OVERVIEW OF SOME NON-INVASIVE SPECTROSCOPIC METHODS OF GLUCOSE LEVEL MONITORING

PRZEGLĄD WYBRANYCH NIEINWAZYJNYCH SPEKTROSKOPOWYCH METOD MONITOROWANIA POZIOMU GLUKOZY

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ABSTRACT

Nowadays over 400 million adults suffer from diabetes worldwide. By 2040 this number will rise to 642 million. In addition, more than 300 million adults have impaired glucose tolerance, which means a high risk of developing the disease in the future. Also, many patients are undiagnosed, which results in severe complications. It is an important social problem, because from the moment of recognition the treatment lasts a lifetime. Currently, mainly devices based on invasive, electrochemical or photosensitive methods to measure glucose concentration in small blood samples, are offered on the market. Hence, the development of a new non-invasive glucose sensor is a desirable goal. Such measurement system should be cost-effective, comfortable and allowing continuous monitoring of glucose levels in blood. There are many reports on new, fast and highly sensitive methods and the most common research direction relates to spectroscopic techniques. Some of them are presented in this paper.

Keywords: diabetes, glucose sensor, spectroscopic techniques

STRESZCZENIE

Obecnie ponad 400 milionów osób dorosłych na całym świecie cierpi na cukrzycę. Do 2040 roku liczba ta ma wzrosnąć do 642 milionów. Ponadto, u więcej niż 300 milionów dorosłych zdiagnozowano upośledzenie tolerancji glukozy, a to stwarza ryzyko rozwoju choroby w przyszłości. Bardzo wiele osób jest niezdiagnozowanych. Cukrzyca stanowi istotny problem społeczny, ponieważ od momentu rozpoznania leczenie trwa przez całe życie. Obecne na rynku urządzenia, to przede wszystkim oferujące inwazyjne techniki pomiarowe: elektrochemiczne lub światłoczułe. Dlatego też prowadzone są intensywne badania mające na celu opracowanie czujników nieinwazyjnych, pozwalających na poprawę komfortu życia, oszczędność i wygodę w pomiarze poziomu glukozy we krwi. W literaturze opisano wiele nowych rozwiązań w tym zakresie, opierających się głównie na technikach spektroskopowych. Niektóre z nich są omówione w niniejszej publikacji.

Słowa kluczowe: cukrzyca, czujniki glukozy, techniki spektroskopowe

1. Introduction

Diabetes is one of the biggest health problem of the 21th century. Each year more and more people are diagnosed, despite our knowledge about new diagnostic and treatment methods. Currently, about 3% more patients with type 1 diabetes are diagnosed each year, particularly among children (0–14 years) [1]. The number of deaths due to the diabetes is over three times bigger than from AIDS and almost ten times than from malaria. Therefore, effective prediction strategy is very important.

2. About diabetes

In diabetic patients an increased glucose level in blood is measured. It results from the insufficient production of insulin by pancreas beta cells or due to improper insulin activity [2]. This leads to the impaired absorption of glucose by cells, accumulation of glucose in body fluids and intercellular spaces, resulting in later stages in infiltration of glucose into urine (glycosuria). In this case also ketoacidosis may occur [3]. Liver cells increase metabolism of fatty acids into ketone bodies as an alternative source of energy. This causes osmotic diuresis resulting in dehydration, hypotension and tachycardia. Chronic hyper-glycemia can cause disorders of eyes, kidneys, nerves, heart and blood vessels.

The incidence of diabetes type mainly depends on age, but environmental and genetic factors also play a certain role. There are three main types of diabetes: type 1 diabetes, type 2 diabetes (in adults) and gestational diabetes. Sometimes the type of diabetes is not clear and additional tests are required to distinguish between type 1 and type 2 diabetes or other, more rare forms of diabetes [4]. Increased level of glucose concentration in blood is accompanied by frequent urination, excessive thirst and blurred vision. High blood glucose concentration is called hyperglycemia (>200 mg/dl) and low levels are referred to as hypoglycemia (<70 mg/dl). Blood sugar level outside the normal range (70–100 mg/dl) causes many of the long-term health problems. Therefore, besides medication, dietary changes physical activity, the frequent monitoring the glucose concentration, is necessary.

Nowadays, mainly invasive and uncomfortable diagnosis techniques, especially for children, are used [5]. Spectroscopic techniques may be alternative methods for blood glucose level measurement.

3. Present reviews about non-invasive spectroscopic techniques

The detection of glucose should be fast, cost-effective, and easy to use at home by potential users. The measurement should have proper accuracy and precision as invasive conventional techniques. The development of new and non-invasive methods is based mainly on optical or dielectrical properties of human tissue. Suitable places for monitoring may be intercellular fluids, sweat or tears [6]. One has to mention that many times such devices have already appeared on the market. However, imprecise measurements and cumbersome calibration cause a withdrawal [7].

4. Perspectives for non-invasive spectroscopic glucose sensors

Nowadays, non-invasive spectroscopic glucose sensors are usually based on spectroscopic techniques, like near-infrared and mid-infrared spectroscopy, bioimpedance spectroscopy, Raman spectroscopy, and thermal emission spectroscopy.

4.1 Bioimpedance spectroscopy

Impedance spectroscopy (IS) is widely used as a diagnostic method in electrochemical examinations to measure dielectric properties of biological tissues. The impedance is defined by following equations:

$$Z(\omega) = \frac{U(\omega)}{I(\omega)} = |Z(\omega)| e^{j\varphi(\omega)} \tag{1}$$

$$Z(\omega) = \mathrm{Re}\,Z + j\,\mathrm{Im}\,Z \tag{2}$$

where Z is impedance, U is voltage, I is current, ω is the radial frequency (the relationship between radial frequency ω (expressed in radians/second) and frequency f (in hertz) is: $\omega = 2\pi f = \varphi$ angle phase, Re Z and Im Z are respectively the real and imaginary part of the impedance.

There are three basic methods of measuring impedance: bridge method, voltage and current method [8]. In each of them, a generator with a frequencies from few Hz to few MHz are used. The most common method is the current method, where the current generator and the voltage detector are connected in parallel with the tissue. The current introduced to a body is constant and independent from the measured impedance. There are two possible options of this method – bipolar and tetrapolar, but the latter is better due to independence from electrode-skin impedance variability. Moreover, this technique allows easy measurement of the phase angle using a phase detector localized between the current generator and detection circuit. Based on obtained data, it is possible to determine the point in the plane *Re*(Z)-*Im*(Z) using the relationships:

$$|Z| = \sqrt{(\mathrm{Re}\,Z)^2 + (\mathrm{Im}\,Z)^2} \tag{3}$$

$$\varphi(\omega) = arctg\,\frac{\mathrm{Im}\,Z(\omega)}{\mathrm{Re}\,Z(\omega)} \tag{4}$$

$$\mathrm{Re}\,Z(\omega) = |Z|\cos\varphi \tag{5}$$

$$\mathrm{Im}\,Z(\omega) = |Z|\sin\varphi \tag{6}$$

The results obtained by this method depend on some external factors like temperature, pressure, humidity, light or concentration of gases. Usually data is expressed graphically as a Bode plot or a Nyquist plot.

Bioimpedance glucose sensors are especially sensitive to intermolecular changes of electromagnetic properties what allows monitoring glycaemia in a wide range of frequencies. It is known that the increase of the glucose concentration causes growth of the impedance in the human blood.

A non-invasive measurement technique based on RF impedance spectroscopy (RIS) has been proposed [9]. The authors designed four electrodes cell probe (glucose concentration in range from 45 mg/dl to 270 mg/dl). Its advantage lies in its simplicity, low cost and short measurement time. Moreover, from the kHz to MHz frequencies range experiments must be performed in solutions of low ionic strength, because high conductivity reduces the phase angle between the real and imaginary parts of the impedance. In the RF (radio frequency) range the influence of polarization is much less pronounced [10]. However, proof of its functionality as a non-invasive glucose monitor in humans has not been presented, so far. The measurement of dielectric properties of biological tissue at audio and RF frequencies is useful for their diagnostic imaging and medical applications of the electromagnetic hyperthermia treatment [11].

A wrist glucose monitor based on impedance spectroscopy has been presented [12, 13, 14]. It is based on sodium transport over the erythrocyte membrane, which is linked to changes in glucose. These transmembraneous sodium fluxes induce changes in impedance fields, which are detected and converted into a glucose concentration. In 2003 it was approved as an adjunctive Type IIb medical device as supplement for standard glucose monitoring. Unfortunately, this appliance did not work, as intended. Basic disadvantage was a patient-tailored calibration procedure that took sometimes 2–3 days and required from user a long time rest (at least 1h) before measuring. Besides, 30% of users had to stop using this sensor because their skin types did not allow the proper measurement. Moreover, relocation of the appliance and any changes in measurement conditions (like temperature or sweat) causes inaccuracies.

4.2 Raman spectroscopy

Raman spectroscopy (RS) is a technique, where vibrational, rotational, and other low-frequency modes in a system, are observed [15]. It is usually used in chemistry for measuring the (bio)chemical composition of a sample.

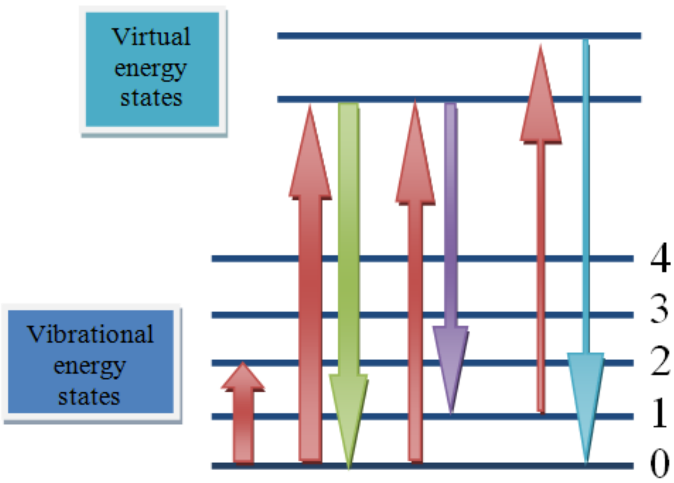

Fig. 1. Energy level diagram showing the states involved in Raman signal.
Red arrow – infrared absorption, green arrow –Rayleigh scattering,
purple arrow – Stokes Raman scattering, blue arrow – anti-stokes Raman scattering

Illuminating the sample with monochromatic light causes inelastic scattering of photons. As a result, a small fraction of illuminating light is scattered with a shifted frequency (due to the different vibrational levels of the molecules) (see Fig. 1). Obtained spectrum provide information about composition of the sample and is described by the following function:

$$i = f(v) \tag{7}$$

where i (the intensity of scattered radiation) is proportional to the fourth power of the frequency (v). In the Raman spectrum the radiation intensity (i) coming from the sample is a linear function of the molar concentration and layer thickness, while in the infrared spectrum this relationship is exponential.

It is known that Raman signal from biological samples, such as skin, is very weak and overlapped by strong fluorescence signals. Other limitation are related to long spectral acquisition times. However, thanks to the advanced data processing and ultrafiltration by high-pass filters, the reduction of fluorescent light background and thus, accurate measurements, are possible. Except for its non-invasiveness and high accuracy, glucose sensor based on Raman spectroscopy should be safe for patients. To protect the skin from irritation or damage, suitable wavelengths range is used. The most common laser illumination is in range from 785 nm to 830 nm [16, 17].

Recently, promising results were reported on Raman spectroscopy as a non-invasive transcutaneous method to measure glucose level [18, 19]. Other reviews presented portable devices based on RS, but still there is no information on its availability on the market [20, 21].

4.3 Near-infrared and mid-infrared spectroscopy

Infrared spectroscopy (IR spectroscopy) is a widely used analytical method based on absorption measurements. It enables very fast and non-destructive identifications of various compounds [22]. The principle of this method is based on the relationship between resonance absorption peaks of the components and its concentration in the sample.

The infrared electromagnetic spectrum, between visible and radio waves, is usually divided into three regions: near, mid, and far infrared. The energy of near IR (800–2500 nm) can excite overtones or harmonic vibrations. The mid-infrared (2500–25000 nm) may be used to study the fundamental vibrations associated with rotational-vibrational structure. The far infrared (25–1000 μm) may be used for rotational spectroscopy.

NIR can typically penetrate deeper into a sample than a mid-infrared radiation. Therefore, NIR-based measurement it is not a very sensitive, but it can be very useful in probing bulk materials with little or no sample preparation. Non-destructive analysis by NIR spectroscopy has got an incredible potential in the non-invasive measurement of blood glucose. However, *in vivo* measurements proved to be not as easy as expected. Strong absorption bands of interstitial water and multiple scattering in bones and muscles cause many problems.

In the past few years, NIR spectroscopy was studied as a non-invasive method of measuring blood glucose through the human tissue. One of the approach is based on the evident relation between blood glucose concentration and the reduced scattering coefficient of the tissue [23]. To determine blood glucose levels on the ear lobe, wavelength of 1550 nm is chosen due to its high signal-to-noise ratio (SNR) for glucose signals and the limited interference. Although, it has a very good accuracy, it is just an experimental device and is not yet FDA (Federal Drug Administration, USA) approved.

Another review presents blood glucose measurement based on attenuated total reflection (ATR) infrared spectroscopy [24]. This technique measures the spectrum of a finger skin layer by means of the Fourier transform infrared spectrophotometer. Infrared light is passed through the diamond prism, where the sample is held. Repeating reflection occurs, making an evanescent wave, which is attenuated by absorbance in sample surface. Changes in the light absorption are related to the concentration of blood glucose. However, this methods needs additional improvements to increase its accuracy.

In 2007, new technique based on differential near-infrared spectrophotometry was developed [25]. It is called Pulse Glucometry and it is based on two instantaneous spectrophotometric measurements in fingertip. Changes in optical absorption between them are caused by blood volume pulsations throughout the cardiac cycle and results as a phoptoplethysmografic signal [26]. This method has been tested on patients with diabetes and seems to be a promising alternative to invasive devices.

A mobile system, using multi-spectral photoplethysmography was developed, as well. Portable device named iSULIN allows for a non-invasive blood parameters measurements (pulse, blood pressure, saturation and blood sugar levels). This invention incorporates novel signal processing algorithm [27]. Before this device will be commercially available, it has to pass many tests.

A physical principle of mid-infrared spectroscopy is similar to that of NIR. As mentioned above, it is a very useful region of electromagnetic spectrum, because of many strong fundamental rotational-vibrational molecular transitions. Compared to NIR, mid-infrared bands of compounds are sharper and interfere less. However, MIR light can penetrate only about 100μm into human skin. Hence, it is possible to measure glucose level in interstitial fluids, but capillary blood is unavailable. Fortunately, there is a strong correlation between glucose concentration in blood and interstitial fluids, what allows to avoid frequent calibration.

Literature presents *in vitro* examination [28], where combination of quantum cascade lasers (1010–1095 cm^{-1}) and photoacoustic detection could replace the conventional measurement using enzymatic test stripes and a drop of blood from the fingertip. Human skin samples in contact with aqueous glucose solutions (physiological glucose range) are investigated by photoacoustic cell (PA) with a different conditions and constantly ventilated by a 10 sccm N2 flow. To determine glucose concentration MIR light is focusing on PA chamber. The beam is absorbed by the sample, which generates an acoustic wave detected with an electret microphone. Similar photoacoustic experiment is reported in [29]. The *in vivo* measurements take place in a gas cell coupled to the finger skin. A preliminary test with healthy volunteers and volunteers suffering from diabetes mellitus demonstrate promising results.

Another approach opens a new path to a non-invasive *in vivo* glucose measurements, where quantum cascade laser is also used to predict blood glucose level [30]. In demonstrated sensor MIR light is delivered to palm by hollow-core fiber. Backscattered light from the skin is collected using a bundle of six fibers, which is coupled directly to a commercial liquid nitrogen cooled mercury cadmium telluride (MCT) detector. Mid-infrared spectroscopy measures signals generated in human skin as a results of different blood glucose concentration. To obtain predictions of examined sugar level partial least squares regression (PLSR), was used. This device was successfully tested in humans.

4.4 Thermal emission spectroscopy

Thermal emission spectroscopy exploits natural mid-IR emission from the human body, especially from the tympanic membrane [31]. Above mentioned emissivity contains spectral information of the blood analyte, which can be directly correlated with blood glucose concentration.

Planck's law describes the relationship between radiance intensity, spectral distribution and temperature of the black body. The spectral characteristic of thermal emission is affected by individual's human tissue composition and concentration of analytes [32]. Also, Kirchhoff's law confirms utility of the tympanic membrane, as an ideal position to measure body temperature. It is possible thanks to sharing its blood supply with the body's temperature regulation center, called hypothalamus.

An experiment described in [33], demonstrates that the emission from glucose can be detected using room temperature detectors in a filter-based spectrometer. A sensor placed in the ear canal can gain a clear view of the membrane and its blood vessels to measure the emitted IR radiation. Compared with the theoretical blackbody radiation described by Planck's and Kirchhoff's laws, the membrane's IR radiation spectrum is transformed by tissue composition. The detecting set includes an IR filter and a thermopile detector. One filter transmits radiation through the thermal emission bands with glucose signatures, while the other IR detector window is covered by a filter capable to transfer radiation that does not include emission bands characteristic to the analyte. Blood spectral characteristics with different contents of glucose will change the emissivity of the tympanic membrane. Thus it is possible to measure the concentration of examined analyte in blood. First non-invasive blood glucose prototype based on thermal emission spectroscopy, has been demonstrated [31]. Performed measurements had clinically acceptable accuracy and individual daily calibration is not necessary.

5. Final remarks

Spectroscopic techniques do not require sensor implantation or *ex-vivo* blood sampling. Sensors for glucose measurements should have the desirable sensitivity and selectivity, disposal or sterilizable tips, and long-term stability. Spectroscopic sensors can meet all of these requirements.

Bioimpedance spectroscopy has shown simplicity, low cost, and fast response solutions, however better calibration process is required. Raman spectroscopy allows carrying out measurements directly from biofluids, but still there is a need to reduce collection times. Infrared spectroscopy is well established analytical technique, where non-destructive and fast analysis is possible. The main problem is a strong absorption bands of water and presence of other absorbers. Mid-infrared spectroscopy offers enhanced sensitivity and selectivity of the information collected from the fingerprint region. Measurements based on thermal emission offer an excellent approach. However, the influence of ear thickness on intensity of radiation should be eliminated.

6. Conclusion

Nowadays, there is a great interest in new non-invasive glucose monitoring system. Nevertheless, *in vivo* measurements face many additional problems caused by blood pulsation, movements of the patient or different skin types. One of the main aim of these investigations is to achieve the high precision, ensuring as low measurement errors level as possible, comparable to classical, invasive methods. Furthermore, the most desirable characteristics, as clinical accuracy, reasonable cost, portability, simplicity of use and elimination of side effects on patients, should be ensured.

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