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REVIEW

Recent advances in noninvasive glucose monitoring

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Abstract: The race for the next generation of painless and reliable glucose monitoring for diabetes mellitus is on. As technology advances, both diagnostic techniques and equipment improve. This review describes the main technologies currently being explored for noninvasive glucose monitoring. The principle of each technology is mentioned; its advantages and limitations are then discussed. The general description and the corresponding results for each device are illustrated, as well as the current status of the device and the manufacturer; internet references for the devices are listed where appropriate. Ten technologies and eleven potential devices are included in this review. Near infrared spectroscopy has become a promising technology, among others, for blood glucose monitoring. Although some reviews have been published already, the rapid development of technologies and information makes constant updating mandatory. While advances have been made, the reliability and the calibration of noninvasive instruments could still be improved, and more studies carried out under different physiological conditions of metabolism, bodily fluid circulation, and blood components are needed.

Keywords: noninvasive, glucose monitoring, diabetes mellitus, blood glucose measurement

Introduction

Diabetes mellitus (DM) is a major cause of mortality and morbidity in every country. In 2011, more than 366 million people had DM worldwide.[1] Due to the world's increasingly aging populations, increasingly unhealthy diets, sedentary lifestyles, and obesity, it is estimated that the prevalence of DM will increase to 552 million people by 2030.[1] DM is an intractable condition in which blood glucose levels cannot be regulated normally by the body alone; it has many complications, including cardiovascular diseases, nephropathy, neuropathy, retinopathy, and amputations.[2] The treatment methods include dietary regulation to control blood glucose levels, oral medication, and insulin injection; however, all of these have adverse effects on the patient's quality of life.

Type 1 diabetes, Type 2 diabetes, and gestational diabetes are three main types of diabetes, although there are some other forms of DM, including congenital diabetes, cystic fibrosis-related diabetes, and steroid diabetes, induced by high doses of glucocorticoids.[3] Type 1 diabetes is an autoimmune disease with pancreatic islet beta cell destruction. It is an autoimmune disorder in which the body cannot produce sufficient insulin. Type 2 diabetes, the most prevalent form, results from insulin resistance with an insulin secretary defect. Both Type 1 and Type 2 diabetes are chronic conditions that usually cannot be cured easily. Gestational diabetes is the term used when a woman develops diabetes during pregnancy. Generally, it resolves after delivery, but it may precede development of Type 2 diabetes later in life.

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The control of blood glucose levels relies on blood glucose measurement. Diabetic patients, whether Type 1 or Type 2, are encouraged to check their blood glucose levels several times per day; currently, the most common means of checking is by using a finger-prick glucose meter.[4] In this way, diabetic patients can obtain a clear picture of their blood glucose levels for therapy optimization and for insulin dosage adjustment for those who need daily injections.

Finger-pricking, however, has several disadvantages. Many people dislike using sharp objects and seeing blood, there is a risk of infection, and, over the long term, this practice can result in damage to the finger tissue. Given these realities, the advantages of a noninvasive technology are easily understood. Further, the finger-prick glucose meter is a discrete glucose measurement device that is not practical for continuous monitoring of blood glucose. Some incidences of hyperglycemia or hypoglycemia between measurements may not be recorded. Thus, the resultant monitoring cannot fully represent the blood glucose pattern. Noninvasive glucose measurement eliminates the painful pricking experience, risk of infection, and damage to finger tissue.

The noninvasive concept was launched more than 30 years ago. Nevertheless, it can be said that most of the noninvasive technologies are still in their early stages of development. Many noninvasive technologies have been described in the literature, and there is an increasing volume of recent research results. Keeping up with the current situation requires constant updating.[5] The results of an Internet search provide much information on this topic, such as overviews of noninvasive technology,[6] the future development of meters and monitors for diabetes,[7] and information about research centers that are developing this technique;"[8] however, the scope of devices is so broad that no single site can keep up. As a result, much of the information is outdated.[9] Therefore, the aim of this review is to present the current state of noninvasive glucose monitoring for diabetes. It will describe the technologies being used, technologies in development, devices being used, and the companies producing these devices. Websites will be mentioned as appropriate.

Noninvasive glucose-monitoring technologies

In this review, we consider noninvasive glucose measurement as any technique that does not involve pricking (breaking) the skin. The different techniques/technologies are listed in alphabetical order. The principles of each technology, together with its advantages and limitations, are discussed.

Bioimpedance spectroscopy

Principles

Bioimpedance is a measure of the resistance to electric current flowing through the tissues of a living organism. The measurement of bioelectrical impedance has proved useful as a noninvasive method for measuring body composition.[10] The impedance spectrum, or dielectric spectrum, is measured in the frequency range of 0.1 to 100 MHz. According to Hillier et al,[11] variations in plasma glucose concentration induce, in red blood cells, a decrease in sodium ion concentration and an increase in potassium ion concentration. These variations cause changes in the membrane potential of red blood cells, which can be estimated by determining the permittivity and conductivity of the cell membrane through the dielectric spectrum.[12–14] In 2003, the company Pendragon Medical Ltd. (Zurich, Switzerland) developed a wrist-band-based glucose monitor called "Pendra." However, this product was soon withdrawn from the market because of poor reliability. Caduff et al are still working on this technology.[15]

Advantages

Bioimpedance spectroscopy does not require the use of statistically-derived, population- specific prediction models. It has the potential advantage of being able to differentiate between extracellular water and intracellular water and, thus, to provide an estimate of body cell mass, thus characterizing the blood bioimpedance properties. The instrument is easy to use and low in cost compared to other devices.

Limitations

The limitation of this technology is that it requires an equilibration process, wherein the user must rest for 60 minutes before starting the measurements.[12] Moreover, some problems remain to be resolved, such as the effects of temperature and body water content (eg, skin moisture, sweat, overall hydration) on readings.[15]

Electromagnetic sensing

Principles

Similar to bioimpedance spectroscopy, this technology assesses dielectric parameters of blood. The difference between them is that an electric current is used in bioimpedance spectroscopy, while the electromagnetic coupling between two inductors is used in electromagnetic sensing.[16,17] The sensor uses electric currents to detect variation of the dielectric parameters of the blood, which may be caused by glucose concentration changes.[18] The frequency range used in this technique is 2.4–2.9 MHz. However, depending on the

temperature of the investigated medium, there is an optimal frequency, where sensitivity to glucose changes reaches its maximum. Determining this frequency is important for the efficacy of the device. Gourzi et al suggested the optimal frequency is 2.664 MHz at 24°C.[16] However, another study of this technology, using pig blood, suggests that the optimal operating frequency is 7.77 GHz at 25°C.[19]

Advantages

Using a specific frequency range can isolate the effect of blood glucose and minimize the characteristics of other substances, such as cholesterol, which might skew readings. In addition, it is relatively safe, as it will not ionize the molecules of the body.

Limitations

Temperature has a strong effect on this form of measurement, because it influences the optimal investigation frequency. Furthermore, Moran et al reported that the blood dielectric parameters depend on several components other than glucose.[18] Therefore, more study of potential confounders is needed before this technology can be considered reliable.

Fluorescence technology

Principles

This technique uses fluorescence reagents to track the presence of glucose molecules in blood. Many approaches exist, such as measuring changes in fluorescence resonance energy transfer between a fluorescent donor and an acceptor, or measuring glucose-induced changes in intrinsic fluorescence of enzymes.[20] One study reported that glucose levels in tears reflect concentrations similar to those in blood, and thus, fluorescence of tears can be used as noninvasive glucose monitoring. Khalil reported that this approach can track blood glucose with an approximate 30-minute lag time and does not suffer from interference from variations in the light intensity of the ambient environment.[21] The photonic sensing is achieved with polymerized crystalline colloidal arrays, which respond to different concentrations through diffraction of visible light.

Advantages

This technology is very sensitive; it can detect single molecules. It causes little or no damage to the body. In addition, it can give results in terms of fluorescence intensity and decay times, both of which are independent of light scattering and fluorophore concentration, which can reduce loss through diffusion or degradation.

Limitations

Photonic sensing can suffer from strong scattering phenomena, especially in fluorescence technology. Moreover, there are limitations, such as short lifetimes and biocompatibility, which need to be dealt with, possibly through the use of colorimetric assays.[22]

Mid-infrared spectroscopy

Principles

Mid-infrared (MIR) spectroscopy employs the same principles as infrared spectroscopy; in other words, it is the absorption measurement of MIR frequency by a sample positioned in the path of an MIR beam. It is based on light in the 2500–25,000 nm region of the spectrum. Absorption differences when MIR light meets human tissues can be represented by certain modeling techniques in spectral quantitative analysis. A partial least squares algorithm is now normally used for multivariate calibration for these constituents.

Advantages

MIR exhibits decreased scattering phenomena, yet increased absorption, because of the higher wavelengths compared with near infrared (NIR) spectroscopy.[23] Light can penetrate skin to a depth of a few micrometers. As a result, only reflected light can be considered, because there is no light transmitted through a body segment. Moreover, another possible advantage of MIR spectroscopy is that the response peaks of glucose and other compounds are sharper with MIR than with NIR, where they are often broad and weak.

Limitations

Poor penetration is the main limitation of MIR. Other limitations, as with NIR, include problems with confounding factors, such as water content in blood.[24]

Near infrared spectroscopy

Principles

Near infrared (NIR) spectroscopy is located in the wavelength region of 730–2500 nm. The principle is similar to that of MIR spectroscopy. NIR spectra are made up of broad bands corresponding to overlapping peaks: the overtones (ie, first, second, third, and combination overtones), formed by molecular vibrations. It allows blood glucose measurement in tissues by variations of light intensity, based on transmittance and reflectance. Heise et al, one of the pioneers in noninvasive blood glucose monitoring, has published much on NIR techniques.[25–27] Raghavachari reported that glucose

generates one of the weakest NIR absorption signals per concentration unit of the body's major components.[28] Maruo et al demonstrated the efficacy of this approach in vivo, using NIR diffuse reflectance spectroscopy through fiber optics on diabetes patients' forearms.[29] The results showed positive signs on the correlation between predicted values and the reference glucose levels. Arnold and Small also reported that, although measurement errors of NIR spectroscopy are too large for clinical purposes, these experimental results demonstrate the possibility of noninvasive blood glucose measurements.[30]

Advantages

The high sensitivity of the photoconductive detectors is the main advantage of NIR spectroscopy. Water is reasonably transparent to the signal bandwidth used by NIR, which makes it possible to use for blood glucose monitoring. In addition, the measuring signal has high energy compared with MIR spectroscopy. Perhaps even more important, this method is less expensive than MIR. Materials are relatively low in cost, and there is a wide range of commercial products available. These advantages make NIR popular in this research area.

Limitations

Despite much promising work, researchers still cannot overcome important shortcomings, in particular, the scanning pressure that must be applied, physiological differences not related to blood glucose, the relatively small fraction of glucose in blood, weak correlation, and hardware sensitivity and stability.

Optical coherence tomography

Principles

Optical coherence tomography is an optical signal acquisition method based on the use of a low coherence light, such as a super luminescent light, an interferometer with a reference arm and a sample arm, a moving mirror in the reference arm, and a photodetector to measure the interferometric signal.[31] Light backscattered from tissues is combined with light returned from the reference arm of the interferometer, and the resulting interferometric signal is detected by the photodetector. The delay correlation between the backscattered light in the sample arm and the reflected light in the reference arm is measured. An increase of glucose concentration in the interstitial fluid causes an increase in refractive index, which in turn creates a decrease in the mismatch between sample and reference indices.

Advantages

This technology provides advantages in signal to noise ratio, high resolution, and depth of penetration, because the interferometric signal can be formed only within the coherence length of the source.

Limitations

Optical coherence tomography may be sensitive to the individual's motions. In addition, although slight changes in skin temperature have negligible effects, changes of several degrees have a significant influence on the signal.[32] Furthermore, there is no clear evidence that this method has advantages compared to other scattering-based techniques.

Optical polarimetry

Principles

Some researchers are trying to apply optical polarimetry in noninvasive glucose monitoring. Because the high scattering coefficients produce complete depolarization when the beam strikes the skin, attention has been focused on the eye, which offers a clear optical medium with a reasonable path length in relation to blood glucose.[33] When light transverses vitreous humor, it is expected to rotate several degrees in relation to the concentration of glucose.

Advantages

As light absorption and scattering in the eye are low, and there are virtually no large proteins in the aqueous humor, the main component in the aqueous humor is glucose; therefore, correlation may exist and relate to determine blood glucose concentration. In addition, this technique makes use of visible light, and the optical components can easily be miniaturized.

Limitations

This technique is sensitive to the scattering properties of the investigated tissue, as scattering depolarizes light. As a result, skin cannot be investigated by polarization technology, because it shows a high scattering effect, particularly in the stratum corneum. In addition, eye movement and motion artifact are general sources of errors in this technique. Furthermore, the specificity of this technique is poor, as several optically active compounds are present in human fluids containing glucose, such as albumin and cholesterol.

Raman spectroscopy

Principles

Raman spectroscopy is based on the use of a laser light to induce oscillation and rotation in human fluids containing

glucose. Because the emission of scattered light is influenced by molecular vibration, it is possible to estimate glucose concentration in human fluids.[34]

This effect depends on the concentration of the glucose molecules. This technique can measure very weak signals, even in human fluids. The wavelength range of Raman spectrum is considered to be 200 cm^{-1} to 2,000 cm^{-1}.[35] Raman spectrum of glucose can be differentiated from those of other compounds in this band.

Advantages

Raman spectroscopy usually provides sharper and less overlapped spectra compared to NIR spectroscopy. The intensity of spectral features is proportional to the concentration of the particular species, and the spectra are less sensitive to temperature changes. Moreover, it is comparatively less sensitive to water, and the interference from luminescence and fluorescence phenomena is only modest.

Limitations

The main limitations are related to instability of the laser wavelength and intensity, and long spectral acquisition times. In addition, as the power of the light source must be kept low to prevent injury, the signal-to-noise ratio is significantly reduced. Moreover, as with NIR spectroscopy, interference from other compounds remains a problem.

Reverse iontophoresis

Principles

Reverse iontophoresis is based on the flow of a low electrical current through the skin, between an anode and cathode positioned on the skin surface. An electric potential is applied between the anode and cathode, thus causing the migration of sodium and chloride ions from beneath the skin toward the cathode and anode, respectively. In particular, it is sodium ion migration that mainly generates the current.[36] This measurement is possible because neutral molecules, such as glucose, are extracted through the epidermis surface during this convective flow. This flow causes interstitial glucose to be transported, collecting at the cathode, where a traditional glucose sensor is placed to measure glucose concentration directly. The "GlucoWatch" device (Cygnus Inc., Redwood City, CA) is based on this technology, and it was approved by the US Food and Drug Administration. The device collects glucose molecules through the cathode disk and measures the amount with a sensor that contains enzyme glucose oxidase. Blood glucose concentration is predicted by comparing the premeasured blood glucose value with the signal generated by glucose molecules collected at the cathode. However, this product was withdrawn from the market due to poor accuracy, skin irritation, and long procedural problems.

Advantages

The advantage of this technology is that the electrodes are easily applied to the skin, by which a physiologically relevant fluid sample is collected, in that there is a correlation between glucose concentration in the physiological fluid and glucose concentration in blood.

Limitations

While reverse iontophoresis technology has great potential, the only device ever marketed using it had such serious practical drawbacks that it was withdrawn from the market. First, the electrodes irritated the skin. Second, the electrodes needed to be in place for at least 60 minutes, which exceeded the patience of many users. Third, readings were inaccurate, especially when the subject was sweating. Fourth, it was not able to detect rapid changes in blood glucose, due to its long "wakeup" time.

Ultrasound technology

Principles

Ultrasound technology is based on low-frequency ultrasound, which penetrates the skin for blood glucose monitoring. While this approach has theoretical potential, it seems that no further works has been done since Lee's group reported their laboratory results on rat skin.[37] A variation, named photoacoustic spectroscopy, is being used, which is based on the use of a laser light for the excitation of a fluid and for measuring the resulting acoustic response.[38] The fluid is excited by a short laser pulse with a wavelength that is absorbed by a particular molecular species in the fluid. Light absorption causes microscopic localized heating in the medium, which generates an ultrasound pressure wave that is detected by a microphone. The principle of the photoacoustic method is that an energy source irradiates the skin surface, causing thermal expansion in the illuminated area. An acoustic wave releases because of the energy of the thermal expansion. The detection of glucose with this technique is based on measuring the changes of the peak-to-peak value of the signal, which varies according to the glucose content of the blood.

Advantages

This technology can provide higher sensitivity than traditional spectroscopy in the determination of glucose, because of the relatively better photoacoustic response of blood, as compared

with water. This makes it easier to distinguish hydrocarbons and glucose.[37] In addition, the laser light wavelengths that can be used have a wide range, from ultraviolet to NIR.

Limitations

The technology is sensitive to interference from some biological compounds, temperature fluctuations, and pressure changes. Moreover, when the laser light transverses a dense medium, the photoacoustic signal may be affected by scattering phenomena, which may possibly cause an adverse effect similar to that of NIR spectroscopy. Another disadvantage is that the instrumentation is expensive and sensitive to environmental parameters.

Challenges ahead for noninvasive glucose monitoring

Various noninvasive technologies have been discussed. Clearly, many research groups are exploring a wide variety of approaches, trying to develop a blood glucose measurement device that can provide stable and reliable results, conveniently and economically. Table 1 shows the most recent works and internet references. Discontinued products, such as GlucoWatch, Diasensor (Biocontrol Technology Inc., Pittsburgh, PA), and Pendra, are not listed.

It is worth noting that not much evidence has proven the analytical feasibility of glucose monitoring by the noninvasive devices listed in Table 1. The supporting documentation provided by the research groups is severely limited; most of the technologies are proprietary, and limited information is disclosed. Although some of the technologies are mentioned in the referred papers, very little specific relevant information is provided. In particular, the judgments of measurement accuracy are completely left out.

At the same time, Table 1 tells us that many research groups are working on this problem, trying to develop new measurement technologies and methods to measure blood glucose noninvasively. One of the main reasons is that existing technologies, such as absorption spectroscopy, are relatively poor in signal-to-noise ratio in relation to blood glucose concentration and spectra response. Due to the huge

Table 1 Information regarding noninvasive glucose monitoring devices

Device/company	Technology	Status	URL
BioSensors Inc.	SEMP technology (bioimpedance spectroscopy)	Appeared in 2010 and is under development	http://www.biosensors-tech.com/
ClearPath DS-120, Freedom Meditech	Fluorescent technology	Appeared in 2007 and is said to be delivered to FDA for approval in 2011	http://freedom-meditech.com/
Cnoga Medical	NIR spectroscopy	Appeared in 2010 and is said to be delivered to FDA for approval in 2011	http://www.cnoga.com/Medical/Products/Glucometer.aspx
C8 MediSensors	Raman spectroscopy	Appeared in 2011 and the current status is investigational device	http://www.c8medisensors.com/us/home.html
Easy Check, Positive ID	Chemical sensing in exhaled breath	Appeared in 2010 and is under development	http://www.positiveidcorp.com/products_easycheck.html
EyeSense	Fluorescent technology	Appeared in 2008 and is still in R&D phase; plan is to launch the device in 2013	http://www.eyesense.com/en/konzept.htm
Glucoband, Calisto Medical Inc.	Bio-electromagnetic resonance	Appeared in 2005 and claimed under pilot production in 2011	http://www.calistomedical.com/
GlucoTrack, Integrity Applications Ltd.	Ultrasonic, conductivity and heat capacity technology	Under clinical trials phase (last checked: 2011)	http://www.integrity-app.com/
Glove Instruments	NIR spectroscopy (optical bridge technology)	Appeared in 2008 and is said to be commercialized soon, in late 2011	http://groveinstruments.com/
OrSense Ltd.	Occlusion technology (proprietary technology)	Appeared in 2006; the company has stated that this product is for market awareness purpose only	http://www.orsense.com/Glucose
SCOUT DS, VeraLight Inc.	Fluorescent spectroscopy	Appeared in 2011 and has received approval from health Canada for commercial distribution	http://www.veralight.com/products.html

Abbreviations: NIR, near-infrared spectroscopy; ID, identification; R&D, research and development; FDA, Food and Drug Administration.

anticipated market for a successful, noninvasive glucose monitoring device, the race for research teams to develop more precise and accurate spectroscopic equipment is heated. Moreover, multivariate training methods are often used in the quantitative analysis that the prediction model is data-dependent, whereas the specificity of measurement is not easy to tackle. Although an improved method is investigated for quantitative analysis that can enhance the correlation of the spectroscopic properties of the glucose molecule with glucose concentration in blood, more effort should be made to rigorously extend the technique to noninvasive blood glucose monitoring.[39]

Moreover, calibration of spectroscopic devices is necessary, because of factors such as light intensity, which may affect the prediction model. As most of the noninvasive technologies are based on some type of optical sensing technique, a time lag may occur between measurements of blood glucose content from different parts of body, which could introduce calibration error. In addition, the force of the measurement area may affect the deformation of the contact point of the tissue. This problem can be solved by applying constant force to the measurement area; however, it would be likely to produce a poor prediction result after a long period of time. This is because different deformations of the tissues may cause diverse absorption or reflection properties, thus affect the resulting signal. In addition, temperature may affect the prediction result, particularly for optical sensing technology, because changes of several degrees may significantly influence the energy level of absorption content. Most importantly, the physiological effect of the human being is the most important factor in noninvasive glucose monitoring. Physiological differences would affect the reliability of different technologies, as they are mainly due to individual metabolism, blood components, and other bodily fluid circulations for body regulation. The absorption spectroscopy mainly detects the glucose molecule, and glucose can be found everywhere in the human body. Hence, it is difficult to have a universal prediction model instead of a single user prediction model, which may need frequent self-calibration.

Conclusion

In this review, the latest technologies and devices for noninvasive glucose monitoring have been described. Unfortunately, none of these technologies have produced a commercially available, clinically reliable device; therefore, much work remains to be done. It is relatively simple to measure data and find correlation with blood glucose levels under the controlled conditions of research laboratories: the challenge is measuring these variables in normal environments. This requires understanding the physical and physiological factors that may affect blood glucose measurement. It is important to notice that noninvasive monitoring will never be achieved without vigorous scientific and clinical evidence. At this stage, we are still far away from achieving the goal of noninvasive blood glucose monitoring, with many technical issues yet to be resolved.

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Disclosure

The authors report no conflicts of interest in this work.

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