22]. Many researchers have achieved a biosensor approach for diabetic diagnosis since exhale breath acetone is a simple diabetes biomarker.

The irradiation of a sample with monochromatic light causes molecules in the sample to scatter incident light, resulting in vibrational spectroscopy. The resulting spectrum describes the absorption of light by the molecules in the sample as a function of frequency, measured in wavenumbers. These spectra can be used to distinguish between distinct functional groups in a material Chapter "Infrared and Raman Spectroscopy Assisted Diagnosis of Diabetics". Surprisingly, the photo-acoustic approach is a technology that allows for a high level of sensitivity throughout the analysis procedure. It goes through the basic principles of photoacoustic spectroscopy and how they may monitor glucose levels Chapter "Photoacoustic Spectroscopy Mediated Non-invasive Detection of Diabetics".

Electrical bioimpedance can be used in both DC and AC applications. Georg Simon Ohm defined the impedance Z in Ohm's law in 1827, where Z is a complex number. Arthur Kennelly [23] was the first to express it in terms of a real (R) and imaginary (jX) portion, where $Z = R + jX$ and "j" is the imaginary operator. A lipid layer covers each cell, primarily for ion transport and protection. A cell membrane may be represented as a capacitor connected to a resistor in parallel. Rm (cellular membrane resistance) can be regarded as significantly greater than Rext (resistance of extracellular medium) at lower frequencies due to the cell membrane's unique isolating characteristic. This action prevents the ionic current from penetrating the cell, forcing it to pass through the extracellular media. Depending on the frequency of the excitation alternate signal, biomatological materials, particularly tissue, exhibit variable dispersion to the applied electrical field. This is due to the different types of free ions found in extracellular and intracellular fluid. The ionic potential generated by the external excitation signal will promote the flow of free ions at lower frequencies, although the cell membrane obstructs this flow, resulting in a high impedance. On the other hand, higher frequencies allow the ionic current to pass through the cell membranes and intracellular contents, lowering the resistance in most situations Chapter "Electrical Bioimpedance Based Estimation of Diabetics".

Millimeter and microwave sensing techniques have the potential to develop a medical device that non-invasively measures blood glucose without the need for finger pricking, a drop of blood, and the use of a test stripe; this allows for the least amount of hassle and the best way to deal with samples to examine and diagnose blood glucose levels Chapter "Millimeter and Microwave Sensing Techniques for Diagnosis of Diabetes". To enhance health outcomes, artificial intelligence (AI) is increasingly being used in medicine to discover patterns in complicated collections of clinically gathered data and self-monitored data. Machine learning (ML) gives computers the capacity to learn without being explicitly programmed ahead of time. Clinical knowledge is enhanced by machine learning algorithms, which have been demonstrated superior to utilizing only one in disease treatment Chapter

"Different Machine Learning Algorithms Involved in Glucose Monitoring to Prevent Diabetes Complications and Enhanced Diabetes Mellitus". Diabetic patients, clinicians, and smart healthcare systems are all areas where artificial intelligence may aid and improve diabetes treatment. AI technologies on diabetes allow for more effective data processing and tools and gadgets to help patients control their condition. Patients with diabetes now have new uses for AI, such as patient surveillance, fast decision-making, and risk prediction [24]. Several sophisticated Artificial Intelligence systems have been widely utilized to enable advanced analyses and give tailored medical help to diabetic patients Chapter "The Role of Artificial Intelligence in Diabetes Management".

With the rise in available data and processing capacity, data-driven techniques are proving to be more efficient. DSS has become more efficient because of improvements in AI/ML and glucose sensor technologies [25]. A diabetic DSS may be divided into two categories: patient DSS and clinical DSS (CDSS) Chapter "Artificial Intelligence and Machine Learning for Diabetes Decision Support". Researchers have mostly concentrated on the manufacturing of electrode surfaces in order to build nonenzymatic glucose sensors [26]. Long-term blood glucose control in diabetic individuals has been demonstrated to extend life expectancy [27]. Chapter Future Developments in Invasive and Non-invasive Diabetes Monitoring outlines the non-invasive glucose monitors that are used to manage diabetes. The benefits and drawbacks of the most recent commercial remote glucose monitoring systems have been evaluated Chapter "Future Developments in Invasive and Non-invasive Diabetes Monitoring".

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Review of Emerging Approaches Utilizing Alternative Physiological Human Body Fluids in Non- or Minimally Invasive Glucose Monitoring

Sunghoon Jang, Yu Wang, and Andre Jang

Abstract Diabetes can cause various acute as well as long-term complications in patients with blood sugar levels of over 600 mg/dL, such as blindness, kidney disease, nervous and circulatory system disease, limb amputations, stroke, and cardiovascular disease (CVD). Frequent and regular blood glucose monitoring by diabetics and physicians is an essential step in the management of diabetes. Over the last five decades, there have been numerous attempts to develop viable painless, non- or minimally invasive blood glucose monitoring techniques to replace all existing invasive methods, such as home blood glucose monitoring, which usually require drawing a blood sample by piercing the skin (typically, on the finger). This method strongly discourages the patients' compliance and has serious drawbacks as the procedure is invasive, causing discomfort, pain, and potential risks of infection or tissue damage. It is highly desired to have alternative non-invasive blood glucose monitoring techniques. This review investigates the principles of three major emerging general technologies, namely optical, Radio Frequency (RF)/microwave, and electrochemical glucose monitoring technologies. These glucose monitoring technologies can be classified as 15 specific techniques that use multivariate regression analyses to correlate feeble optical, Radio Frequency (RF)/microwave, or electrochemical signals from various body fluids to physiological glucose concentration. This review also offers how-to utilize glucose-sensing techniques to target variable areas by sampling physiological human body fluids as an alternative diagnostic medium to blood; for example, interstitial fluid, urine, sweat, ocular fluids, and saliva all

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contain traces of blood glucose. The feasibility of adopting these emerging technologies in the commercial market is discussed regarding safety, cost-effectiveness, data management, and accuracy.

Keywords Blood glucose monitoring · Diabetics · Non- or minimally invasive · Optical · RF/Microwave · Electrochemical · Targeting areas · Physiological human body fluids

1 Introduction

Diabetes mellitus, commonly referred to as diabetes, is a disease in which the body does not produce or properly use insulin, causing high blood sugar levels over a prolonged period. This chronic disease is among the top leading causes of death globally that require long-term medical attention [1]. Often, diabetes can lead to many serious medical problems. These include blindness, kidney disease, nervous and circulatory system disease, limb amputations, stroke, and cardiovascular disease (CVD) [2, 3]. According to data from the 2020 National Diabetes Statistics Report, diabetes was the seventh leading cause of death in the United States, and an estimated 34.2 million children and adults or 10.5% of the United States population, including 7.3 million undiagnosed people—2.8% of all U.S. adults have diabetes. The estimated direct and indirect costs of diabetes-related health care in the United States have risen to approximately $327 billion annually in 2017 from $188 billion in 2007, a $90 billion in direct medical costs. Diabetes is a disproportionately expensive disease; in the United States, the individual medical cost per person associated with diabetes increased from $8417 to $9601 between 2012 and 2017. In 2017, the individual cost of health care was $16,750 for diabetes, while about $9600 of this amount was attributed to diabetes [4, 5].

The recent multi-center NIH studies have indicated that the health risks associated with diabetes are significantly reduced when the blood glucose levels are well and frequently controlled, indicating that it is prudent to measure the blood glucose as often as five or six times a day. Thus, it is very important that proper monitoring be done by diabetics at home or work [6]. At present, all existing home blood glucose monitoring methods require drawing a blood sample by piercing the skin (typically, on the finger). This method strongly discourages a patients' compliance and has serious drawbacks because the procedures are invasive [7].

Additionally, a recent Mayo Clinic report listed 10 ways to avoid diabetes complications. Their recommendations included: (1) Commit to managing your diabetes. (2) Do not smoke. (3) Keep your blood pressure and cholesterol under control. (4) Schedule regular physicals and eye exams. (5) Keep your vaccines up to date. (6) Take care of your teeth. (7) Pay attention to your feet. (8) Consider a daily aspirin. (9) If you drink alcohol, do so responsibly. (10) Manage your stress [8]. However, not included in this list are just as important as regular exercise and choosing water as your primary beverage.

2 Alternative Physiological Body Fluids to Blood

Since a non-invasive method of monitoring blood glucose would present major advantages over existing invasive techniques, many research groups have attempted to propose numerous attractive alternatives in terms of non- or minimally invasive glucose-sensing techniques within the physiological glucose concentrations (18–450 mg/dl) in human blood. These approaches have demonstrated promising results through in/ex vivo and in vitro experimental/clinical glucose evaluations. Through our previous study, we attempted to review the number of emerging non- or minimally invasive techniques and methods and provided a comprehensive list in terms of applying alternative physiological body fluids as opposed to blood [9].

Physiological body fluids are highly complex mixtures of a variable concentration of cells, proteins, macromolecules, metabolites, small molecules, including glucose [9, 10]. Although blood is the most commonly studied body fluid and is considered as the gold standard medium for detecting glucose concentration, other emerging biological body fluids such as interstitial fluid (IF), urine, sweat, saliva, or ocular fluids, are more accessible due to the significant advance of nanotechnology. The amount of glucose contained in the biological body is proportional to its concentration in the blood. These fluids have been utilized as attractive alternative sample media for non-invasive continuous monitoring. The glucose level in these body fluids is identical to the glucose concentration in the blood plasma. Table 1 summarizes the comparison and contrast of the key aspects, including glucose concentration for diabetics and non-diabetics, pH level, and time lag of the various physiological body fluids under the current review.

Blood has been the gold-standard medium for glucose monitoring since measurements carried out in this fluid were first introduced in 1953 [25, 26]. Blood is

Table 1 A summary of relevant glucose concentrations, time lag, and pH values measured in physiological body fluids of diabetics and non-diabetics

Body fluid	Glucose concentration for non-diabetics (mg/dl)	Glucose concentration for diabetics (mg/dl)	pH level	Time lag (min)
Blood	70–130 [2, 11]	36–720 [2, 11, 12]	7.35–7.45 [10, 12]	–
Interstitial fluid	65–118 [13, 14]	35.8–400 [12–14]	7.20–7.40 [10, 12]	~10 [14, 15]
Urine	10.8–27.1 [16, 17]	50.1–100 [16, 18]	4.50–8.00 [10, 12]	~20 [16, 19]
Sweat	1.1–1.98 [10, 12, 20]	0.18–18.0 [10, 12, 20]	4.60–6.80 [10, 12]	~20 [18]
Saliva	4.14–10.3 [12, 21, 22]	9.91–31.9 [21–23]	6.20–7.40 [10, 12]	~15 [23]
Ocular fluids	1.8–9.0 [18, 24]	9.01–90.1 [18, 20, 24]	6.50–7.50 [10, 12, 24]	~10 [10, 24]

Time lag is the time required to diffuse blood from the capillaries to the tissues [9]

complex plasma containing metabolites and electrolytes (sodium, potassium, chloride, calcium, bicarbonate, glucose, urea, and creatinine) [10]. The sensor using electrochemical/amperometric enzyme electrodes and transducers, employed the non- or enzyme glucose oxidase (GOx) and glucose dehydrogenase (GDH) utilizing the biochemical reaction, has become the most popular and commercially available blood glucose monitoring method in the market because of its suitable sensitivity, wide selectivity, good reproducibility, and easy manufacturability at relatively low cost, although it is an invasive method [26]. Several non-invasive methods are used to detect and monitor the glucose level in the blood, including Absorbance spectroscopy such as Near and Mid Infrared spectroscopy, Raman spectroscopy, Photoacoustic spectroscopy, Fluorescence spectrophotometry, Bio-impedance spectroscopy, Optical coherence tomography, and Thermal emission spectroscopy [27–37].

Interstitial fluid is the extracellular fluid that fills the spaces between most of the body's tissue cells and makes up a substantial portion of the liquid environment of the body. It has significant potential for medical diagnostics as it closely resembles blood plasma in composition but contains less protein [10, 38]. Since tiny molecular biomarkers are exchanged as biochemical information between blood and subcutaneous ISF through diffusion, the correlation between ISF and blood can be used to indirectly obtain the diagnostic information of patients. Methods for monitoring glucose via the skin have become very popular in recent years, where these approaches have been developed to counteract the challenges associated with patient compliance and invasive monitoring. Some of these approaches include Reverse iontophoresis, Electrochemical methods, Electromagnetic techniques, Metabolic heat conformation, Microwave resonator-based technique, Sonophoresis, and Bio-impedance spectroscopy [39–47].

Urine is a commonly collected sample for clinical and nonclinical testing, especially due to the ease of collection, usually without invasive procedures. Urine is composed of inorganic salts and organic compounds, including proteins, hormones, and a wide range of metabolites, including glucose [10, 48]. It is related to applying an enzyme and nanomaterials-based biosensor as important methods for monitoring glucose concentration within the physiologic range, including Colorimetric biosensing utilizing Enzymatic nanomaterials, Laser-generated photonic nanosensor, and Photonic crystal-based biosensor [48–51].

Sweating is a primary biological role of thermoregulation. Sweat is considered one of the most accessible body fluids for glucose detection. Sweat is easily accessible for sampling with sufficient quantities and rapid reproduction compared to all other body fluids. Sweat is an acidic electrolyte-rich fluid, and its production is induced by exercise, resulting in the secretion of metabolites, such as lactate, glucose, alcohol, and uric acid [10, 12]. More recent studies suggest a direct correlation between sweat and blood glucose concentration, although glucose levels in sweat are of a much smaller concentration than those in blood. Wearable sweat-based continuous glucose monitoring biosensors include non- or Enzyme-based electrochemical techniques, Optical fiber long-period grating (LPG), and Electrochemically enhanced

iontophoresis integrated with feedback transdermal drug delivery module are under development [43–45, 52–55].

Saliva is increasingly recognized as an attractive diagnostic fluid because it can be collected non-invasively without employing specific devices or trained personnel. More recent studies investigated and confirmed a significant correlation between salivary and blood glucose levels in diabetics and non-diabetics. Saliva is a complex mixture of 99.5% water and 0.5% electrolytes (amylase, lipase, mucin, glycoproteins, glucose, and antimicrobial enzymes) [10, 56]. Saliva can be utilized as an alternative to blood and can be monitored by a non-invasive measuring salivary glucose. Some non-invasive techniques for saliva glucose monitoring have been studied include Enzyme-based electrochemical/Amperometric/Colorimetric nano-biosensor and Functionalized carbon nano-tube FET/organic electrochemical transistor [23, 43–45, 56–61].

Ocular fluids include tears, aqueous humor, and vitreous humor, which are promising fluids because the glucose concentration of ocular fluids is highly correlated to blood glucose. Monitoring the glucose concentration in the fluids is considered a relatively new technique that is a worthwhile alternative to invasive methods for repetitive or continuous monitoring. Ocular fluids excreted from the body as an extracellular fluid contain glucose water, mucin, lipids, lysozyme, lactoferrin, lipocalin, lacritin, immunoglobulins, glucose, urea, sodium, and potassium [10, 12, 23]. Research working towards non-invasive monitoring methods of glucose in the ocular fluids consists of Chronoamperometric technique, Electrode/electrochemically embedded contact lens, CMOS/Amperometric needle-type electrochemical method, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, and Optical polarimetry [62–68].

3 Emerging Non- or Minimally Invasive Glucose Monitoring Techniques

Through the literature search for the current review, we learned that techniques for non- or minimally invasive monitoring glucose via the skin had become the most popular approach in recent years, where these methods have been developed to counteract the challenges associated with patient compliance and invasive monitoring [18, 27]. The description and target areas of the leading approaches are presented in Table 2, mainly classified as Optical technology, including Absorbance spectroscopy, Raman spectroscopy, Photoacoustic spectroscopy, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, and Metabolic heat conformation. The availability of the non- or minimally invasive glucose monitoring devices in the market is also shown in Tables 2, 3 and 4, respectively. Some devices have been withdrawn from the market due to inaccuracy, unreliability, inconsistency,

Table 2 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as optical technology

Optical technology		
Specific technique	Description	Target areas (body fluids)
Absorbance spectroscopy[a,b,c]	Measures transmittance, reflectance (including diffuse reflectance), and interaction of the light when directed over the sample tissues for analytical purposes. Near-infrared absorption spectroscopy (**NIR**) uses a beam of light with 750–2500 nm. Mid-infrared absorption spectroscopy (**MIR**) uses 2500–10,000 nm, which are focused on the body to determine glucose concentration within tissues. The light and sample tissue interactions produce molecular-specific vibrational information of the absorption and scattering phenomenon in the infrared spectral domain [12, 27, 28]	Fingertip, palm, forearm, inner lip, and earlobe (blood and interstitial fluid) [12, 27, 28]
Raman spectroscopy[b,c]	Applies a spectroscopic technique using the scattering phenomenon of monochromatic light to observe vibrational and rotational states within molecules. When single-wavelength light hits a target, it produces scattered light traveling in all directions. The degrees of scattering due to glucose molecules are purely dependent on their concentration levels [27, 29]	Finger, arm, eye, wrist, hand (ocular fluids and blood) [27, 29]
Photoacoustic spectroscopy[b,c]	Employs laser pulses with a wavelength that is absorbed by a specific molecule in the body fluid to produce localized heating, dependent on the specific heat capacity of the targeted tissue, and measures the effect of light absorption to detect a glucose concentration in blood based on the velocity of ultrasonic waves generated in glucose solution by the photoacoustic principal [30, 69]	Finger, arm, and earlobe (blood and interstitial fluid) [12, 30, 69]

(continued)

Table 2 (continued)

Optical technology		
Optical coherence tomography (OCT)[c]	Includes optical methods with ultrasound, impedance, and heat capacitance. This technique applies the principles of low coherence interferometry with coherent radiation and determines the glucose concentration present by detecting the changes of optical characteristics of bio-tissues at micrometer resolutions, including intensity/delay of the reflected/scattered and transmitted light upon interaction with the subcutaneous tissue by employing an interferometer with coherent light, with a wavelength between 800 and 1300 nm [31, 32]	Forearm and eye (ocular/interstitial fluids and blood) [31, 32]
Fluorescence spectrophotometry[a,c]	Applies the principle of fluorescent light emission of an ultraviolet laser beam (340–400 nm) after absorbing radiation of a different energy level which causes a wavelength difference. The measurement of the concentration of glucose molecules in the blood is conducted utilizing a sensitive protein and intensity of fluorescence which are proportional [33, 34]	Finger, abdomen, upper arm, and eye (blood, ocular/interstitial fluids) [33, 34]
Ocular spectroscopy[c]	Utilizes the specially designed hydrogel-based disposable tear glucose-sensing contact lenses, which change color depending on the glucose concentrations. The fluorescence response from the lenses can be monitored using simple excitation and emission detection devices and serves as the tool for blood glucose detections from the tears [35, 36]	Eye (tears) [35, 36]

(continued)

Table 2 (continued)

Optical technology		
Metabolic heat conformation[a,b,c]	Measures physiological parameters associated with the generated quantity of metabolic heat dissipation, blood flow rate of local tissue, and degree of blood oxygen saturation between the skin and contacted conductor corresponding to the glucose concentration by employing the system consisting of thermal, humidity, infrared, and optical sensors [41, 42]	Fingertip, earlobe, and forearm (blood and interstitial fluid) [12, 41, 42]
Optical polarimetry[c]	Applies the phenomenon of the optical activity, which is a certain rotation of the polarized plane of the incident light (400–780 nm) passing through the aqueous humor of the eye and glucose, known as an optically active molecule. When the light is passed through the cornea and across the anterior chamber of the eye, the polarimetric signal that is converted into a time-varying voltage by the photodetector varies linearly with changes in glucose concentration [67, 68]	Eye (ocular fluids) [67, 68]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

Table 3 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as electrochemical technology

Electrochemical technology		
Specific technique	Description	Target areas (body fluids)
Reverse iontophoresis[a,c]	Applies a passage of low electrical current to enhance the transport of both charged and polar, neutral compounds across the skin to drive ions between two electrodes from the interstitial fluid and onto the skin's surface, where they can be analyzed in terms of glucose concentration. Transdermal reverse iontophoresis (RI) is a non-invasive technique that can sample body fluids across intact skin to achieve the purpose of blood glucose detection [39, 40]	Wrist, arm, and leg (sweat and interstitial fluid) [12, 39, 40]
Enzymatic electrochemical electrode[a,c]	Analyzes the glucose oxidation that took place in the presence of GOx, oxygen, and water to form gluconic acid and hydrogen peroxide. The hydrogen peroxide is then electrochemically oxidized at the electrode, which converts glucose oxidase activity into an analytical electrical signal in proportion to glucose concentration based on the rate of glucose oxidation by dioxygen, measured by the formation of hydrogen peroxide. Highly selective enzymatic reactions can be used to diminish the influence of electroactive interfering species [43, 44]	Finger, arm, and skin (blood, saliva, urine, tears, interstitial fluid, and sweat) [10, 12, 43, 44]

(continued)

Table 3 (continued)

Electrochemical technology		
Non-enzymatic amperometric electrode[a,c]	Uses metal–organic framework (MOF)-based nanocomposites and provides an alternative to an enzymatic method, which is impossible to implant into the human body for the long term and in situ monitoring since the immobilized enzyme would degrade quickly. Cost-effective non-enzymatic amperometric glucose biosensors with high sensitivity, selectivity, and stability could be commercially more feasible [43, 45, 46]	Finger, arm, eye, and skin (blood, saliva, urine, tears, interstitial fluid, and sweat) [12, 43, 45]
Colorimetric detection[a,c]	Determines the glucose concentration with the aid of a color reagent. When glucose is oxidized by glucose oxidase into D-gluconic acid plus hydrogen peroxide, the hydrogen peroxide is then detected with a highly specific colorimetric probe. In an enzymatic analysis, the color reaction is preceded by a reaction catalyzed by an enzyme [48, 49]	Finger, arm, eye, urine, and skin (sweat, tears, and urine) [12, 19, 48, 49]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

Table 4 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as RF/microwave technology

RF/microwave technology		
Specific technique	Description	Target areas (body fluids)
Microwave resonator-based[a,c]	Utilizes the interaction between electromagnetic waves and biological tissues since microwaves' reflection, transmission, and absorption are closely related to the dielectric properties of tissues, where the dielectric constant varies with glucose fluctuations. Microwaves can easily penetrate biological tissues of millimeter thickness, so glucose concentration variation in ISF has much higher sensitivity on phase and magnitude response of the sensor than its variations in blood [70–74]	Finger, hand, wrist, arm, and earlobe (interstitial fluid and blood) [12, 70–74]
Bio-impedance spectroscopy[a,c]	Measures the glucose-dependent electrical impedance changes as a function of frequency and provides proof of a change in blood impedance with glucose level fluctuations. Impedance is recorded as a frequency bypassing RF current between 100 Hz and 100 MHz across human biological tissues and skin. The glucose molecule is measured by its concentration-dependent interaction with red blood cells [75–78]	Thumb, upper arm, wrist, and abdomen (interstitial fluid and blood) [12, 69, 75, 77, 78]
Sonophoresis[a,c]	Uses low-frequency (20 kHz) ultrasound to increase skin permeability and causes expansion and contraction of gaseous inclusions that open pathways for interstitial fluids to transport glucose to the epidermis, where it is measured transdermally with the combination of the low-profile cymbal array and an electrochemical glucose sensor consisting of amperometric electrodes and a novel glucose oxidase hydrogel. This technique creates micropores in the skin to enable the interstitial fluid containing glucose to come outside [69, 79]	Arm, wrist, and abdomen (interstitial fluid and blood) [12, 69]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

and other issues. Meanwhile, others have never been introduced due to their unclear circumstance issues.

Electrochemical technology includes Reverse iontophoresis, Enzymatic electrochemical electrodes, Non-Enzymatic amperometric electrodes, and Colorimetric detection method, all presented in Table 3.

RF/Microwave detection technology includes Microwave resonator-based method, Bio-impedance spectroscopy, and Sonophoresis, presented in Table 4.

4 Conclusions

This study aimed to present and review the latest specialized approaches in emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as optical, electrochemical, and RF/Microwave methods. These glucose monitoring methods convert the weak optical, electrochemical, or electromagnetic signal to glucose concentration. We also investigated the non- or minimally invasive glucose monitoring techniques which utilize various physiological body fluids as an alternative diagnostic medium. These techniques have a great potential for monitoring blood glucose levels as they increase accuracy, selectivity, sensitivity, and reliability of the measurement that would satisfy medical use criteria and meet the expectation as a less expensive alternative.

Our current study learned that optical and microwave methods have advantages over electrochemical methods because they offer purely non-invasive and continuous monitoring without stimulating discomfort to the human body. However, invasive or minimally invasive electrochemical glucose meters with more advanced enzyme and electrode materials have significantly improved because they are considered more reliable and affordable. Electrochemical diagnostic devices are equipped with software-based analytical performance and data management, capable of updating device features without recalibration, and less expensive. Therefore, the current dominating electrochemical glucose sensors in the commercial market will not be easily replaced even if they are invasive until promising non-invasive glucose meters with the more sensitive, efficient, intelligent, robust, and reliable measurements that can satisfy medical use criteria is introduced to the market.

5 Future Trends

This review covers the research progress of the latest technologies and their methods of non- or minimally invasive glucose monitoring with alternative physiological body fluids such as interstitial fluid, urine, sweat, ocular fluids, and saliva instead of blood glucose concentration. Considerable progress has been made in developing viable non- or minimally invasive glucose sensors in recent years due to devoted research efforts and the revolution of biomaterials, medicine, nanotechnology, and computer

science. Although there have been many dedicated research efforts with numerous progressions to develop a non- or minimally invasive glucose monitoring sensor, there are still several obstacles to achieving acceptable glucose monitoring because of the complicated nature of the operation and measurement process.

Through our more recent searches, we also learned that several non- or minimally invasive glucose monitoring devices using optical, electrochemical, and RF/microwave technologies had been introduced commercially in the market, and others are close to commercializing. However, we concluded that these methods are still far from being clinically reliable to meet market expectations. They require further systemic development and clinical evaluations due to a lack of consistency, stability, accuracy, and reliability. The remarkable advances in an emerging trend to integrate a series of functional modules, data mining algorithms, wireless communications, machine learning algorithms, and computational signal processing led to significant achievements allowing the creation of new hypotheses that enable deeper understanding and further investigations of non- or minimally invasive glucose monitoring devices. AI-driven wearable monitoring devices may be introduced to the current market, making it possible to collect a diverse range of continuous physiological signals to accurately monitor the following: glucose levels in diabetics, sweat, anxiety, heart rate, blood pressure, nutrition, calorie intake, and COVID-19 related symptoms in advance. Further continued development of sophisticated decision support hardware and software systems will yield great opportunities to introduce more reliable and affordable non-invasive glucose monitoring systems in the broad commercial market for medical use within the very near future.

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Conflict of Interest None.

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