Iranian Journal of Medical Physics
Vol. 11, No. 2 & 3, Spring & Summer 2014, 224-232
Received: September 12, 2013; Accepted: March 15, 2014

Review Article

Non-invasive Optical Techniques for determination of blood Glucose levels: A Review Article

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Abstract

This article reviews the development of non-invasive optical techniques for determination of blood glucose concentrations in diabetic patients. Early diagnosis and daily management are essential for ensuring the healthy life of diabetic patients. The determination of blood glucose concentration with common devices involves the chemical analysis of blood samples, which are obtained by pricking the finger or extracting blood from the forearm. Pain, discomfort, and inconvenience, associated with current invasive methods, have necessitated the investigation of non-invasive measurement techniques. Non-invasive monitoring of blood glucose level offers several advantages, including absence of pain and biohazard materials, non- exposure to sharp objects, increased testing frequency and consequently, tighter control of glucose concentration. Considering these potential advantages commercialization of non-invasive glucose monitoring devices has become a subject of increasing interest. Several optical technologies have the potential to provide viable non-invasive measuring devices. this review study aimed to describe the major optical technologies for non-invasive glucose monitoring and compare their advantages and disadvantages.
second scenario) better than other methods in presence of a typically low false positive rate equal to 3%.

Keywords: Diabetes, Glucose, Non-invasive, Optical techniques.

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1. Introduction

Scientists have always been interested in studying human's health and happiness. So far, many investigations have been conducted to assess human physiology and pathology.

In the 21st century, a disease, called diabetes mellitus (or Diabetes), became highly prevalent among human population. Diabetes is a major world health concern, which is characterized by high glucose concentration in blood and body tissues. It is a metabolic disorder in which the pancreas underproduces (type II diabetes) or does not produce (type I diabetes) insulin [1]. Insulin, a hormone produced by the pancreas, is needed by body cells in order to use glucose, which is the major source of energy for the human body.

It is estimated that the total number of diabetic people worldwide is about 180 million. Approximately 4 million deaths are caused by diabetes each year (9% of deaths worldwide) [2]. According to several studies, which evaluated the prevalence of diabetes, approximately 366 million people are likely to suffer from diabetes by 2030 [3, 4]. The same study demonstrated that the most important demographic change related to the global prevalence of diabetes the increased proportion of diabetic patients below the age of 65 years [5].

Without treatment, diabetes can lead to various adverse consequences. Considering the prevalence of this disease individuals may face problems such as blindness, kidney failure and nerve damage. It can also contribute to the acceleration of hardening and narrowing process of the arteries (atherosclerosis), which lead to strokes, coronary heart disease, and other blood vessel diseases [6].

Treatment and management of diabetes can be quite costly. If diabetes becomes as prevalent as predicted, total direct healthcare expenditure on diabetes will be 213 to 396 billion dollars worldwide, in 2025. It should be noted that the medical costs of a person with diabetes are 2-5 times higher than a person without diabetes [7].

Healthcare professionals advise diabetic patients on the appropriate monitoring regimen for their condition. Diabetics, who use insulin (all type I and many Type II diabetic patients), test their blood glucose more frequently (3 to 10 times per day). Assessment of the daily fluctuations of blood improves the understanding of patients and doctors for assessing the effectiveness of previous insulin dose and to determining the next dose. Indeed, home blood glucose measurement can be an important tool for self-management of motivated diabetic patients, it is also essential for tight blood glucose control [8].

Reasonable insulin control can be achieved relatively simple in most cases using electrochemical glucose biosensors (glucometer). and the invention of this technology was one of the most important steps in managing diabetes, since it facilitates intensive therapy, which reduces the risk of long-term complications. In fact, 85% of the current world market for biosensors, with an estimated worth of 6.9 billion dollars, is occupied by glucometers [9].

Blood glucose monitoring with a glucometer involves pricking the finger with a lancet (a small, sharp needle), putting a drop of blood on a test strip, and placing the strip into a meter which displays the blood glucose level. Most current methods for self-monitoring of blood glucose are invasive, i.e., they require a blood sample for each test, usually obtained from a fingertip [6].

Current blood glucose tests (finger stick testing) are associated with pain and inconvenience for the patient, due to disruption in the daily life, and fear of hypoglycemia, which is caused by tight glucose control. Also, these monitoring methods are difficult to perform in long-term diabetic patients due to calluses on the fingers. Therefore, a non-invasive method for blood glucose measurement would contribute to a significant increase in the

quality of life of 180 million diabetic patients and a significant reduction of health care costs [2].
In recent years, many optical techniques have been investigated for finding a non-invasive method [10-16]. This overview focused on a description of these optical glucose-monitoring techniques, which are the fastest growing segment of diagnostic testing, currently under development by diagnostic equipment manufacturers.

2. Technologies for Non-Invasive-Glucose Monitoring

2.1 Near Infrared Spectroscopy (NIRS)

The NIRS spectral region is commonly used in reported methods. This region has several spectral windows where hemoglobin, melanin, and water absorption band intensities are low enough to allow the penetration of light in the tissue, and enable non-invasive spectral measurements [17].
This method is based on the use of an external light source on the body with a wavelength range of 750– 2500 nm [18]. NIRS allows glucose measurement in tissue depths of 1-100 millimeters, with a decrease in penetration depth in order to increase wavelength values. The light, focused on the body, is partially absorbed and scattered due to its interaction with chemical components within the tissue.
Attenuation of light in tissues is described according to light transport theory, by the equation (1):

$$I = I_0 e^{\mu_{eff}} \quad (1)$$

Where I is the reflected light intensity, I_0 is the incident light intensity, $\mu_{eff}$is the effective attenuation coefficient, and d is the optical path length in the tissue [19]. On the other hand, μ_{eff} can be expressed as(2):

$$\mu_{eff} = [3\mu_a(\mu_a+\mu_s)]^{1/2} \quad (2)$$

μ_a is the absorption coefficient and μ_s is the scattering coefficient. The μ_a of a tissue can be influenced by changes in glucose concentration through changes in absorption corresponding to water displacement or changes in its intrinsic absorption [20].
Changes in glucose concentration also affect the intensity of light scattered by the tissue (μ_s.). Overall, glucose concentration could be estimated by variations of light intensity both transmitted through a glucose-containing tissue and reflected by the tissue itself, Transmission or reflection (localized or diffuse) of light can be measured by proper detectors.
One of the limitations of NIRS for non-invasive determination of glucose is the smaller absorption coefficient of glucose in the NIR band compared to water. Thus, the weak glucose spectral bands overlap other stronger overtones and combination bands of water, hemoglobin, proteins, and fats. Another limitation is non-specific scattering coefficient, which is, the effect of glucose on the refractive index of a medium [21].
Also, glucose measurement may be interrupted by physical and chemical parameters such as variations in blood pressure, body temperature, skin hydration, and triglyceride and albumin concentrations [22]. Environmental variations including changes in temperature, humidity, carbon dioxide, and atmospheric pressure may lead to errors, too. Changes in glucose can themselves introduce other confounding factors [23, 24].
The major problem with NIRS for blood glucose monitoring is the necessity for frequent recalibration. NIRS does not only measure one specific signal for glucose, but rather evaluates many signals that are neither glucose specific nor linked to glucose levels in a linear fashion. Unfortunately, studies of glucose measurement in vivo using NIRS have shown unfruitful results.

2.2 Mid -Infrared Spectroscopy (Mid-IRS)

Mid-IRS is based on the use of light with a wavelength in the range of 2500–10000 nm [19]. The physical principle is similar to NIRS. However, compared to NIRS, Mid-IRS exhibits decreased scattering, and increased absorption, given the higher wavelengths. Therefore, tissue penetration of light can reach a few micrometers in human tissues, and only

reflected or scattered light can be considered [25].
A possible advantage of Mid-IRS over NIRS is that glucose-produced Mid-IR bands, as well as other compounds, are sharper than those of NIR, which are often broad and weak. However, one important limitation in the use of this method is poor penetration. In addition, Mid-IRS is affected by similar problems and confounding factors as NIRS (although glucose bands potentially improve). For instance, some studies have shown the significant dependence of skin Mid-IRS on its water content [26].

2.3 Raman Spectroscopy

Raman scattering, discovered by Raman and Krishnan in 1928, provides a way to measure molecular composition through inelastic scattering [27]. The frequency shift of the scattered light is a direct measure of the vibrational frequency (i.e., energy) of the molecule. Each molecule has its own distinct vibrational frequency or frequencies. Thus, the frequency spectrum of the Raman-scattered light provides a unique fingerprint by which the molecule can be identified [28].
Raman spectroscopy of biological tissue was initially introduced using Fourier transform (FT) Raman spectroscopy in NIR region because in contrast to the visible wavelength range, water absorption and background due to laser-induced auto-fluorescence are both smaller in the NIR, thus enabling deeper penetration depth and observation of order-of-magnitude weaker Raman peaks [29, 30].
Raman spectroscopy is based on the use of laser induced oscillation and rotation in solution molecules [21, 22]. Molecular vibration, which depends on the agent concentration in the solution, affects the consequent emission of scattered light. Therefore, it is possible to derive an estimation of glucose concentration in body fluids, where glucose is present.
The Raman spectrum is usually considered in the interval of 200–1800 cm^{-1} [31, 32]. In this band, Raman spectrum of glucose is clearly differentiable from that of other compounds. In fact, Raman spectroscopy usually provides sharper and less overlapped spectra compared to NIRS.
The modest interference from luminescence and fluorescence phenomena are the other advantages of this method [33]. Application of fixed wavelength lasers is quite cost-effective [25]. Recently, an improvement in traditional Raman spectroscopy has been proposed (surface-enhanced Raman spectroscopy), which may increase the sensitivity of acquisition and/or decrease the acquisition time [34]. Through the introduction and improvement of lasers, charge coupled devices, and other optical components, quantitative analysis became possible via this method.
Instability of laser wavelength intensity of acquisition and long spectral acquisition time are the limitations of this method. Moreover, similar to other techniques previously described interference by other compounds remains a major issue**.**

2.4 Photoacoustic Spectroscopy (PA)

For the detection of weak absorbance in liquids and gases, PA spectroscopy can be used [35]. PA measurement is an alternative detection technology for light interaction with tissues [36, 37].
PA signal is related to the properties of a clear medium by the equation (3):

$$PA = k\left(\beta v^n / C_p\right) E_0 \mu_a \qquad (3)$$

where PA is the signal amplitude, k is a proportionality constant, E_0 is the incident pulse energy, β is the thermal expansion coefficient, v is the speed of sound in the medium, n= *is a constant between 1 and* 2, C_p is the specific heat, and μ_a is the light absorption coefficient [21, 28].
For the first time, Fainchtein provided a detailed analysis of the generation and propagation of PA signals in blood [38], and Mac-Kenzie studied the PA effect on glucose solution in the low scattering case [36]. In this study, PA signal generation was assumed to be associated with initial light absorption by glucose molecules. Solutions were excited by NIR laser pulses in the range of 1000–1800

nm, at wavelengths that corresponded to NIR absorption of glucose. There was a linear relationship between PA signal and glucose concentration in aqueous solutions [36].
In a different approach, ultraviolet laser pulses at 355 nm were used. PA time profiles were analyzed to yield μ_{eff}, which is related to changes in the refractive index of the medium, induced by changes in glucose concentration [39]. In 2002, Glucon presented a novel PA application in the Diabetes Technology Meeting [40]. However, further research is required to understand PA origination and propagation in tissues and its use for non-invasive glucose determination.

2.5 Polarization Changes

When polarized light passes through a solution with optically active solutes (such as chiral molecules), the light rotates its polarization plane by a certain angle, which is in accordance with the concentration of the optically active solutes [21]. Glucose is a chiral molecule, and its light rotation properties have been well established. Indeed, investigation of glucose-induced polarization changes proposed the first non-invasive technique for glucose measurement in humans [41].
Visible light can be used in this method and the optical components can be easily miniaturized [42]. However, this technique is sensitive to the scattering properties of the investigated tissue, since these properties lead to the depolarization of light, therefore, skin cannot be investigated by polarimetry [22]. Moreover, this technique has low specificity, since several optically active compounds are present in human glucose-containing fluids, such as ascorbate and albumin.

2.6 Optical Coherence Tomography (OCT)

OCT, a method based on the principle of low-coherence interferometry, uses 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 photo-detector to measure the interferometric signal [43]. The scattered back-reflected light from the tissues is combined with the light returned from the reference arm of the interferometer, and the resulting interferometric signal is detected by the photo-detector. A block diagram of the experimental system is presented in Figure 1 [28].

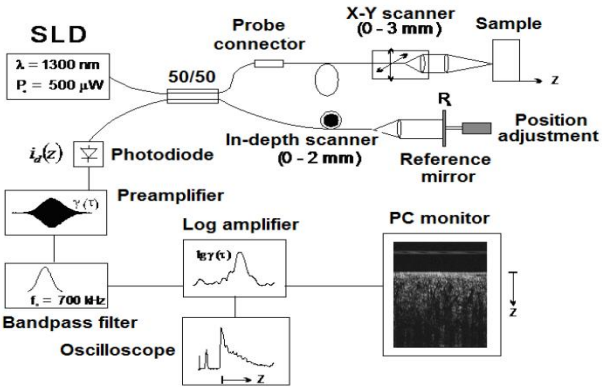

Figure 1. OCT system used in glucose monitoring studies[28].

It is possible to scan tissues up to a depth of about 1 mm by moving the mirror in the reference arm of the interferometer [28]. Use of a second mirror in the sample arm enable tissue surface scanning. Therefore, this technique has facilitates in-depth and lateral scanning for obtaining two-dimensional images with high resolution.
Tissue scattering properties are highly dependent on the ratio of the refractive index of scattering centers (e.g., cellular components, and proteins) to the refractive index of the interstitial fluid. In fact, when glucose concentration increases in interstitial fluid, its refractive index increases as well, this determines the decrease in refractive index mismatch and scattering coefficient [44, 45]. Therefore, based on the OCT data, generated by the backscattered light, it is possible to get an estimation of glucose concentration in the interstitial fluid.
The sensitivity of this technique to motion artifacts is one of its limitations. Moreover, although small changes in skin temperature have negligible effects, changes of several degrees significantly, influence on the signal [46].

2.7 Photonic Crystal

Asher's group has developed a photonic sensing material from polymerized crystalline colloidal arrays (PCCAs) for non-invasive glucose sensing [47, 48].

PCCAs are periodic crystalline colloidal arrays of spherical polystyrene colloids, polymerized within thin hydrogel films. The arrays will act as a diffraction grating for white light and detect a specific diffracted wavelength at a specific glancing angle between the incident light propagation direction and the diffracting planes [47, 49].

Bragg diffraction depends on the refractive index of the system (solvent, hydrogel, and colloids) and the spacing between the diffracting planes (d-spacing) Incorporation of charged species or change in electric charge in the PCCAs causes the arrays to expand and thus changes the spacing spacing between the diffracting planes. Then the diffraction pattern changes and leads to a wavelength shift in the light reflected off the array [47, 49].

Several studies have shown the ability of PCCA films for the detection of metal ions [50], creatinine [51], and glucose [49, 52].

Asher's group constructed a glucose photonic sensor in the form of a thin acrylamide diffracting PCCA hydrogel film containing glucose oxidase or phenyl boronic acid crystals as molecular recognition elements [47, 48]. Attachment of glucose changes the charge distribution. Glucose capture by glucose oxidase or phenyl boronic acid results in a change in *d*-spacing in the Bragg equation and causes shifts in the wavelengths of the diffracted light [49, 52].

2.8 Fluorescence technology

When skin is excited by ultraviolet light, it fluoresces at 370 and 455 nm [28]. With the development of spectrophotofluorometer (SPF) by Bowman at National Institutes of Health, use of fluorescence in medicine became increasingly prevalent in the 1950's [53]. However, application of fluorescence for glucose monitoring effectively began in 1980's, when Schultz, by employing an optical fiber-based indwelling approach, used a naturally occurring glucose-binding protein Concanavalin A in a competitive binding assay with a high, molecular weight dextran [54, 55]. In addition, a new approach using a synthetic receptor, known as boronic acid, was introduced in the 1990s [56].

In addition to these approaches, an enzymatic approach, which used glucose oxidase (GOx) was developed to measure intrinsic fluorescence of GOx [57-59]. In the late 1990's, researchers started to assess a glucose sensor, using the deactivated apo-GOx enzyme, which used the enzyme as a receptor rather than a catalyst [60]. Studies in this area showed that apo-GOx can retain its high specificity, after these investigations, new advances were made in the development of a new biosensor in 2000's [61-63]. To date, several receptors including glucose-binding lectins [64], apo-enzymes [65], and synthetic boronic acid receptors [66] have been employed for glucose detection.

Fluorescence-based systems are receiving increasing attention given their high sensitivity. This system cause little or no damage to the host system and enable the Measurement of fluorescence intensity as well as fluorescence decay times.

However, the use of ultraviolet light in tissues could lead to strong scattering and fluorescence phenomena. Moreover, even when using different wavelengths, the fluorescence phenomenon can depend not only on glucose, but also on several parameters, such as skin melanin, hemoglobin, and epidermal thickness [67].

3. Conclusion

Over the last decades, noticeable attempts have been made for the development of a non-invasive glucose sensor. Development of a non-invasive method would considerably improve the quality of life for diabetic patients, facilitate glucose monitoring, and reduce complications and mortality associated with this disease. While such a sensor has not been materialized yet, progress has been quite significant. This progress is due to not only

long-term experience with these tools, but also the availability of increased computing power, necessary for exploring many possible orders of application.

In this review, we presented a description of main optical technologies for non-invasive glucose monitoring. The emergence of new detection methods, improvements in measurement technologies and methods of noise reduction have contributed to non-invasive glucose monitoring. Advances have been made in understanding and resolving the specificity, compartmentalization, and calibration issues of non-invasive glucose measurements. The possibility of developing a non-invasive optical glucose sensor within the next twenty years is not far-fetched, given the progress in methodology, instrumentation, and understanding of potential problem. Sensitivity to multiple physiological, environmental, and activity factors, which often changing in the ordinary daily life, have caused some of the technologies have not been exploited in a device yet, while some others have led to a device at least in advanced prototype condition. Furthermore, it is reasonable to expect that more than one optical approach may result in a successful sensor.

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