Opt Quant Electron (2016)48:217
DOI 10.1007/s11082-016-0490-5

Noninvasive blood glucose monitoring in the terahertz frequency range

Olga Cherkasova[1] · Maxim Nazarov[2] · Alexander Shkurinov[2,3,4]

Received: 13 November 2015 / Accepted: 23 February 2016

Abstract Human skin optical properties were studied in vivo using terahertz (THz) time-domain spectroscopy. For the attenuated total internal reflection (ATR) the silicon Dowe prism was used. The measurements were carried out on six volunteers with normal blood glucose concentration and in good health. A standard oral glucose tolerance test was also performed. The ATR spectra of palm skin were consecutively measured at 0–90 min after glucose intake. The variations of the ATR spectra of human skin were correlated with the changes in blood glucose level. The amplitude of ATR signal of human palm skin increased and the phase decreased when glucose concentrations in blood rose above the normal level. Our results demonstrate the possibility of a non-invasive real-time measurement of blood glucose concentration.

Keywords Terahertz time-domain spectroscopy · Attenuated total internal reflection · Human skin · Glucose · Water

1 Introduction

Accurate and efficient assessment of blood glucose concentration is critical in clinical management of many pathological conditions in human population. There is a direct relationship between the level of glucose in the blood of patients with diabetes and the probability of

This article is part of the Topical Collection on Laser technologies and laser applications.

Guest Edited by José Figueiredo, José Rodrigues, Nikolai A. Sobolev, Paulo André and Rui Guerra.

✉ Olga Cherkasova
o.p.cherkasova@gmail.com

[1] Institute of Laser Physics of SB RAS, pr. Lavrentyeva, 13/3, Novosibirsk, Russia 630090

[2] Institute on Laser and Information Technologies of RAS, 1 Svyatooserskaya St., Shatura, Russia 142092

[3] Lomonosov Moscow State University, Leninskie Gory, GSP-1, Moscow, Russia 119991

[4] National Research Tomsk State University, Lenina Avenue, 36, Tomsk, Russia 634050

Published online: 02 March 2016

developing complications of the disease (Fowler 2008). So monitoring of glycemic status is considered to be a cornerstone of diabetic patients care. Measurements of glucose concentration in blood are best determined by standardized laboratory techniques using blood plasma biochemistry analyzers. However, disadvantages are long measurement time, and a relatively large sample volume needed to obtain the results (Rebel et al. 2012; Summa et al. 2014). During the last 20 years, many portable blood glucometers for humans have appeared on the market. They are readily available, inexpensive, and provide immediate results while utilizing small quantities of capillary blood (Rebel et al. 2012; Clarke and Foster 2012). However, control of diabetes mellitus involves daily self-monitoring of blood glucose by finger puncture several times a day to obtain a blood sample for further analysis. This procedure is invasive, painful, non-safe and unpleasant for patients. In the past decades much attention had been paid to the development of spectroscopic methods for noninvasive glucose measuring. These approaches include polarimetry (Cameron and Anumula 2006), near-infrared spectroscopy (Burmeister et al. 2000), Raman spectroscopy (Lambert et al. 2005), photoacoustics (Ren et al. 2015) and optical coherence tomography (He et al. 2012).

Terahertz time-domain spectroscopy (THz-TDS) has not yet found wide application in this field. A distinctive feature of this method is the possibility of measuring directly the refractive index, absorption coefficient, and hence complex permittivity spectrum of the sample in a single scan and in a broad frequency range (Newnham and Taday 2008). Water has much influence on THz transmission and reflection from bio-objects, since water has strong absorption and dispersion in GHz and THz ranges. Since the energy of THz photons is insufficient to ionize molecules in biological systems (Angeluts et al. 2014b), THz spectroscopy appears to be a promising tool for bio and medical research. These circumstances make it possible to develop a rapid diagnostics method (Pickwell and Wallace 2006; Parrott et al. 2011; Truong et al. 2012; Angeluts et al. 2014a; Cherkasova et al. 2014).

The application of THz spectroscopy for studies of both normal human skin (Pickwell et al. 2004; Nazarov et al. 2010; Echchgadda et al. 2013; Zaytsev et al. 2015a, b) and skin pathologies (Pickwell and Wallace 2006; Zaytsev et al. 2015a, b IEEE) in vivo has been reported previously. We found no studies of the human skin optical characteristics when glucose concentration in blood is varied. However, it has previously been shown that the transmission coefficient of animal ear skin in subTHz (0.03–0.04) and THz (0.34) frequency ranges correlates with blood glucose concentration (Sigel et al. 2014; Sun et al. 2013). In the present paper, we describe the studies of human skin using THz-TDS in vivo. We measured the ATR spectra of human skin at normal blood glucose concentration and their variations during a standard oral glucose tolerance test. The observed results highlight the prospects of the described technique for the use in non-invasive real-time measurement of blood glucose concentration.

The paper is organized as follows. In Sect. 2 we describe the experimental setup for THz–TDS and the samples under study. In Sect. 3 we present the experimental ATR spectra of human palm skin in vivo. In Sect. 4 we discuss the features of human skin THz response for volunteers with high blood glucose concentrations by comparing skin-related experimental results with Debye model of the dielectric function of glucose aqueous solution. Section 5 summarizes the main results of the present paper.

2 Experimental techniques

The THz time-domain spectrometer used in the study was described previously (Nazarov et al. 2008; Cherkasova et al. 2009). We used the radiation of a Ti:sapphire laser with a wavelength of 790 nm and a pulse duration of 90 fs with 1 wt average power. For THz

emission, the semiconductor (LT-GaAs) surface was used. For THz detection the electro-optical ZnTe crystal of 1 mm thickness was used. The Fourier transform of the measured pulse time profile provides the complex spectrum comprising information on the refractive and absorption indices of the medium where the pulse has been reflected or transmitted. We do not use maximal spectral resolution of 10 GHz in the experiments with wet bio samples, because all known spectral features are at least 200–1000 GHz wide in this case. Thus 20 ps time scan is enough to get all useful information.

The experiments were carried out using the attenuated total internal reflection (ATR) optical scheme (Newnham and Taday 2008) with a silicon ($n_{Si} = 3.42$ in all THz range) right angle Dowe prism (Fig. 1), with p-polarized radiation. The penetration depth (δ in Fig. 1) of radiation inside the sample decreases with frequency from 1000 to 30 microns within the frequency range used (0.1 – 2.5 THz) (Nazarov et al. 2010; Angeluts et al. 2014a).

Figure 2 shows a typical ATR spectrum from human skin and a reference signal from a clean prism surface in our spectrometer. In this case within the reliable frequency range 0.3–2.0 THz we have a dynamic range of two orders of magnitude. A sharp dip at 1.7 THz in both spectra is due to a strong absorption by atmospheric water vapor; as a result some artifacts are observed in the extracted ATR spectra at 1.6–1.8 THz.

The reflection from the free base of the prism was used as the reference signal Er(ω), in the second measurement the sample was placed on the prism base—Es(ω). In addition to the simplicity of the reference-signal measurement, the method of attenuated total internal reflection has another advantage compared with the conventional reflection, the ATR amplitude $|Rp(\omega)| = |Es(\omega)|/|Er(\omega)|$ is relatively high. The phase spectra are calculated as $Phase(\omega) = -\arg(Es(\omega)/Er(\omega))$.

The ATR spectra Rp(ω) allow one to extract the conventional absorption coefficient—α(ω) and refraction index—n(ω), through complex dielectric function ε(ω) as follows:

$$\varepsilon = \frac{\left(\frac{1+Rp}{1-Rp}\right)^2 \pm \sqrt{\left(\frac{1+Rp}{1-Rp}\right)^4 - \sin^2(2\Theta)\left(\frac{1+Rp}{1-Rp}\right)^2}}{2\cos^2\Theta}, \tag{1}$$

$$\alpha = \frac{\omega}{c}\mathrm{Im}(\sqrt{\varepsilon}); \quad n = \mathrm{Re}(\sqrt{\varepsilon}), \quad \omega = 2\pi f \tag{2}$$

Here $\theta = 57°$ is the incidence angle inside the prism (Fig. 1). We used a weakly focused THz beam (the signal was concentrated in 4·8 mm^2 area), hence θ has a Gaussian distribution between 53° and 61°, which leads to artifactural increase of reflection amplitude at frequencies lower than 0.2 THz (see Figs. 3, 4), which limits the application range of Eq. (1). For the case of well described pure water, we confirm the applicability of Eqs. 1–2 and 6, see Fig. 3 and Fig. 6 below.

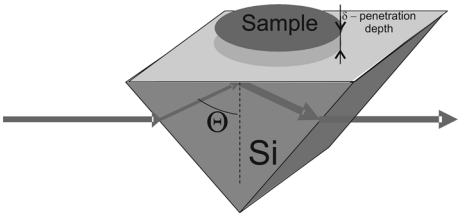

Fig. 1 Scheme of the attenuated total reflection measurement

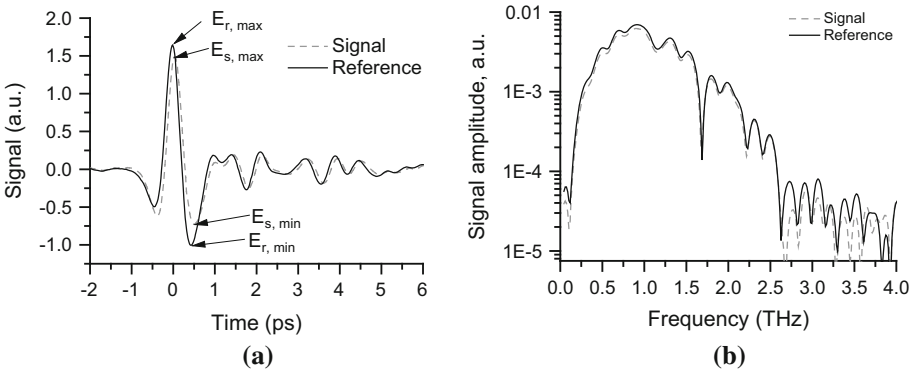

Fig. 2 Reference (*solid black line*) and sample (*dash grey line*) ATR signals. **a** In time-domain, **b** in frequency domain. Reference—ATR spectrum from clean prism surface, signal—ATR spectrum from human skin

Since the temporal shape of reflected THz pulse E(t) is not changed considerably (see Fig. 2a), we may use the pulse amplitude and time position as the integrated characteristics of ATR amplitude and phase. In particular, we use:

$$R_{int} = (E_{s,max} - E_{s,min})/(E_{r,max} - E_{r,min}); \quad \Delta T = t(E_{s,max}) - t(E_{s,max}) \tag{3}$$

Here E_s indicates signal, E_r – reference, E_{max} and E_{min} are corresponding maximal and minimal values in the time-domain, $t(E_{max})$ is the time moment of maximal E value. This way of data analysis is more stable to experimental artifacts and it can be used (see Fig. 6 below) in the case of the absence of sharp spectral features.

The measurements were carried out on six volunteers. They were in good health and had a normal blood glucose concentration (4.2–5.9 mM). The study was performed in accordance with Good Clinical Practice (GCP) and with the 1964 Helsinki declaration and its later amendments. All volunteers signed an informed consent agreement. The standard oral glucose tolerance test using 75 g of glucose was performed with all volunteers (Standards

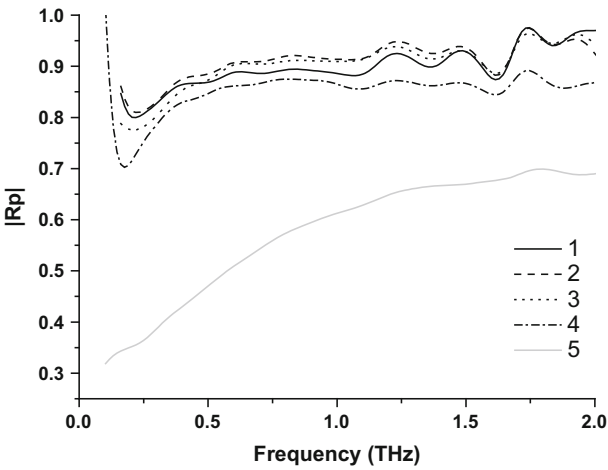

Fig. 3 The ATR spectra of the intact human skin (*lines 1–3*), glycerinated human skin (*line 4*) and water (*line 5*). $|R_p|$ is the ATR amplitude normalized to the reflection from the surface of the prism without the sample

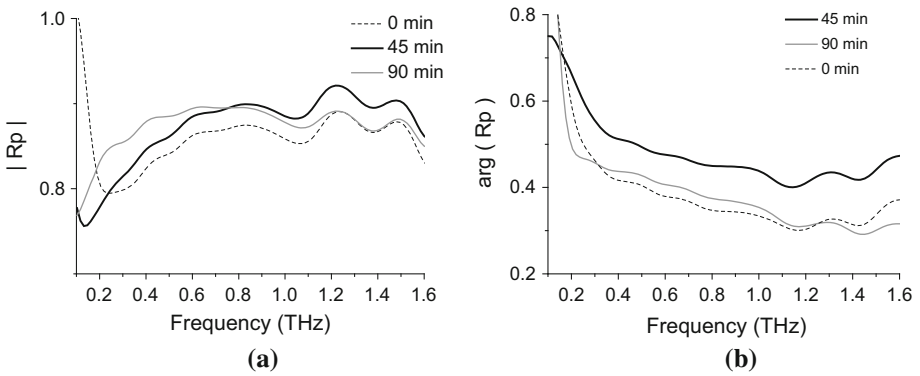

Fig. 4 The ATR amplitude |Rp| (**a**) and phase arg(Rp) (**b**) of human skin at different times (0, 45, 90 min) after ingesting the glucose solution

of Medical Care in Diabetes 2014). The blood glucose concentration was determined with a commercial glucometer "OneTouch Ultra" (USA). The volunteers pushed their palm to the prism base for 3 min to obtain a reflection spectrum. It is important to have good optical contact between the skin and the prism. We used a 0.2 ml 84 % glycerol solution in distilled water to improve this optical contact and to increase the THz field penetration depth into the skin. The processing time of glycerol was 10 min. The ATR spectra of skin on the palm of the hand in vivo were consequently measured 0–90 min later after glucose intake.

3 Results

The ATR spectra of three independent measurements of an intact human skin and skin treated by glycerol for 10 min of the same volunteer are shown in Fig. 3. Broad "peaks" at 1.2; 1.4; 1.7 THz are experimental artifacts of our spectrometer. The effect of glycerol on the ATR spectrum of palm skin is that the decline of $|R_p|$ at frequencies lower than 0.5 THz became more pronounced. This is primarily the consequence of the improved optical contact between palm and prism surface and the fact that most of the THz field reaches the dermis containing water. The ATR amplitude of the intact human skin is 0.90 ± 0.01 (SD) at 1.0 THz. Errors related to measurements repeatability were estimated from a series of three independent scans, and they do not exceed 1.3 %.

Then we examined the effect of ingestion of glucose solution on the ATR spectra of human palm skin. It is known that for 30 min after glucose ingesting its concentration in the blood increases significantly (Rebel et al. 2012). The ATR spectra of human palm skin after ingesting glucose solution are shown in Fig. 4. The largest variations ATR spectra are observed for the 0.1–0.5 THz frequency range. The amplitude and phase of ATR signal of human palm skin are changed when blood glucose concentrations rise above the normal levels. In the case of measuring the reflection from the skin at different glucose concentrations in blood, changes in the phase are more pronounced. Surprising is the observed reflection difference after glucose intake at high (>1 THz) frequencies, where THz penetration inside tissue is of the order of 30 microns (Nazarov et al. 2010), here in epidermis there should be no blood vessels with glucose.

The correlation of the ATR amplitude of human skin and glucose concentration in blood is demonstrated in Fig. 5. In this case we use ATR amplitude R_{int} integrated over the used frequency range, and time shift ΔT (see Eq. 3). It can be seen that the variations of the optical characteristics of human skin correlate with the changes in blood glucose level.

4 Discussion and modeling

Human skin has a complex multilayered structure in which several subsystems are interlaced, including blood vessels and capillaries, the sebaceous glands, various extensions of the nervous system, hair and their follicles (Schaefer and Redelmeier 1996). Conventionally the skin is described as divided in two major layers. The inner layer, the dermis, is 1–4 mm thick. It consists mainly of connective tissue composed of collagen fibers. Other dermal structures include nerves, blood vessels, lymph vessels, muscles, and gland units. The outer layer, the epidermis, is typically 40 microns thick, but it can be much thicker on loadbearing areas such as palms and soles (Caspers et al. 2003; Bashkatov et al. 2005). The penetration depth of the THz radiation in the tissue is frequency dependent in ATR method and is of the order of 30–1000 microns (Nazarov et al. 2010), thereby enabling to obtain spectral information primarily from the epidermis at frequencies above 1 THz and from dermis at frequencies below 0.3 THz. The water content of epidermis layer is as low as 15 %, and the protein and lipid contents are 70 and 15 %, respectively (Schaefer and Redelmeier 1996). Because of this, the reflection spectrum of skin differs significantly from that of water in absolute values, but spectral shape is still mainly determined by Debay relaxation of water molecules as we can see in Figs. 3 and 6.

It has previously been shown that the use of glycerol enhances the THz wave penetration depth in tissues (Genina et al. 2010; Oh et al. 2013; Kolesnikov et al. 2014). We used glycerol to reduce the reflection between the epidermis and dermis and to improve optical contact between palm skin and prism surface. The reflection spectrum of glycerinated human skin is shown in Fig. 3 (line 4). The mechanism of glycerol action on the skin is replacement of water molecules in the tissues (Genina et al. 2010, 2015). The absorption coefficient of glycerol at 1 THz is three times smaller than that of water (Oh et al. 2013).

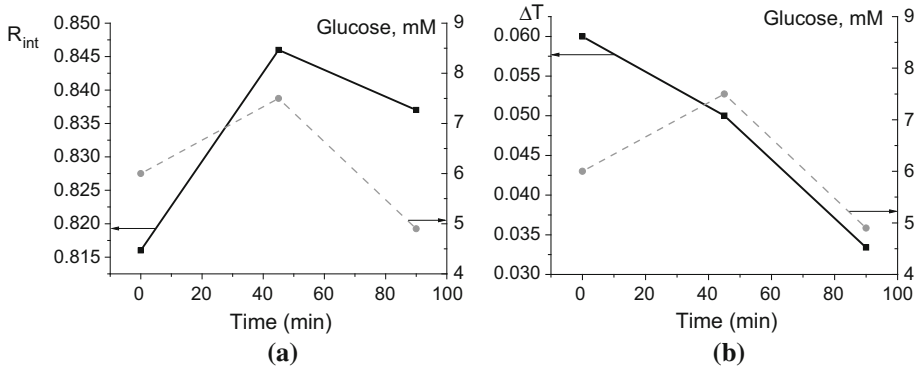

Fig. 5 The ATR amplitude R_{int} (**a**) and time shift ΔT (**b**) of human skin and glucose concentration in blood (mM) versus time (min) after glucose intake

As glycerol applied to the skin is absorbed, the volume fraction of water content in the skin decreases and, finally, the THz waves penetrate deeper into the tissue.

The spectral shape of the biological tissue is mainly determined by water present in it, having a strong dispersion at low frequencies. The main features of dielectric permittivity of water are described by simple Debye model (Raicu and Feldman 2015):

$$\varepsilon_{water} = \varepsilon_{\infty} + \frac{\Delta\varepsilon_1}{1 + i\omega\tau_D} + \cdots \tag{4}$$

where $\Delta\varepsilon_1 \approx 75$ is the dielectric strengths of the Debye term with relaxation time $\tau_D \approx 9$ ps, $\varepsilon_{\infty} \approx 3$ is the dielectric constant in the high frequency limit. When using THz-TDS involving the spectral range of 0.1–3.0 THz, the Debye model usually takes into account the second "fast" Debye term and the high frequency ($\omega_0/2\pi \approx 5.3$ THz) Lorentz term (Markelz 2008; Yada et al. 2008; Shiraga et al. 2013; Fitzgerald et al. 2014; Penkov et al. 2015). We have previously shown (Cherkasova et al. 2015, 2016) that the presence of glucose does not affect significantly the additional terms even in saturated solution, and for clarity, we limit ourselves to a substantial and influential contribution to the main, "slow" term.

The spectrum of the optical characteristics of the skin in the THz range can be represented as a spectrum of effective medium consisting of "dry tissue" (ε_{tissue}) and an aqueous solution (ε_{water}) of glucose, hemoglobin and other blood components (Feldman and Puzenko 2009; Ney and Abdulhalim 2011). All these components have been studied in the solid state and it was shown that only polycrystalline glucose has pronounced spectral features within this THz range (Nazarov et al. 2010). Anyway, in the presence of water all those components, including glucose have a smooth, structureless spectrum with low dispersion and absorption increasing with frequency. The dielectric response of such medium can be roughly described by a constant, complex dielectric function. The best fit for our experimental data is obtained with $\varepsilon_{tissue} = 3.5 - i{\cdot}0.3$ (Fig. 6).

Within the rough skin model as a sum of homogeneous "dry tissue" and a glucose solution, the complex permittivity of skin ε_{result} can be expressed by the equation:

$$\varepsilon_{result}(\omega) = \varepsilon_{water}(\omega) \cdot (C_{water}) + \varepsilon_{tissue} \cdot (1 - C_{water}) \tag{5}$$

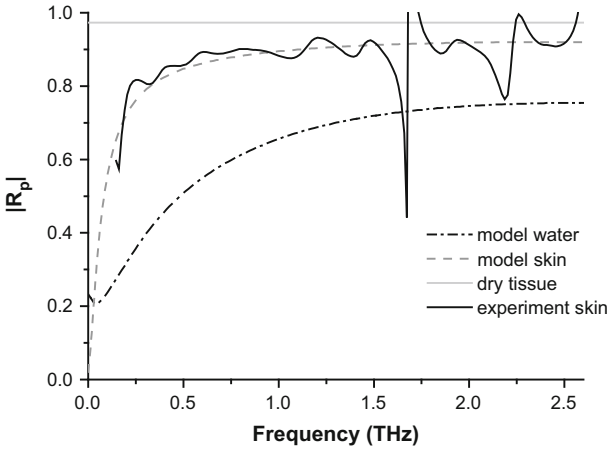

Fig. 6 The model ATR spectra of "dry tissues"(*solid grey line*), water (*dash dot line*) and model skin (*dash line*), consisting of water and "dry tissue". A *black line* shows the experimental ATR spectrum of glycerinated skin

Here C_{water} is volume concentration of water solution. Of course more complicated and precise effective media models are known for the skin (Bennett et al. 2011; Heh and Tan 2012) but the difference between the predictions of those models are less than the present experimental errors, so we use the simplest one.

Knowing the dielectric function of the solution, Rp(ω) is calculated using Fresnel formula:

$$\hat{R}_p(\omega) = \frac{\hat{n}^2(\omega)\cos(\theta) - \sqrt{\hat{n}^2(\omega) - \sin^2(\theta)}}{\hat{n}^2(\omega)\cos(\theta) + \sqrt{\hat{n}^2(\omega) - \sin^2(\theta)}}, \quad \hat{n}(\omega)^2 = \varepsilon(\omega)/n_{Si}^2 \tag{6}$$

Note, that Eq. 1 is just a transformation of Eq. 6. Analysis of the experimental ATR spectra (Fig. 3) was performed by comparing the experimental skin spectra with the dielectric function of skin model ε_{result} (5). Figure 6 shows a good agreement with experiment. By approximating the experimental results by Eqs. (4–6) we get the volume fraction of the aqueous solution in the probed skin layer (20 ± 3 %). So, we may predict the features of the experimental ATR spectra at a normal glucose concentration in human blood.

The next step will explain the observed changes in the experimental ATR spectra after ingesting the glucose solution (see Fig. 4). When water molecules are physically or chemically bound to biomolecules (sugars, proteins), the relaxation time of bound water τ_D increases, which affects the shape of the GHz and THz spectra of such solutions (Fuchs and Kaatze 2001; Raicu and Feldman 2015). Note, that the method of microwave dielectrometry has previously shown the changes in the ratio of free/bound water in diabetic rat erythrocytes (Shatalova et al. 2011). Assuming that the observed spectral changes are due to changes in the state of water, we selected one of the parameters of the Debye model of aqueous solution, namely τ_D, leading to the spectral changes observed in the experiment (Fig. 7). This change in the response of bound water can be the reason of the observed changes in our experiments at increasing glucose concentration in blood. We have previously demonstrated that when the concentration of glucose in blood rises to 24 mM, $\Delta\varepsilon_1/\tau_D$ ratio decreases 1.2 times (Cherkasova et al. 2015, 2016). From the GHz data (Fuchs and Kaatze 2001) we know, that mostly τ_D increases in this case, but not $\Delta\varepsilon_1$. When the concentration of glucose in water grows from 0 to 4 mol/L, τ_D increases approximately

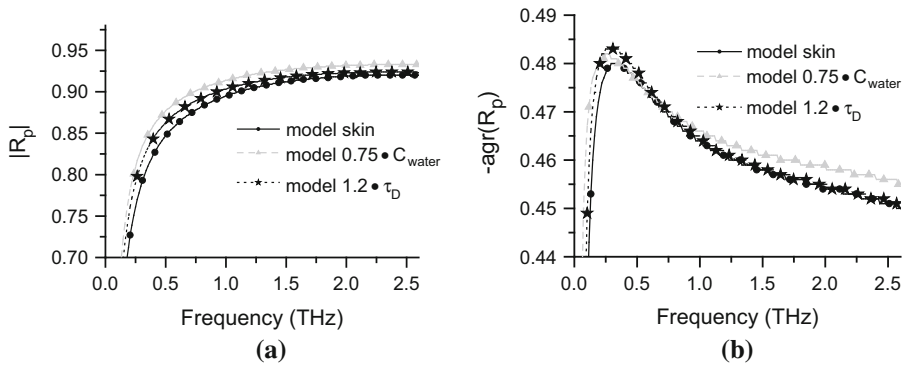

Fig. 7 The ATR amplitude |R| (**a**) and phase arg(R) (**b**) of model skin (*circles*) at a slow relaxation time (*stars*) and water concentration changes (*triangles*)

from 10 to 100 ps. In the case of ATR at frequencies above 0.1 THz, this leads to almost uniform increase in the amplitude and phase of the reflection coefficient (See Fig. 7).

To explain the observed changes in the experimental ATR spectra after ingesting the glucose solution we propose the working hypothesis. It is known that glucose concentration in the aqueous solution leads to a decrease in $\Delta\varepsilon_1/\tau_D$. In the effective medium (skin), such changes occur for 20 % of the volume, as we have shown above. These changes alter the ATR spectrum of skin (Eqs. 1–4). Figure 7 confirms our hypothesis and shows that the change in the ATR amplitude and phase of model skin are determined only by variations of the slow Debye process. Another explanation may be proposed to account for the observed changes in the experimental ATR spectra after ingestion of glucose solution: glucose affects the concentration of water in the skin. Figure 7 demonstrates how this hypothesis should work. Using THz-TDS as broadband and integrated spectroscopy we can separate these two cases—change in the response of bound water (τ_D) or change in water concentration (C_{water}). But signal to noise ratio and measurements repeatability in in vivo measurements should be considerably improved for that purpose.

Hyperglycemia causes an increase in osmolarity of the blood, which leads to the loss of fluid by cells (intracellular dehydration), an increase in the blood microcirculatory disturbances and changes in the aggregation of erythrocytes. When we observe changes of the ATR spectra after ingestion of glucose solution we see the effect that has a high level of blood glucose concentration on tissue and skin. It has previously been shown that in vivo variations of blood glucose affect the biophysical characteristics (e.g. dielectric and optical) of skin and underlying tissue at various frequencies (Caduff et al. 2009). Many factors affect the properties of the skin, and only a combination of different types of sensors may help to avoid mistakes (Zanon et al. 2013). Our experimental approach may be useful in addition to other existing methods of evaluation blood glucose concentration in vivo.

5 Conclusion

We measured human skin spectra in vivo using THz–TDS and ATR optical scheme. The ATR spectra of palm skin were consecutively measured at 0–90 min after glucose intake at standard oral glucose tolerance test. We used glycerol to improve the optical contact between the palm skin and the surface of the prism and to increase the sensitivity of our method. The largest variations of the ATR spectra were observed within the 0.1–0.5 THz frequency range. These variations of the optical characteristics of human skin were correlated with the changes in blood glucose level. The ATR amplitude of human palm skin increased when the glucose concentrations in blood rose above the normal level. The changes observed in the spectra are described with good accuracy by the reduction in the ratio $\Delta\varepsilon_1/\tau_D$ in the Debye model of the glucose aqueous solution. This change in the response of bound water is the reason of the sensitivity of in vivo THz skin measurements to high glucose concentration in blood. Thus we identified the main reason and consequences of variation in the human skin THz response when the level of glucose in the blood is increased. Our results demonstrate the possibility of non-invasive real-time measurement of blood glucose concentration.

Acknowledgments This work has been supported by RFBR (grant No. 13-02-01364) and The Tomsk State University Academic D.I. Mendeleev Fund Program.

References

Angeluts, A.A., Balakin, A.V., Evdokimov, M.G., Esaulkov, M.N., Nazarov, M.M., Ozheredov, I.A., Sapozhnikov, D.A., Solyankin, P.M., Cherkasova, O.P., Shkurinov, A.P.: Characteristic responses of biological and nanoscale systems in the terahertz frequency range. Quantum Electron. **44**(7), 614–632 (2014a)

Angeluts, A.A., Gapeyev, A.B., Esaulkov, M.N., Kosareva, O.G., Matyunin, S.N., Nazarov, M.M., Pashovkin, T.N., Solyankin, P.M., Cherkasova, O.P., Shkurinov, A.P.: Study of Terahertz-Radiation-Induced DNA Damage in Human Blood Leukocytes. Quantum Electron. **44**(3), 247–251 (2014b)

Bashkatov, A.N., Genina, E.A., Kochubey, V.I., Tuchin, V.V.: Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm. J. Phys. D Appl. Phys. **38**, 2543–2555 (2005)

Bennett, D.B., Li, W., Taylor, Z.D., Grundfest, W.S., Brown, E.R.: Stratified media model for terahertz reflectometry of the skin. IEEE Sens. J. **11**(5), 1253–1262 (2011). doi:10.1109/JSEN.2010.2088387

Burmeister, J.J., Arnold, M.A., Small, G.W.: Noninvasive blood glucose measurements by near-infrared transmission spectroscopy across human tongues. Diabetes Technol. Ther. **2**(1), 5–16 (2000)

Caduff, A., Talary, M.S., Mueller, M., Dewarrat, F., Klisic, J., Donath, M., Heinemann, L., Stahel, W.A.: Non-invasive glucose monitoring in patients with Type 1 diabetes: a Multisensor system combining sensors for dielectric and optical characterisation of skin. Biosens. Bioelectron. **24**(9), 2778–2784 (2009). doi:10.1016/j.bios.2009.02.001

Cameron, B.D., Anumula, H.: Development of a real-time corneal birefringence compensated glucose sensing polarimeter. Diabetes Technol. Ther. **8**(2), 156–164 (2006)

Caspers, P.J., Lucassen, G.W., Puppels, G.J.: Combined in vivo confocal Raman spectroscopy and confocal microscopy of human skin. Biophys. J. **85**, 572–580 (2003)

Cherkasova, O.P., Nazarov, M.M., Smirnova, I.N., Angeluts, A.A., Shkurinov, A.P.: Application of time-domain THz spectroscopy for studying blood plasma of rats with experimental diabetes. Phys. Wave Phenom. **22**(3), 185–188 (2014)

Cherkasova, O.P., Nazarov, M.M., Angeluts, A.A., Shkurinov, A.P.: The investigation of blood plasma in the terahertz frequency range. Opt. Spectrosc. **120**(1), 55–63 (2016)

Cherkasova, O.P., Nazarov, M.M., Shkurinov, A.P., Fedorov, V.I.: Terahertz spectroscopy of biological molecules. Radiophys. Quantum Electron. **52**(7), 518–523 (2009)

Cherkasova, O.P., Nazarov, M. M., Shkurinov, A.P.: The investigation of blood and skin THz response at high glucose concentration. In: IEEE 40th international conference on infrared, millimeter, and terahertz waves (IRMMW-THz 2015): proceedings, F1E4 (2015)

Clarke, S.F., Foster, J.R.: A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. Br. J. Biomed. Sci. **69**(2), 83–93 (2012)

Echchgadda, I., Grundt, J.A., Tarango, M., Ibey, B.L., Tongue, T., Liang, M., Xin, H., Wilmink, G.J.: Using a portable terahertz spectrometer to measure the optical properties of in vivo human skin. J. Biomed. Opt. **18**(12), 120503 (2013)

Feldman, Yu., Puzenko, A., Ishai, P.B., Caduff, A., Davidovich, I., Sakran, F., Agranat, A.J.: The electromagnetic response of human skin in the millimetre and submillimetre wave range. Phys. Med. Biol. **54**, 3341–3363 (2009)

Fitzgerald, A.J., Pickwell-MacPherson, E., Wallace, V.P.: Use of finite difference time domain simulations and Debye Theory for modelling the Terahertz reflection response of normal and tumour breast tissue. PLoS One **9**(7), e99291 (2014). doi:10.1371/journal.pone.0099291

Fowler, M.J.: Microvascular and macrovascular complications of diabetes. Clin. Diabetes **26**(2), 77–82 (2008)

Fuchs, K., Kaatze, U.J.: Molecular dynamics of carbohydrate aqueous solutions. Dielectric relaxation as a function of glucose and fructose concentration. Phys. Chem. B. **105**(10), 2036–2042 (2001)

Genina, E.A., Bashkatov, A.N., Sinichkin, YuP, Tuchin, V.V.: Optical clearing of skin under action of glycerol: ex vivo and in vivo investigations. Opt. Spectrosc. **109**(2), 225–231 (2010)

Genina, E.A., Bashkatov, A.N., Sinichkin, YuP, Yanina, IYu., Tuchin, V.V.: Optical clearing of biological tissues: prospects of application in medical diagnostics and phototherapy. J. Biomed. Photon. Eng. **1**(1), 22–58 (2015)

He, R., Wei, H., Gu, H., Zhu, Z., Zhang, Y., Guo, X., Cai, T.: Effects of optical clearing agents on noninvasive blood glucose monitoring with optical coherence tomography: a pilot study. J. Biomed. Opt. **17**(10), 101513 (2012)

Heh, D.Y., Tan, E.L.: Modeling the interaction of terahertz pulse with healthy skin and basal cell carcinoma using the unconditionally stable fundamental ADI-FDTD method. Prog. Electromagn. Res. B **37**, 365–386 (2012)

Kolesnikov, A.S., Kolesnikova, E.A., Popov, A.P., Nazarov, M.M., Shkurinov, A.P., Tuchin, V.V.: In vitro terahertz monitoring of muscle tissue dehydration under the action of hyperosmotic agents. Quantum Electron. **44**(7), 633–640 (2014)

Lambert, J.L., Pelletier, C.C., Borchert, M.: Glucose determination in human aqueous humor with Raman spectroscopy. J. Biomed. Opt. **10**(3), 031110 (2005)

Markelz, A.G.: Terahertz dielectric sensitivity to biomolecular structure and function. IEEE J. Sel. Top. Quantum Electron. **14**(1), 180–190 (2008)

Nazarov, M.M., Shkurinov, A.P., Kuleshov, E.A., Tuchin, V.V.: Terahertz time-domain spectroscopy of biological tissues. Quantum Electron. **38**, 647–654 (2008)

Nazarov, M., Shkurinov, A., Tuchin, V.V., Zhang, X.-C.: Terahertz tissue spectroscopy and imaging. In: Tuchin, V.V. (ed.) Handbook of Photonics for Biomedical Science, pp. 591–617, CRC Press, USA (2010)

Newnham, D.A., Taday, P.F.: Pulsed terahertz attenuated total reflection spectroscopy. Appl. Spectrosc. **62**(4), 394–398 (2008)

Ney, M., Abdulhalim, I.: Modeling of reflectometric and ellipsometric spectra from the skin in the terahertz and submillimeter waves region. J. Biomed. Opt. **16**(6), 067006 (2011)

Oh, S.J., Kim, S.-H., Jeong, K., Park, Y., Huh, Y.-M., Son, J.-H., Suh, J.-S.: Measurement depth enhancement in terahertz imaging of biological tissues. Opt. Express **21**(18), 21299–21305 (2013)

Parrott, E.P.J., Sun, Y., Pickwell-MacPherson, E.: Terahertz spectroscopy: its future role in medical diagnoses. J. Mol. Struct. **1006**, 66–76 (2011)

Penkov, N., Shvirst, N., Yashin, V., Fesenko Jr, E., Fesenko, E.: Terahertz spectroscopy applied for investigation of water structure. J. Phys. Chem. B **119**(39), 12664–12670 (2015)

Pickwell, E., Cole, B.E., Fitzgerald, A.J., Pepper, M., Wallace, V.P.: In vivo study of human skin using pulsed terahertz radiation. Phys. Med. Biol. **49**, 1595–1607 (2004)

Pickwell, E., Wallace, V.P.: Biomedical applications of terahertz technology. J. Phys. D Appl. Phys. **39**, R301–R310 (2006)

Raicu, V., Feldman, Y.: Dielectric relaxation in biological systems: Physical principles, methods, and applications. Oxford University Press, Oxford (2015)

Rebel, A., Rice, M.A., Fahy, B.G.: The accuracy of point-of-care glucose measurements. J. Diabetes Sci. Technol. **6**(2), 396–411 (2012)

Ren, Z., Liu, G., Huang, Z.: Determination of glucose concentration based on pulsed laser induced photoacoustic technique and least square fitting algorithm. Proc. SPIE **9619**, 96190M (2015). doi:10.1117/12.2190601

Schaefer, H., Redelmeier, T.E.: Skin Barrier, Principles of Percutaneous Absorption. Karger AG, Basel (1996)

Shatalova, T.A., Gorobchenko, O.A., Ovsyannikova, T.N., Gladkih, A.I., Nikolov, O.T., Gatash, S.V.: Influence of type 2 diebetes on dielectric characteristics of rat erythrocytes. Biophysical Vestnik. **26**(1), 94–103 (2011)

Shiraga, K., Ogawa, Y., Kondo, N., Irisawa, A., Imamura, M.: Evaluation of the hydration state of saccharides using terahertz time-domain attenuated total reflection spectroscopy. Food Chem. **140**(1–2), 315–320 (2013)

Sigel, P.H., Lee, Y., Pikov, V. (2014) Millimeter-Wave Non-Invasive Monitoring of Glucose in Anesthetized Rats. In: IEEE 39th International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz 2014): proceedings, T2/D-8 (2014)

Standards of Medical Care in Diabetes—2014. Diabetes Care.**37**, Suppl. 1, S14–S80 (2014)

Summa, N.M., Eshar, D., Lee-Chow, B., Larrat, S., Brown, D.C.: Comparison of a human portable glucometer and an automated chemistry analyzer for measurement of blood glucose concentration in pet ferrets (Mustela putorius furo). Can. Vet. J. **55**, 865–869 (2014)

Sun, C-K., Tsai, Y-F., Chen, H.: United States Patent Application Publication. US 2013/0289370 A1 (2013) http://www.faqs.org/patents/app/20130289370#ixzz3HQzAOszh

Truong, B. C. Q., Tuan, H. D., Kha H.H., Nguyen H.T.: (2012) System identification for Terahertz wave's propagation and reflection in human skin. In: IEEE, 364–368 (2012). doi:10.1109/CCE.2012.6315929

Yada, H., Nagai, M., Tanaka, K.: Origin of the fast relaxation component of water and heavy water revealed by terahertz time-domain attenuated total reflection spectroscopy. Chem. Phys. Lett. **464**, 166–170 (2008)

Zanon, M., Giovanni Sparacino, G., Facchinetti, A., Talary, M.S., Mueller, M., Caduff, A., Cobelli, C.: Non-invasive continuous glucose monitoring with multi-sensor systems: a monte carlo-based methodology for assessing calibration robustness. Sensors **13**, 7279–7295 (2013). doi:10.3390/s130607279

Zaytsev, K.I., Kudrin, K.G., Karasik, V.E., Reshetov, I.V., Yurchenko, S.O.: In vivo terahertz spectroscopy of pigmentary skin nevi: pilot study of non-invasive early diagnosis of dysplasia. Appl. Phys. Lett. **106**, 053702 (2015a). doi:10.1063/1.4907350

Zaytsev, K.I., Gavdush, A.A., Chernomyrdin, N.V., Yurchenko, S.O.: Highly Accurate in Vivo Terahertz Spectroscopy of Healthy Skin: variation of Refractive Index and Absorption Coefficient Along the Human Body. IEEE Trans. Terahertz Sci. Technol. **5**(5), 817–827 (2015b)