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Review of emerging approaches in non- or minimally invasive glucose monitoring and their application to physiological human body fluids

Abstract

The frequent blood glucose monitoring by the diabetics and physicians is a very essential step in the management of the diabetes because this devastating disease can lead the patients to blindness, kidney disease, nervous & circulatory system disease, limb amputations, stroke and cardiovascular disease (CVD). There have been numerous attempts to develop viable painless non- or minimally invasive blood glucose monitoring techniques over the last five decades in order to replace all existing methods of home blood glucose monitoring require drawing a blood sample by piercing the skin. This review describes the principles of two main emerging general technologies such as optical and electrochemical glucose monitoring methods, which represent 12 specific techniques applying multivariate regression analyses converting feeble optical or electrochemical signal to glucose concentration. This review article also deals with advances utilizing integration of glucose sensing techniques into targeting areas by sampling potential alternative physiological human body fluids to blood such as interstitial fluid, urine, sweat, ocular fluids and saliva contain traces of blood glucose.

Keywords: blood glucose monitoring, diabetics, non- or minimally invasive, optical, electrochemical, targeting areas, physiological human body fluids

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Abbreviations: OCT, optical coherence tomography; GOx, glucose oxidase**;** GDH, glucose dehydrogenase; IF, interstitial fluid; CVD**,** cardiovascular disease

Introduction

Diabetes mellitus, commonly referred to as diabetes, is a serious disease in which the body doesn't produce or properly use insulin so there are high blood sugar levels over a prolonged period which represents one of the major health problems in society and a chronic disease that requires long-term medical attention.[1] Often, diabetes can lead to many serious medical problems. These include blindness, kidney disease, nervous & circulatory system disease, limb amputations, stroke and cardiovascular disease (CVD).[2,3] According to data from the 2017 National Diabetes Statistics Report, an estimated 30.3 million children and adults in the United States including 7.2 million undiagnosed people - 9.5 percent of the U.S. population in 2011 - have diabetes and the estimated cost of diabetes-related health care in the United States is risen to approximately $245 billion annually in 2012 from $174 billion in 2007, including $68.6 billion in direct medical costs.[4,5] Diabetes is a disproportionately expensive disease; in the United States in 2012, the individual cost of health care was $13,700 for people with diabetes, while about $7,900 of this amount was attributed to diabetes.[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 at work.[6] At present all existing methods of home blood glucose monitoring require drawing a blood sample by piercing the skin (typically, on the finger). This method strongly discourages a patients' compliance and has the serious drawbacks because the procedure is invasive.

Alternative physiological body fluids to blood

Since a non-invasive method of monitoring blood glucose would present major advantages over current existing methods which are using invasive techniques, many research groups have attempted to propose numerous attractive alternatives in terms of non- or minimally invasive glucose sensing techniques within physiological glucose concentrations (18-450mg/dl) in human blood demonstrating the promising results through *in/ex vivo* and *in vitro* experimental/clinical glucose evaluations. Human body fluids such as interstitial fluid, urine, sweat, ocular fluids and saliva contain traces of bold glucose are more accessible due to the significant advance of nanotechnology. Physiological body fluids are highly complex mixtures of a variable concentration of cells, proteins, macromolecules, metabolites and small molecules including glucose.[7,8] Although blood is the most commonly studied body fluid and 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 containing traces of glucose are more accessible due to the advance of nanotechnology and they have been utilized as attractive alternative sample media for non-invasive continuous monitoring. The glucose level in the body fluids is identical with the concentration of glucose in the blood plasma. Table 1 summarizes 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 current review.

Table 1 Summary of relevant glucose concentrations, lag time, and pH values measured in physiological body fluids of diabetics and non-diabetics. (Time lag is the time required to diffuse blood from the capillaries to the tissues)

Body fluid	Glucose concentration for non-diabetics	Glucose concentration for diabetics	pH level	Time lag
Blood	70 – 130mg/dl[2,9]	36 –720mg/dl[2,8,9]	7.35 –7.45[7,8]	----------
Interstitial Fluid (IF)	65 –118mg/dl[50,51]	35.8 –400mg/dl[8,50,51]	7.20 –7.40[7,8]	~ 10mins[51,52]
Urine	10.8 –27.1mg/dl[53,54]	50.1 –100mg/dl[53,55]	4.50 –8.00[7,8]	~ 20mins[53,56]
Sweat	1.1 –1.98mg/dl[7,8,57]	0.18 –18.0mg/dl[7,8,57]	4.60 –6.80[7,8]	~ 20mins[55]
Saliva	4.14 –10.3mg/dl[8,58,59]	9.91 –31.9mg/dl[18,58,59]	6.20 –7.40[7,8]	~ 15mins[60]
Ocular fluids	1.8 –9.0mg/dl[17,43]	9.01 –90.1mg/dl[17,18,43]	6.50 –7.50[7,8,43]	~ 10mins[7,43]

Blood

Blood has been the gold-standard medium for glucose monitoring, since measurements carried out in this fluid was first introduced in 1953.[9,10] Blood is complex plasma containing metabolites and electrolytes (sodium, potassium, chloride, calcium, bicarbonate, glucose, urea and creatinine),[7] The sensor used electrochemical/ amperometric enzyme transducers, which employed the non- or enzyme glucose oxidase (GOx) and glucose dehydrogenase (GDH) utilizing the biochemical reaction, has been the most popular and commercially available blood glucose monitoring method in the market due to its suitable sensitivity, wide selectivity, good reproducibility and easy manufacturability at relatively low cost, although it is invasive method.[11] There are several non-invasive methods used to detect and monitor the glucose level in 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.[11–19]

Interstitial fluid

Interstitial fluid is the extracellular fluid that fills the spaces between most of the cells of the body and provides 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.[7,20] 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, Sonophoresis, Electromagnetic techniques, and metabolic heat conformation.[21–30]

Urine

Urine is a commonly collected sample for clinical and nonclinical testing, especially due to the ease of collection, usually without the need for invasive procedures. Urine is composed of inorganic salts and organic compounds, including proteins, hormones, and a wide range of metabolites including glucose.[7,31] It is involved with the application of an enzyme-based nanomaterials based biosensor as important methods for the monitoring glucose concentration within physiologic range including Colorimetric biosensing utilizing enzymatic nanomaterials, Laser-generated photonic nanosensor, and Photonic Crystal Based Biosensor.[32–34] Sweating is a primary biological role of thermoregulation, the body fluid has been considered as one of the most accessible for the glucose detection. Compared to all other body fluids, sweat is the easiest to get access for sampling with sufficient quantities and rapid reproduction. Sweat is an acidic electrolyte-rich fluid whose production is induced by exercise which results in secretion of metabolites such as lactate, glucose, alcohol and uric acid.[7,8] More recent studies suggest that there is a direct correlation between the sweat and blood glucose concentration, although glucose levels in sweat is much smaller concentration than that in blood. Wearable sweat-based continuous glucose monitoring biosensors include non- or Enzyme-based electrochemical technique, Optical fiber long-period grating (LPG) and Electrochemically enhanced iontophoresis integrated with a feedback transdermal drug delivery module are under development.[27–29,35–38]

Saliva

Saliva is increasingly recognized as an attractive diagnostic fluid because it can be collected non-invasively without employing specific device or trained personnel. More recent studies investigated and confirmed that there is 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).[7,39] Saliva may become an alternative to blood and could be monitored by non-invasive method of measuring salivary glucose. Some non-invasive techniques for saliva glucose monitoring have been studied including Enzyme-based electrochemical/Amperometric/ Colorimetric nano-biosensor and Functionalized carbon nano-tube FET/ organic electrochemical transistor.[27–29,39–42]

Ocular fluids

Ocular fluids include tears, aqueous humor, and vitreous humor which are promising fluids because glucose concentration of ocular fluids is shown to be highly correlated to blood glucose. Monitoring the glucose concentration in the fluids has been considered relatively new technique which is a worthwhile alternative to invasive method for repetitive or continuous monitoring. Ocular fluids can be excreted from the body as an extracellular fluid containing glucose water, mucin, lipids, lysozyme, lactoferrin, lipocalin, lacritin, immunoglobulins, glucose, urea, sodium, and potassium.[7,8,43] Research groups working towards non-invasive monitoring methods of glucose in the ocular fluids include Chronoamperometric technique, Electrode/ electrochemical embedded contact lens, CMOS/Amperometric needle-type electrochemical method, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, and Optical polarimetry.[44–49]

Emerging non- or minimally invasive glucose monitoring techniques

Through the literature search for current review, we learned that techniques for non- or minimally invasive monitoring glucose

via the skin have become most popular approach in recent years, where these approaches have been developed to counteract the challenges associated with patient compliance and invasive monitoring.[17,26] The leading approaches have been presented in Table 2 mainly classified as Optical and Electrochemical detection technology include Absorbance spectroscopy, Raman spectroscopy, Photoacoustic spectroscopy, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, Metabolic heat conformation, Bio-impedance spectroscopy, Reverse iontophoresis, Enzymatic or Non-Enzymatic electrodes, and Colorimetric method. Table 2 also summarized about principle, target areas/body fluids of the latest emerging techniques in non- or minimally invasive glucose monitoring.

Table 2 Summarized about 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 and electrochemical technology

General technology	Specific technique	Description	Target areas (Body Fluids)
Optical	Absorbance spectroscopy	Utilizes both the absorption & scattering phenomenon of the light when directed over the sample tissues for analytical purposes. Near-infrared absorption spectroscopy (NIR) uses a beam of light with a wavelength in the range of 750 – 2,500 nm and Mid-infrared absorption spectroscopy (MIR) uses 2,500 – 10,000 nm, which are focused on the body to determine the concentration of glucose within tissues. The light and sample tissue interactions produce molecular specific vibrational information of the absorption and scattering phenomenon in the infrared spectral domain.[8,11]	Fingertip, palm, forearm, inner lip and earlobe (blood, interstitial fluid)[8,11]
	Raman spectroscopy	Applies a spectroscopic technique used the scattering phenomenon of the light to observe vibrational, rotational, and other low-frequency modes in human fluids containing glucose. The degrees of scattering for glucose molecules are purely dependent on its concentrations levels.[11,12]	Finger, arm, eye and wrist (aqueous humor, blood)[11,12]
	Photoacoustic spectroscopy	Utilizes the laser light for the body fluid excitations and measures the effect of light absorption to detect a glucose concentration in a blood based on the velocity of ultrasonic waves generated in glucose solution by the photoacoustic principal.[13]	Finger, arm and earlobe (blood, interstitial fluid)[8,13]
	Optical coherence tomography (OCT)	Utilizes the super luminescent light and determines the glucose concentration present by assessing the intensity/delay of the reflected/scattered and transmitted light upon interaction with the subcutaneous tissue by employing an interferometer with a low coherent light source.[14,15]	Forearm and eye (interstitial fluid, blood)[14,15]
	Fluorescence spectrophotometry	Involves the absorption and the emission of an ultraviolet laser beam (340 – 400 nm) to measure the concentration of glucose molecules in blood by means of sensitive protein and intensity of fluorescence which are proportional.[16,17]	Finger, abdomen, upper arm, and eye (blood, interstitial fluid, aqueous humor, tears)[16,17]
	Ocular spectroscopy	Utilizes the specially designed hydrogel based eye contact lenses which change color depending on the glucose concentrations. These color change serves as the tool for blood glucose detections from the tears.[18]	Eye (tears)[18]
	Metabolic heat conformation	Involves the measurement of physiologic indices related to metabolic heat dissipation, blood flow rate and degree of blood oxygen saturation corresponding to the glucose concentration by applying thermal, humidity, and optical sensors.[25,26]	Fingertip, earlobe, and forearm (blood, interstitial fluid)[8, 25,26]
	Bio-impedance spectroscopy	Measures the dielectric properties of a tissue. Impedance is recorded as a function of frequency by passing a small AC current across a tissue. Glucose is measured by its concentration-dependent interaction with red blood cells.[21,22]	Thumb, upper arm, wrist, and earlobe (interstitial fluid, blood)[8, 21,22]
	Reverse iontophoresis	Uses a passage of electrical current over the skin to drive ions from the interstitial fluid and onto the surface of the skin, where they can be analyzed in terms of glucose concentration.[23,24]	Wrist, arm, and leg (sweat, interstitial fluid, sweat) [8,23,24]
Electro-chemical	Enzymatic electrode	Utilizes an electrode instead of O_2 to take up the electrons needed to oxidize glucose and produce an electronic current in proportion to glucose concentration. Highly selective enzymatic reactions can be used to diminish the influence of electroactive interfering species.[27,28]	Finger, arm, and skin (blood, saliva, urine, tears, interstitial fluid, sweat)[7,8,27,28]
	Non-Enzymatic electrode	Provides an alternative to enzymatic methods, which is impossible to implant into the human body for the long term and in situ monitoring due to the immobilized enzyme would degrade quickly. Cost-effective non-enzymatic electrochemical glucose biosensors with high sensitivity, selectivity and stability could be commercially more feasible.[27,29]	Finger, arm, eye and skin (blood, saliva, urine, tears, interstitial fluid, sweat)[8,27,29]
	Colorimetric detection	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 enzymatic analysis, the color reaction is preceded by a reaction catalyzed by an enzyme.[30]	Finger, arm, eye and skin (sweat, tears, urine)[4,8,53]

Conclusion

This study aimed to present and review the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as optical and electrochemical method which convert the feeble optical or electrochemical signal to glucose concentration. We also presented the description of the non- or minimally invasive glucose monitoring techniques with utilizing various physiological body fluids as alternative diagnostic medium may have a great potential for monitoring blood glucose levels with the enhanced sensitivity and reliability of the measurement that would satisfy medical use criteria and the cost of the proposed testing device would be significantly lower than for existing invasive methods. Through current study, we have discussed the latest technologies and methods for non- or minimally invasive glucose monitoring with alternative physiological body fluids to blood. We acknowledged that considerable progress has made in the development of viable glucose sensors in recent years due to devoted research efforts and the revolution of nanotechnology/ biomedical science. Although there has been much research dedicated efforts with considerable progressions to develop a non- or minimally invasive glucose monitoring sensor, there are still several challenges related to the achievement of reliable and acceptable glucose monitoring due to the complicated nature of the operation and measurement process. Unfortunately, none of these technologies have been introduced commercially available in the market as a clinically reliable device at this stage because they are required further clinical evaluations before approval for medical use. Meanwhile, invasive glucose meters have made a significant improvement because they are considered more convenient and affordable diagnostic devices in terms of software based analytical performance, data management, cost-effectiveness, and updated device features without recalibration. Therefore, the currently dominating electrochemical glucose sensors in the commercial market will not be easily replaced even if they are invasive until promising non-invasive glucose meter with affordable sensitivity and reliability of the measurement that would satisfy medical use criteria and the cost-effectiveness is introduced to the market.

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Conflict of interest

The author declares no conflict of interest.

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