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Review

Current development in non-invasive glucose monitoring

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Abstract

Painless control of blood glycemic levels could improve life quality of diabetes patients, enabling a better regulation of hyper- and hypoglycaemia episodes and thereby avoiding physiological complications. Although research groups have been trying for decades to separate non-invasive glucose information from interference compounds, none of the available commercial devices offers enough precision to replace lancet approaches.Many reviews have already been published on this topic, but the great amount of information available and the fast development of technologies require a continuous update in the research status. Besides the description of current in-vivo methods and the analysis of devices available commercially, one also explains treatment algorithms useful for multivariate analysis.

Keywords: Blood glucose monitoring; Diabetes mellitus; Non-invasive measurement; Transcutaneous sensors

Contents

1. Introduction

Glucose is the main carrier of energy in the human organism, with recommended levels between 4.9 mmol/L and 6.9 mmol/L in whole or capillary blood [1]. The sugar concentration in blood is controlled by the islet cells in the pancreas through the production of the glucagon hormone This hormone raises the level of blood sugar, and insulin, responsible for helping the body to change glucose into

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energy [2]. World wide, 150 million people suffer from disturbances in the endocrine metabolic regulation, called diabetes. Approximately 10% of cases result from insulin deficiency (type 1), which often starts during childhood and requires giving this hormone usually many times a day. Insulin resistance (type 2) corresponds to 90%, occurring more in people over 40 years old. Additional cases also are related to pregnancy, where 2% of women have gestational diabetes [3]. Any kind of diabetes can be dangerous because long-term excess of glucose (hyperglycemia) can cause blindness, damaged nerves and kidneys (renal failure), or even increase the risk of heart diseases, strokes, and birth defects. Low levels (hypoglycemia), however, can result in confusion, coma and even death [4].

Fig. 1 shows different classifications of blood glucose monitoring: invasive, minimally invasive and non-invasive. Fully invasive systems can be either bedside clinical devices or self-monitoring meters. Bedside monitors are suitable for intensive care units and use sensors with an accuracy of approximately 1% [5]. Such systems allow continuous monitoring, therefore increasing the amount of clinical information.

Systems which puncture the skin are still standard techniques for home monitoring (6–7% accuracy) reading glucose concentrations through electrochemical, colorimetric or optical disposable strips for finger-prick blood samples [6]. Efforts have been made in order to reduce the level of invasiveness by decreasing the blood sample volume to a few microlitres, and measuring areas of the body less sensitive to pain than fingertips, such as the forearm, upper arm, or thigh. Drawbacks of such systems area lack of control during sleeping or manual activities, undiscovered episodes of hyper- or hypoglycaemia, risks of infection, nerve damage and the discomfort of pricking the finger several times a day, which painful activity often leads to non-compliance [7].

Minimally invasive measurements sample the interstitial fluid (ISF) with subcutaneous sensors [8]. Even in this method the discomfort causes difficulties to the patient's therapy. Therefore, research groups are working to develop non-invasive glucose control devices [9]. Unfortunately, so far there are no reports or patents which show that such non-invasive methods have the same accuracy as invasive procedures.

Although there are many complete reviews of painless blood glucose techniques [10–12], the great volume of recent research results in this field requires a constant update. Therefore, besides the description of important measurement approaches, this work also shows available devices on the market with their technologies and measurement sites. Because absorption spectroscopy is a widely sensing method, the wavelengths used in non-invasive tests will also be described. In addition, algorithms for multivariate analysis will be presented, showing that recent improvements in technologies and multiparameter measurements may still enable improved accuracy of the predictions.

2. Non-invasive glucose monitoring

One option to painless intermittent glucose control is the substitution of blood with other fluids that could contain glucose, like saliva, urine, sweat or tears [13,14]. But continuous monitoring could only be accomplished through direct

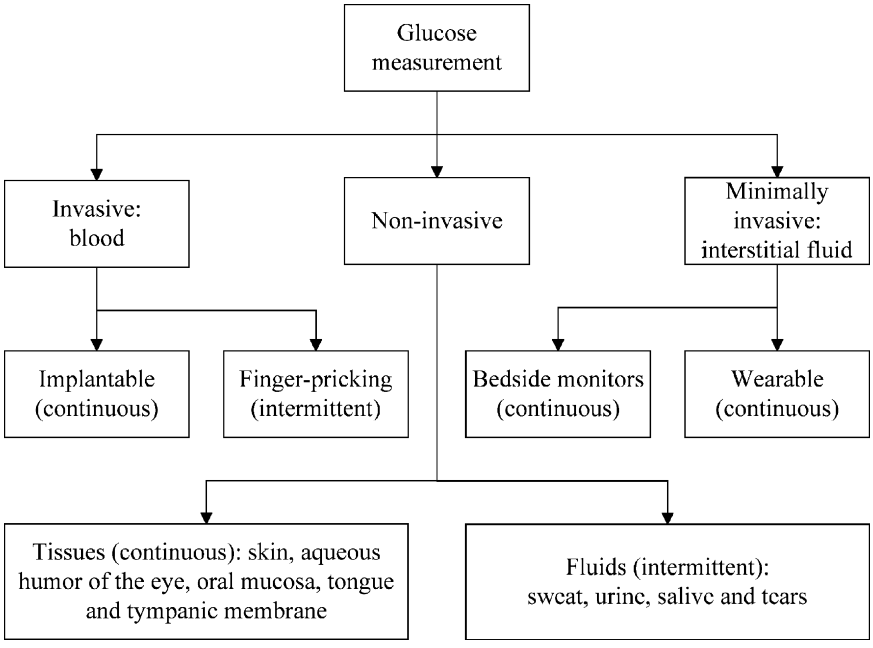

Fig. 1. Overview of technologies for non-invasive blood glucose control.

measurement of body tissues such as skin, cornea, oral mucosa, tongue or tympanic membrane [15,16]. Non-invasive glucose transducers should be capable of detecting weak blood signals through intervening tissues (bone, fat, skin, etc.), and in addition, separate information on glucose from that of other overlapping constituents of higher concentration (proteins, urea, uric acid, hemoglobin, water, etc.). Such sensors can measure, either by a direct approach based on the chemical structure of the glucose molecule, or indirectly by measuring blood sugar effects on some secondary process, such as temperature or pH changes [17].

Non-invasive investigations have been already published using technologies like reverse iontophoresis, polarimetry, metabolic heat conformation, ultrasound, thermal emission, electromagnetic, photoacoustic, Raman, light absorption and bioimpedance spectroscopy. Together with the choice of technique and sample region, one should also give attention to parameters of the measurement environment. For example, in the case of transdermal monitoring, sweating, skin color, surface roughness, tissue thickness, breathing artifacts, blood flow, body movements, ambient temperature, pressure and sample duration also influence the results [18,19]. Table 1 shows the most cited non-invasive techniques, target site and internet reference.

2.1. Reverse iontophoresis

The method of iontophoresis has been used for many decades and utilizes electrical current to deliver charged drug compounds through the skin. Non-invasive monitoring, however, uses transport of glucose in the opposite direction to that of normal medicaments (from the skin outward), therefore this process has been called 'reverse iontophoresis' [20]. The GlucoWatch monitor is a wrist-watch glucose control device manufactured by Animas Technologies that utilizes such technique with two independent potentiostat circuits [21]. This measurement is possible because neutral molecules, such as glucose, are extracted through the epidermis surface via this electro-osmotic flow to the iontophoretic cathode, along with Na^+ ions.

Glucose concentrations extracted through the skin with mA currents are in μM ranges; therefore, the amperometric circuit needs to detect glucose from 50 pmol to 200 pmol. In this electrode, blood sugar is collected in hydrogel discs containing the enzyme glucose oxidase (GOx). These hydrogels, which need to be often replaced, constitute the electrolyte of an amperometric biosensor, working with nA currents to detect H_2O_2 generated by the glucose oxidase-catalyzed reaction [22]. After the solute extraction and measurement phases, mathematical algorithms predict glucose level in the display. This processing not only uses the biosensor response, but also skin temperature and perspiration fluctuations, through thermo transducers and conductivity sensors available in the device [23]. The system is able to read glucose values every 10 min for up to 13 h. Correlation coefficients between biographer and finger-stick measurements are about 0.865, although the approval by U.S. Food and Drug Administration (FDA) for an auxiliary method, without replacing invasive control, such a device is no longer available due to its unsatisfactory performance. Some disadvantages of the technology include the time delay compared with blood values, skin irritation, inaccuracies of results, long calibration procedures and a 2–3 h warm-up period [24,25]. Another reverse iontophoresis device available is the GluCall from KMH Company, which requires 70 min to warm up and measures glucose values every 20 min for up to 6 h.

2.2. Absorption spectroscopy

When light meets biological tissues it can suffer reflection, scattering and transmission being proportional to the structure and chemical components of the sample. The possibility of molecular differentiation is, therefore, the reason why the majority of continuous glycemic monitoring efforts are focused in the optical signature spectrum of glucose.

Many spectroscopical investigations have been done in visible and near infrared (NIR) range, namely around 590–950 nm [26], 1212–1850 nm [27–29] and 2120–2380 nm [30]. Such spectra are chosen since water absorbance is weak, the measuring signal has high energy and there is a wide number of commercial light transducers available. These wavelengths are found in the therapeutic window (600–2500 nm) allowing the use of reflectance for superficial layers analysis and transmittance in deep tissues measurements [31].

On the other hand, the use of middle infrared (MIR) spectra (mostly between 8382 nm and 9708 nm) [32–34] gives more distinct glucose peaks. However, unfortunately these spectra have limited light penetration, excluding use in transmittance tests. An alternative to increasing optic penetration is the measurement with attenuated total reflection (ATR) [35], which uses a light beam guided through a crystal by total reflection. If the crystal surface is placed in contact with the skin, the electromagnetic field created by the reflected light reaches the dermis, where the interstitial fluid contains most of the skin glucose [36]. Therefore, changes in the beam absorption should reflect the optics characteristis from blood sugar. The use of squalane oil in the crystal interface seems to improve quantitative prediction [37].

Table 2 shows a review of optic spectroscopy targets and wavelengths. In order to compensate for the high absorbance by the tissue, some groups have chosen to measure with laser diodes. The SugarTrack (with 650 nm, 880 nm, 940 nm and 1300 nm) and Sensys (750–2500 nm) are examples of optical equipments for continuous glucose monitoring. Another alternative to improve measurements is occlusion spectroscopy, reported by the company Orsense. This technique temporarily stops the blood flow at the fingertip with the projection of light at 610 nm and 810 nm [38].

Table 1
Groups of non-invasive blood glucose research

Company	Technology	Target tissue	URL
Abbott	Fluorescence	Contact lens – tears	http://www.abbott.com
Animas Technologies	Extraction of interstitial fluid	Wrist skin	http://www.glucowatch.com
Biocontrol Technology	NIR spectroscopy	Forearm skin	http://www.mendosa.com/painless.htm
Biopeak Corporation	Fusion Spectroscopy	Wrist skin	http://www.biopeak.com
BioTex	NIR spectroscopy	Skin	http://www.biotexmedical.com
Calisto Medical	Bio-electromagnetic resonance	Wrist skin	http://www.calistomedical.com
Ciba Vision	Light spectroscopy	Contact lens – tears	http://www.devicelink.com/ivdt/archive/03/05/008.html
Fluent Biomedical Corp.	Light spectroscopy	Skin	http://www.fluentbio.com
Fovioptics	Light spectroscopy	Retinal	http://www.diabetesnet.com/diabetes_technology/fovioptics.php
GlucoLight Corporation	Optical coherence tomography	Not available	http://www.glucolight.com
Glucon	Photoacoustic	Forearm skin	http://www.glucon.com
Infratec	Thermal emission spectroscopy	Tympanic membrane	http://www.diabetesmonitor.com/meters.htm
Inlight Solutions	NIR spectroscopy	Skin	http://www.inlightsolutions.com
Integrity Applications	Ultrasound, conductivity and heat	Ear lobe skin	http://www.integrity-app.com
Instrumentation Metrics	NIR spectroscopy	Skin	http://www.instrumentationmetrics.com
KMH	Extraction of interstitial fluid	Wrist skin	http://www.glucall.net/english_html/main/index_english.jsp
Life Trac	Light spectroscopy	Skin	http://www.sugartrac.com
Light Touch Medical	Raman infrared spectroscopy	Skin	http://www.lightouchmedical.com
Medicontract (Diabetic Trust)	NIR spectroscopy	Skin	http://www.medicontract.com
NIR DIagnostics	NIR spectroscopy	Skin	http://www.nirdiagnostics.com
Optiscan Biomedical Corporation	Mid infrared spectroscopy	Skin	http://www.farir.com
Orsense	Occlusion optic spectroscopy	Finger tip skin	http://www.orsense.com
Pindi	Radiomolecular magnetism (RMM)	Not available	http://www.pindi.com
PreciSense	Fluorescence resonance energy transfer	Skin	http://www.precisense.dk
Q Step Technologies	Polarized light	Eye iris	http://www.qstep.com
RetiTech	Fluorescence	Retinal	http://www.diabetesnet.com/diabetes_technology/retitech.php
Samsung fine Chemicals Company	Electromagnetic radiant ray	Finger skin	http://www.sfc.samsung.co.kr/en
Sensys Medical	NIR spectroscopy	Skin	http://www.sensysmedical.com/home.html
Sentek Group	Crystalline colloidal array	Eye	http://www.diabetesnet.com/diabetes_technology/sentek.php
Solianis Monitoring (Pendragon)	Bioimpedance	Wrist skin	http://www.solianis.com
Sontra Medical (Bayer Diagnostics)	Ultrasonic–electrochemical	Skin	http://www.sontra.com
SpectRx	Laser microporation	Skin	http://www.spectrx.com
Spire	Laser spectroscopy	Skin	http://www.spirecorp.com
Heinz Nixdorf-Chair for Medical Electronics (TUM)	Mid infrared Spectroscopy and bioimpedance	Finger tip skin	http://www.lme.ei.tum.de
VeraLight	Fluorescence spectroscopy	Forearm skin	http://www.veralight.com
Visual Pathways	Visual pigment bleaching	Anterior chamber of the eye	http://vispath.com
VivoMedical	Electrochemical sweat measurement	Finger tip skin	http://www.vivomedical.com
Biocontrol Technology, Incorporated	NIR spectroscopy	Forearm skin	http://www.americandiabetes.com/diasensor.htm
Hitachi	Metabolic heat conformation	Finger tip skin	http://www.hitachi.com/New/cnews/040223.html

2.3. Photoacoustic spectroscopy

Photoacoustic spectroscopy (PAS) is based on ultrasonic waves created by tissue absorption of pulsating light [39]. When laser beams meet cells, heat is generated, causing pressure variations in the sample. These acoustic signals can be detected through a piezoelectric transducer, and with the specific incident wavelengths reflect optical properties of glucose in blood [40]. PAS non-invasive glycemic monitoring devices, like the Aprise from the Glucon company, are already available in the market. Although this method was shown to correlate with blood sugar levels, it is still necessary to improve the reproducibility and sensitivity in order to decrease interferences from other substances.

2.4. Polarimetry

The linear polarization vector of light can be rotated by the path characteristics like thickness, temperature and concentrations of the crossed sample. Therefore, polarimetry

Table 2
Researches in non-invasive glucose light spectroscopy

Research group (year)	Target site	Wavelength (nm)
Cho et al. (2004)	Finger skin	470–950
Baba et al. (2003)	Eye	532 and 635
Cote et al. (1992)	Eye	633
Gabriely et al. (1999)	Finger skin	780–2500
Saratov et al. (2004)	Skin	590, 750 and 950
Yeh et al. (2003)	Forearm skin	590, 660, 890 and 935
Heinemann et al. (1998)	Skin	800
Zhao et al. (2002)	Finger skin	905
Robinson et al. (1992)	Finger skin	870–1300
Fischbacher et al. (1997)	Skin	950–1200
Tenhunen et al. (1998)	Finger skin	1500–1850
Maruo et al. (2003)	Forearm skin	1600
Kasemsumran et al. (2006)	Forearm skin	1212–1805
Burmeister et al. (1999)	Tongue	1612, 1689 and 1731
Schrader et al. (2004)	Eye	1859–1528 and 1394–909
Olesberg et al. (2006)	Skin	2040 and 2380
Malchoff et al. (2002)	Tympanic membrane	8500 and 9600
Kajiwara et al. (1993)	Oral mucosa	3424, 9259 and 9708
Tamura et al. (2004)	Finger skin	5714–10526

has been used for a long time in the pharmaceutical and nutritional industries to measure the level of compounds such as glucose. Many studies are trying to apply this technique in non-invasive glycemic assays. However, skin is not the optimal target, since high scattering coefficients produce complete depolarization of the beam. Therefore, most investigators focus their attention on the aqueous humor of the eye, which offers a clear optical media with a reasonable path length and has a time lag of maximal 5 min in relation to blood glucose concentrations [41]. The average width of the anterior chamber of a human eye is 1 cm, which gives an expected rotation of 4.562 millidegrees for normal glucose level (5.55 mmol/L) at a wavelength of 633 nm [42].

There are two possible optical paths for polarimetric tests in the eye, as shown in Fig. 2. The first uses transmittance configuration where the polarized light passes laterally through the cornea [43]. In the second approach, the incident beam on the cornea travels into the eyeball, reflecting in the retina, and returning with information on glucose concentration in the aqueous humor [44].

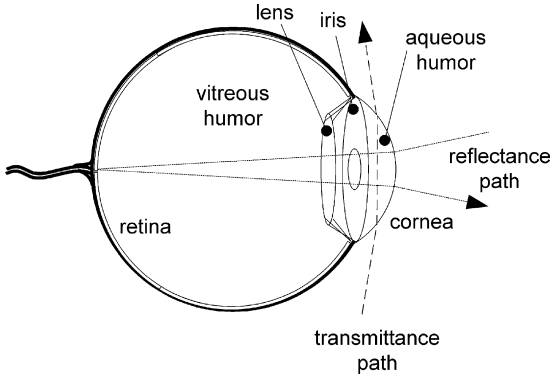

Fig. 2. Transmittance and reflectance optical paths for polarimetric tests in the eye.

Although polarimetry methods suffer negligible influence from temperature and pH fluctuations, it is still necessary to address some problems in order to successfully quantify concentrations in-vivo [45]. Some limitations are safety regulations on light exposure to the eye, motion artifacts, optical noises of other substances and the development of techniques to measure small angles. Recent studies used a Faraday rotator with a single-mode flint glass fibre to improve optic sensitivity of the system, which results showed a resolution of 0.55 mmol/L for glucose [46]. Finally, a modified intraocular lens and a liquid-crystal polarization modulator driven by a sinusoidal signal were also proposed, to allow in-vivo measurements of the human eye [47,48].

2.5. Fluorescence

It is known that glucose levels in tears reflect concentrations similar to those in blood. Therefore, fluorescence is also a sensing technology to painless monitoring [7]. This system can track blood glucose with an approximate 30 min lag time and does not suffer interference from fluctuations in the light intensity of the ambient surrounding. The photonic sensing is done with polymerized crystalline colloidal arrays which respond to different concentrations through diffraction of visible light [49].

The sensor can be disposable colorless contact lenses, requiring excitation and detection devices. Recent results of in-vivo assays with such transparent lenses excited in 488 nm showed results correlate with control glucose levels. On the other hand, long-term studies of confort and toxicity still need to be performed [50]. Extra equipment could be discarded through the use of colored contact lenses. By changing color in response to the concentration of glucose in the tears, patients could look into a mirror and compare the sensor color to a precalibrated color strip [51] Some limitations still need to be solved in colorimetric assays, such as resolution, short lifetimes and biocompatibility [52].

2.6. Raman spectroscopy

The process where a small fraction of scattered light shows wavelengths different from that of the exciting beam is known as the Raman effect. This type of spectroscopy uses laser radiation sources from visible to the MIR range and measures very weak signals in the transparent samples. The measured photons normally have higher wavelength and lower intensity (10^{-3} times) than the original light, therefore requiring longer collection periods than other optical methods [53]. Water has weak scattering indexes, which is the reason why the Raman assays are not affected by interference from this substance. Another advantage is that the resulting bands are narrow and have distinct peaks, easing the task of separating signals, in contrast to absorption spectroscopy [54]. A recent study reports measurements of glucose in aqueous humor

with a 785 nm laser source. An optical fibre was used to focus the beam on the anterior chamber of porcine eyes and also to receive the resulting spectrum. Results suggest that Raman signals from glucose in MIR range can be detectable with this system. Nevertheless, one should still analyse photothermal damage danger in non-invasive ocular measurements before addressing human tests [55].

2.7. Metabolic heat conformation

The metabolic heat conformation (MHC) method involves measurements of physiologic indices related to thermal generation, blood flow rate, hemoglobin, and oxyhemoglobin concentrations, which should correspond to the glucose levels in the blood [56]. Since such a method can suffer strong interference of environmental conditions, it is mostly used as auxiliary data to glucose quantification.

The first tests used three different temperature measurements (surface finger, ambient room, and background radiation) derived from the fingertip during 10 s. In addition, multiwavelength spectroscopy with six wavelengths (470 nm, 535 nm, 660 nm, 810 nm, 880 nm, and 950 nm) was performed, helping to improve glucose signals. The first MHC prototype, shown in Fig. 3, has a correlation coefficient of 0.91 in laboratory conditions, but the company Hitachi intends to improve its performance in order to obtain sale approval [57].

2.8. Thermal emission spectroscopy

Thermal emission spectroscopy measures IR signals generated in the human body as a result of glucose concentration changes. One promising application of this technology uses similar concept as standard clinical tympanic membrane thermometers, with the addition of specific wavelengths for glucose fingerprint (9.8 μm and 10.9 μm). This membrane information is important, because it shares the blood supply with the centre of temperature regulation in the hypothalamus. In addition, signals from blood vessels in this organ have to cross a smaller path length than in skin or oral mucosa sites. A prototype was calibrated and tested in patients demonstrating reproducibility and predicting glucose concentrations with a mean error of 0.638 mmol/L [58]. Body movements and ambient temperature are the most significant sources of noise in such approach.

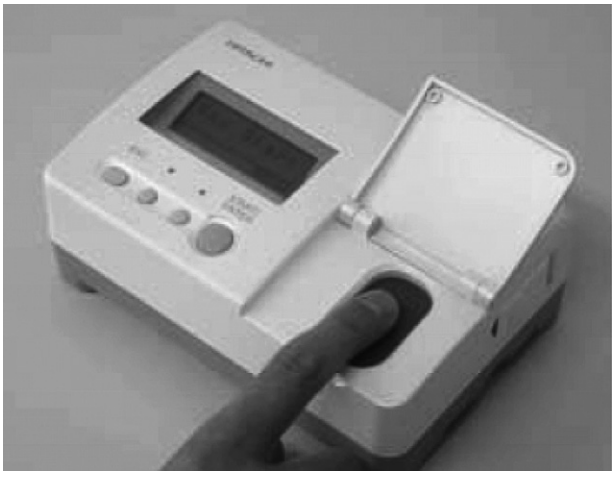

Fig. 3. Metabolic heat conformation blood sugar monitoring device from Hitachi.

2.9. Bioimpedance spectroscopy

The first study of non-invasive continuous glucose monitoring system involving impedance spectroscopy was published by Caduff's group in 2003. As result from this research, the company Pendragon developed a wrist glucose monitor called Pendra. The equipment gatheres information of a LC resonance circuit from 1 MHz until 200 MHz, with the skin working as dielectric from the capacitor. One limitation of this research is that it requires an equilibration process, where the patient must rest for 60 min before starting measurements [59].

Pendra was approved in May 2003 in the Conformité Européenne (CE) and for a short time it was available on the market for approximately €3000. A post-marketing reliability study showed a difference of 52% (4.3% of the readings in the dangerous zone E from Clarke error grid) when compared with a lancet device [60]. Therefore, this equipment is suitable only for a small group of customers, whose local dielectric skin characteristics show a minimum resonance frequency [61]. In 2005 Pendragon was closed, but Caduff's impedance work has still been investigated through the company Solianis Monitoring [62].

2.10. Ultrasound

Reverse iontophoresis is not the only method of extracting non-invasive glucose molecules from skin. Sonophoresis, which usually enhances transdermal delivery of drugs, can also serve this purpose [63]. This technique uses a piezoelectric transducer to create 20 kHz ultrasound (US) that increases cutaneous permittivity to interstitial fluid, enabling glucose to be transported to the epidermis surface. Analyte concentrations can therefore be determined with standard electrochemical glucose sensors. Initial in-vivo laboratory results have been described predicting glycemic values in rat skins through US [64].

2.11. Electromagnetic

Electromagnetic sensors based on Eddy currents have been able to detect variation of the dielectric parameters of the blood, which can also be caused by glucose concentration changes [65]. Conductivity detection of blood inside a plastic tube was possible at a resonant frequency of 2.664 MHz in static and moving samples, showing a glycemic sensitivity of 4.4 mmol/L [66]. Studies from Öz group can also be described in magnetic glucose assays. This work reported

that even localized nuclear magnetic resonance (NMR) has shown good performance to detect glycogen metabolism in the human brain [67].

3. Conclusions

An increase of the signal-to-noise ratio (SNR) is still required for all non-invasive assays. This should be accomplished with a new generation of transducers and methods. The parallel monitoring of more than one parameter should also help to improve sensitivity. Initial studies have already been reported with simultaneous monitoring of bioimpedance and near-infrared spectroscopy in the skin [68]. The Glucotrack device from the company Integrity Applications is a commercial multiparameter monitoring device, where glucose is predicted with ultrasound, conductivity, and heat capacity.

In addition, attention must be given to the data treatment. In order to extract analyte-specific information from tissues measurements, methods such ridge regression, artificial neural networks (ANN), principal component analyze (PCA) and partial least squares (PLS), which is the most common in spectrum treatment, can be used. Both PCA and PLS can reduce significantly the number of input variables, the reason why some researches use resulting factors from these algorithms as input in neural networks, which predict glycemic levels [69,70]. Another alternative to improve signal-to-noise-ratio in data is the use of digital filters with the above tools which, besides eliminating undesired overlapping substances, can also decrease temperature influences [71].

Since continuous glucose monitors generate high amounts of information, data management of diabetes patients should be innovated in order to allow approaches such as transcutaneous blood sugar control. Some commercial invasive glucometers already offer the possibility of telematic monitoring, where glycemic results are transferred via modem or mobile phones to doctors [72]. When glucometers automatically send measured levels, physicians are able to quickly intervene before metabolic anomalies cause any severe damage, improving the therapy efficiency [73]. In addition, the implementation of telemedicine systems also facilitates patient education, decreasing the cases of non-compliance.

At present there are no commercially available non-invasive glucose monitors and many improvements are still needed in order to have the same precision as standard methods with blood samples. An approach similar to pulse oximetry, but focused in the glucose molecule seem to be the most appealing optical technology for further investigations [74]. Nevertheless, electrical impedance and temperature could still be used to improve transcutaneous results.

In the controlled conditions of research laboratories it is relatively simple to measure data and find correlation with blood glucose levels. The challenge is to establish stable calibration models which are able to measure in the normal circumstances of a patient's life. Finally, the new generation of bloodless glucose instruments should have technologies to eliminate interfering species and competing biochemical pathways with low cost, fast response, accuracy and simple calibration procedures, improving the comfort of patients and also avoiding long-term complications.

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Conflict of interest

No financial and personal relationships with other people or organisations that could inappropriately influence (bias) my work.

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