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

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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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