Continuous noninvasive monitoring of changes in human skin optical properties during oral intake of different sugars with optical coherence tomography

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Abstract: The objective of this study was to evaluate the effects of blood glucose concentration (BGC) on in vivo human skin optical properties after oral intake of different sugars. In vivo optical properties of human skin were measured with a spectral domain optical coherence tomography (SD-OCT). Experimental results show that increase of BGC causes a decrease in the skin attenuation coefficient. And the maximum decrements in mean attenuation coefficient of skin tissue after drinking glucose, sucrose and fructose solution are 47.0%, 36.4% and 16.5% compared with that after drinking water, respectively (p < 0.05). The results also show that blood glucose levels of the forearm skin tissue are delayed compared with finger-stick blood glucose, and there are significant differences in the time delays after oral intake of different sugars. The time delay between mean attenuation coefficient and BGC after drinking glucose solution is evidently larger than that after drinking sucrose solution, and that after drinking sucrose solution is larger than that after drinking fructose solution. Our pilot studies indicate that OCT technique is capable of non-invasive, real-time, and sensitive monitoring of skin optical properties in human subjects during oral intake of different sugars.

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1. Introduction

Diabetes mellitus, often referred to as diabetes is a group of metabolic diseases in which a person has high blood sugar. Diabetes is widespread nowadays. Over 300 million people in the world are affected [1]. Currently, there are a few dozen commercialized devices for detecting blood glucose levels [2]. This high blood sugar will often cause symptoms of frequent urination, increased hunger and increased thirst. The two types that affect the general population are known as Type 1 and Type 2 diabetes. Type 1 diabetes is an autoimmune disease with pancreatic islet beta cell destruction. This results in the inability to maintain glucose homoeostasis. Susceptibility to Type 1 largely inherited, but there are also environmental triggers that are not fully understood. Of those with Type 1 diabetes, 50-60% of patients are under 18 years of age [3]. Type 2 diabetes is characterized by insulin resistance
and deficient beta cell function [4]. Both Type 1 and Type 2 diabetes are chronic conditions that usually cannot be cured easily. The present method by which many diabetics control their blood glucose levels is by a finger prick several times a day to obtain a drop of blood, in which the glucose is then determined by an analytical chemical reaction. This invasive procedure limits the frequency of monitoring and so may give inadequate control of the long-term complications of the disease. Thus, a continuous, noninvasive method for monitoring body glucose levels would be of great advantage [5].

Various optical methods proposed for noninvasive glucose monitoring include absorption and scattering of light in the near-IR spectral range [6], Raman spectroscopy [7–10], polarimetry [11–13], photoacoustics [14, 15] and time-of-flight spectroscopy [16, 17]. Although these techniques are promising, they require further development to provide clinically acceptable accuracy, specificity, and reproducibility. Optical coherence tomography (OCT) was proposed previously for blood glucose monitoring and was tested in vivo [18–22] and in vitro [23, 24]. It was shown that OCT is capable of detecting changes in blood glucose concentration as small as a clinically acceptable value of 20 mg/dl [19, 20]. The optical properties themselves can potentially provide information to monitor tissue metabolic status or to diagnose diseases. In particular, some possible approaches are based on the effect of glucose on light transport in tissue. It has been reported that glucose also changes the optical scattering properties of tissues [5, 25–31]. Light scattering occurs in tissues because of the mismatch of refractive index between the extracellular fluid (ECF) and the membranes of the cells composing the tissue. In the near-infrared region (NIR), the refractive index of the ECF is \( n_{\text{ECF}} = 1.348-1.352 \), while the refractive index of the cellular membranes and protein aggregates is in the range \( n_{\text{cell}} = 1.350-1.460 \) [29]. It is well known that adding sugar to water increases the refractive index of the solution. Similarly, adding glucose to blood in turn raises the refractive index of the ECF, which will cause a change in the scattering characteristics of the tissue as a whole. Hence, tissue glucose levels are correlated with scattering coefficients based on changes in the refractive index of the ECF. Of late, measurements on light scattering by blood show promising correlation between blood glucose and reduced scattering coefficient [25]. At the same time, monitoring of glycemic status in patients with diabetes requires determination of blood glucose concentration. Significant efforts have been made by several groups in the past few decades to develop a biosensor for noninvasive blood glucose analysis.

OCT is a non-invasive technique that provides micron-scale imaging of tissue [32]. In addition to offering high resolution morphological images, OCT is capable of quantitatively estimating total attenuation coefficient (\( \mu_t \)) by fitting the A-line measurements [33–36]. \( \mu_t \) is the summation of absorption coefficient (\( \mu_a \)) and scattering coefficient (\( \mu_s \)). As \( \mu_a \) is much smaller than \( \mu_s \), \( \mu_s \) is almost equal to \( \mu_t \) and is a good estimate of the local scattering properties [37–39]. The skin consists of three major layers: stratum corneum (SC), epidermis, and connective tissue of dermis, which is the only layer containing a developed blood microvessel network. The OCT technique allows measurement of glucose-induced changes in the skin optical properties directly from the dermis. However, one limitation of previous studies performed with OCT system is that they all tested the skin optical properties during oral glucose intake with OCT. Our daily diet covers various kinds of sugar, such as glucose, fructose, sucrose, and so on. Meals containing different sugars can cause different changes in human skin optical properties and different postprandial blood glucose responses in human subjects. This may affect the results of noninvasive blood glucose monitoring with optical methods.

In this paper, the objectives of our study were to continuously monitor the alterations of in vivo human skin optical properties during oral intake of different sugars with a spectral domain OCT (SD-OCT) system, and we also quantitatively analyzed the different effects of sucrose, fructose and glucose on human skin optical properties, respectively.
2. Methods and materials

2.1 OCT system

The experiments were performed with a SD-OCT system. It is made by Shenzhen MOPTIM Imaging Technique Co., Ltd., China. A schematic of the OCT system was shown in the literature [40]. The optical source used in this system is a low-coherence broadband super luminescent diode with a wavelength of 830 ± 40 nm and an output power of 5 mW. The SD-OCT system provides an axial resolution of 12 μm and a transverse resolution of 15 μm in free space, determined by the focal spot size of the probe beam. The signal-to-noise ratio of the OCT system is measured to be 120 dB. Two-dimensional (2-D) images are obtained by scanning the incident beam over the sample surface in the lateral direction and in-depth (A-scan) scanning by the interferometer. The acquisition time per OCT image is about 180 ms, corresponding to an A-scan frequency of 2000 Hz. A computer is used to control the OCT system with a data acquisition software written in Lab View 7.2-D. OCT images obtained in the experiment were stored in the computer for further processing.

2.2 Materials and measurements

The experiments were carried out on 32 volunteers (16 males and 16 females) aged 23 to 29 years (mean age 26 years). They were in good health, took no medication, and were selected from the same racial groups randomly. A signed informed consent was obtained from all subjects before the experiments. OCT images were taken from the left forearms. We choose the forearm to monitor skin optical properties because it is convenient to operate for measurement. Before each individual experiment, the detected area should be shaved to eliminate influences to the experimental results by the fine hair on the arm [41].

Three types of sugar used in this study were glucose, fructose and sucrose, respectively. Glucose and fructose are monosaccharides that can be absorbed in the small intestine through the mucosal membranes by simple diffusion [42]. Then, glucose enters into the bloodstream directly. Fructose is transported into the liver for metabolism [43]. A large proportion of ingested fructose was converted to glucose in the liver and stored as glycogen [44]. Sucrose is a disaccharide that is too large to cross the mucosal membranes. Sucrose is rapidly hydrolyzed in the stomach, and then sucrose equivalent glucose and fructose can be resorbed in the small intestine with no specific delay by simple diffusion [42, 45]. After the metabolism of fructose and sucrose, the concentration of fructose in peripheral blood is very low and far less than the concentration of glucose, so glucose is the major sugar in the blood circulation [42, 44]. Previous study has demonstrated that for healthy subjects on oral administration of identical amounts of glucose, fructose, and sucrose, glucose caused the maximum rise in blood glucose concentration (BGC) and fructose caused the minimum rise in BGC [45].

In this study, 32 healthy volunteers were randomly divided into four groups, A, B, C and D, and 8 subjects in each group. Each volunteer was asked to orally administer 50 g glucose dissolving in 400 ml water in group B. In group C, each volunteer was asked to orally administer 50 g sucrose dissolving in 400 ml water. In group D, each volunteer was asked to orally administer 50 g fructose dissolving in 400 ml water. Group A, acts as a control group, orally administer equivalent volume of water only. The experiments were performed in all volunteers starting at 8:00 A.M. (time = 0) after an overnight fast. Each subject was asked to drink the solution in two minutes. During the measurement, each volunteer was asked to remain still to minimize motion artifacts, and no food and drinks were permitted. BGC was monitored serially at about 10 min intervals using one touch ultra easy glucose analyzers. Whole-blood samples were drawn from the subject’s fingertips. The duration of each individual experiment was about 160 min. Before oral administration of sugars, the detected regions of subjects were measured for about 10 min to establish a baseline by OCT. Then continuous monitoring of tissue optical properties was performed for up to 150 min. Each
volunteer has completed the experiments. The room temperature was maintained at 20°C throughout the experiment, so as to eliminate influences caused by temperature fluctuation [46].

2.3 Methods

In order to characterize the changes of skin optical properties during oral intake of different sugars, the attenuation coefficients of each group were calculated from the 2-D OCT image, as it carries the information of the reflected light intensity distribution in depth of the tissue. The reflected light intensity depends on the tissue optical properties. For media with absorption as described by the single scattering approximation, the light travels in a ballistic way, and Beer’s law can be applied to calculate the total OCT attenuation coefficient: \( \mu_t = \mu_a + \mu_s \). These are physical properties unique to the biological tissue, which play a vital role in the assessment of the tissue feature [37, 47, 48]. In this current OCT system case, the measured signal is defined as [37, 47–49]:

\[
\left[ \left\langle i^2(z) \right\rangle \right]^{1/2} = \left( \left\langle i^2 \right\rangle_0 \right)^{1/2} \left[ \exp(-2\mu_z) \right]^{1/2}.
\]  

where the \( \left\langle i^2(z) \right\rangle \) is the photodetector heterodyne signal current received by an OCT system from the probing depth \( z \) and the mean square heterodyne signal \( \left\langle i^2 \right\rangle_0 \). The result of the OCT study is the measurement of optical backscattering or reflectance \( R(z) \sim \left[ \left\langle i^2(z) \right\rangle \right]^{1/2} \) from a tissue versus axial ranging distance, or depth, \( z \). The reflectance depends on the optical properties of tissue, i.e., the total attenuation coefficient \( \mu_t \). Thus, combined with Eq. (1) and \( R(z) \) it follows that the reflected power can be approximately proportional to \( -\mu_0 z \) in exponential scale according to the single scattering model:

\[
R(z) = I_0 a(z) \exp(-\mu_0 z).
\]  

Here \( I_0 \) is the optical power launched into the tissue sample and \( a(z) \) is the reflectivity of the tissue sample at the depth of \( z \). Therefore, measurement of OCT reflectance for depths \( z_1 \) and \( z_2 \) allows for approximately evaluating the attenuation coefficient and its temporal behavior. This evaluation is due to reduction of the tissue-scattering coefficient caused by increased BGC in the tissue if reflectivity \( a(z) \) is considered as weakly dependent on depth for a homogeneous tissue layer. The \( \mu_t \) theoretically can be obtained from the reflectance intensity measurements at two different depths, \( z_1 \) and \( z_2 \) [37, 47–49]:

\[
\mu_t = \frac{1}{\Delta z} \ln \left[ \frac{R(z_1)}{R(z_2)} \right].
\]  

Where \( z_1 \) and \( z_2 \) are two different depths for A-scan (z-axis); \( \Delta z = |z_1 - z_2| \); and \( R(z_1) \) and \( R(z_2) \) are magnitudes of reflectance for these scanning depths [50]. Noise is inevitable in the measurement, thus a final result should be obtained using a least-square fitting method in order to improve the accuracy of determining \( \mu_t \) value. An averaged intensity profile as a function of depth was obtained by averaging the 2-D images laterally over approximately 1 mm, which was enough for speckle noise suppression. A best-fit exponential curve was applied to the averaged intensity profiles of each group since the noise in the measurement is unavoidable. The data acquisition and processing are shown in Fig. 1. In this study, the depth interval of 500–600 µm from the skin surface was chosen to calculate the attenuation coefficient by Eq. (3). Because near the dermis–hypodermis junction at 500–600 µm where the most prominent glucose-induced changes were found [20].

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2.4 Statistical analysis

The data from all samples were presented as means ± SD and analyzed by an SPSS 16.0 software paired-test. The p < 0.05 value indicated significant difference.

3. Results and discussion

Figure 2 shows the OCT signal intensity versus depth profiles recorded from human skin in vivo after oral intake of glucose solution (group B), sucrose solution (group C), fructose solution (group D) and water (control group, group A) at 50 min, respectively. We can see from Fig. 2 that OCT signal intensity in human skin after drinking sucrose solution (group C) is markedly higher than that after drinking water (group A) in the depth range of about 450 to 1200 um at 50 min, and OCT signal intensity after drinking glucose solution (group B) is higher than that after drinking sucrose solution (group C) in the depth range of about 450 to 1200 um at 50 min. However the OCT signal intensity in human skin after drinking fructose solution (group D) is nearly the same with that after drinking water (group A) at 50 min, and there is merely small difference in the OCT signal intensity between group D and group A in the depth range of 800 to 1200 um at the same time. These differences in the OCT signal intensity in human skin between control group and experimental group were mainly caused by the differences in blood glucose concentration after oral different sugars intake.

Figure 3 displays the average attenuation coefficients recorded from human skin in vivo and BGCs recorded from finger-stick blood glucose monitoring after oral intake of different sugars and water, respectively. The BGCs were monitored serially at about 10 min intervals.
The blue dotted line in Fig. 3(a) shows that mean BGC of the volunteers in control group keeps to normal fasting blood glucose level [51] and undergoes tiny fluctuations in 0 to 150 min. The red solid line in Fig. 3(a) represents that mean attenuation coefficient of skin tissue in control group is estimated to be about $(2.52 \pm 0.16) \text{mm}^{-1}$ and undergoes tiny fluctuations from 0 to 150 min. The two lines in Fig. 3(a) indicate that the changing trends in mean attenuation coefficient of skin tissue and mean BGC in control group are accordant.

Fig. 3. Averaged attenuation coefficients of skin tissue and corresponding BGCs of the volunteers after they oral intake of different sugar solutions and water, respectively. (a) control group, (b) glucose solution, (c) sucrose solution, (d) fructose solution

In Fig. 3(b), the blue dotted line represents that mean BGC of the volunteers after oral intake of glucose solution slowly increases with increasing time in 0 to 30 min, and quickly increases with increasing time in 30 to 40 min, but slowly decreases with increasing time in 40 to 120 min, and falls to normal fasting blood glucose level in 120 to 150 min and the maximum mean BGC is $(171.2 \pm 14.4) \text{mg/dl}$ at about 40 min. The red solid line in Fig. 3(b) shows that mean attenuation coefficient of skin tissue after drinking glucose solution slowly decreases from $(2.51 \pm 0.14)$ to $(1.85 \pm 0.11) \text{mm}^{-1}$ in a time range from 0 to 30 min, and rapidly decreases from about $(1.85 \pm 0.11)$ to $(1.33 \pm 0.09) \text{mm}^{-1}$ in a time range from 30 to 58 min, but slowly increases from about $(1.33 \pm 0.09)$ to $(1.68 \pm 0.10) \text{mm}^{-1}$ in a time range from 58 to 104 min, and undergoes tiny fluctuations from 104 to 150 min. The maximum and minimum values of mean attenuation coefficients are estimated to be $(2.51 \pm 0.14) \text{mm}^{-1}$ at 0 min and $(1.33 \pm 0.09) \text{mm}^{-1}$ at about 58 min, respectively. Figure 3(b) displays that the changing trends in mean attenuation coefficient of skin tissue and mean BGC after drinking glucose solution show the reverse. The maximal value of mean BGC is estimated to occur at about 40 min, and minimum value of mean attenuation coefficient is estimated to occur at
about 58 min. It is obvious that there is a time delay between mean attenuation coefficient and BGC, and the time delay is estimated to be about 18 min.

In Fig. 3(c), the blue dotted line shows that mean BGC of the volunteers after oral intake of sucrose solution also slowly increases with increasing time in 0 to 30 min, and quickly increases with increasing time from 30 to 40 min, but also slowly decreases with increasing time from 40 to 100 min, and falls to normal fasting blood glucose level from 100 to 150 min and the maximum mean BGC is (169.2 ± 14.1) mg/dl at about 40 min. The red solid line in Fig. 3(c) shows that changing trend in mean attenuation coefficient of skin tissue after drinking sucrose solution is similar to that after drinking glucose solution, and the maximum and minimum values of mean attenuation coefficients are estimated to be about (2.53 ± 0.15) mm$^{-1}$ at 0 min and (1.61 ± 0.10) mm$^{-1}$ at about 54 min, respectively. We can see from Fig. 3(c) that the changing trends in mean attenuation coefficient of skin tissue and mean BGC of the volunteers after drinking sucrose solution also show the reverse. The maximal value of mean BGC is estimated to be about (169.2 ± 14.1) mg/dl at about 40 min, and minimum value of mean attenuation coefficient is estimated to be (1.61 ± 0.10) mm$^{-1}$ at about 54 min. It is evident that there is also a time delay between mean attenuation coefficient and BGC, and the time delay is estimated to be about 14 min.

In Fig. 3(d), the blue dotted line displays that mean BGC of the volunteers after oral intake of fructose solution keeps to normal fasting blood glucose level from 0 to 150 min. The mean BGC is only a little higher than normal fasting blood glucose level from 40 to 50 min, and the maximum mean BGC is (104.6 ± 8.6) mg/dl at about 40 min. The red solid line in Fig. 3(d) represents that changing trend in mean attenuation coefficient of skin tissue after drinking fructose solution is similar to that after drinking water. Besides the minimum mean attenuation coefficient of skin tissue in group D is estimated to be (2.12 ± 0.12) mm$^{-1}$ at about 52 min, and mean attenuation coefficient is estimated to be (2.54 ± 0.15) mm$^{-1}$ and undergoes tiny fluctuations from 0 to 150 min. The two lines in Fig. 3(d) display that the changing trends in mean attenuation coefficient of skin tissue and mean BGC after drinking fructose solution show the reverse. The maximal value of mean BGC is estimated to be about (104.6 ± 8.6) mg/dl at about 40 min, and minimum value of mean attenuation coefficient is estimated to be about (2.12 ± 0.12) mm$^{-1}$ at about 52 min. It is clear that there is also a time delay between mean attenuation coefficient and BGC, and the time delay is estimated to be about 12 min.

Figure 3 reveals significant differences in changing trends of mean BGC (blue dotted lines) and mean attenuation coefficients (red solid lines) after oral intake of different sugars and water, respectively. Obtained results show different increases in mean BGC after oral intake of different sugars compared with that after drinking water (control group), respectively. Their maximum increments in mean BGC are 102.4% for group B, 99.8% for group C and 23.6% for group D compared with mean BGC of control group, respectively. The increase of BGC causes a decrease in the skin attenuation coefficient. The different increments in mean BGC cause different decreases in mean attenuation coefficients after oral intake of different sugars compared with that after drinking water, respectively. Their maximum decrements in mean attenuation coefficients are 47.0% for group B, 36.4% for group C and 16.5% for group D compared with mean attenuation coefficient for control group (group A), respectively.

Because glucose has low absorption relative to other tissue constituents at 850 nm, the absorption coefficient is negligibly affected by glucose concentration [25]. Consequently, the decreases in the attenuation coefficients of skin tissue result in decreases in the scattering coefficients after oral intake of different sugars. Previous studies also indicate that an increase of glucose concentration in the physiological range decreases the total amount of tissue scattering [25–31]. It is obvious that the results of our study and previous studies [25–31] are accordant. The results also indicate that blood glucose levels of the forearm skin tissue are delayed compared with finger-stick blood glucose, and there are significant differences in the
time delays after oral intake of different sugars, respectively. The time delay between mean attenuation coefficient and BGC in group B is evidently larger than that in group C, and that in group C is larger than that in group D. Previous studies indicate that during rapid changes in blood glucose, the forearm glucose levels may be delayed by 30 min on average when compared with finger-stick blood glucose in humans [52, 53]. Our results are consistent with the previous studies. The time delay may be caused by many factors. In this study, the OCT signals were obtained from the forearms, and blood glucose values were measured from fingertips. Previous studies showed that there were real concentration differences in blood glucose concentration for various tissues after rapid blood glucose changes [52, 54]. It needed time for the blood compartment to harmonize glucose concentrations in the blood of various tissues after a glucose challenge [54], and dermal blood flow is 5 - 20 times higher at the fingertip than that at the forearm for human [55], thus the time delay occurred.

4. Conclusion

Our results demonstrate that increase of BGC causes a decrease in the skin attenuation coefficient, and the results also show significant differences in changing trends of mean attenuation coefficients after oral intake of different sugars compared with that after drinking water (control group), respectively. The results of this study also demonstrate that there are different decreases in mean attenuation coefficients after oral intake of different sugars compared with that after drinking water, respectively. Their maximum decrements in mean attenuation coefficients are 47.0% for group B, 36.4% for group C and 16.5% for group D compared with mean attenuation coefficient for control group, respectively. The results from our study also demonstrate that there is a time delay between mean attenuation coefficient and BGC. And the time delay in group B is evidently larger than that in group C, and that in group C is larger than that in group D. Our results indicate that blood glucose levels of the forearm skin tissue are delayed compared with finger-stick blood glucose, and there are significant differences in the time delays after oral intake of different sugars, respectively. The results of our pilot study indicate that the OCT technique is capable of non-invasive, real-time, and sensitive monitoring of skin optical properties in human subjects during oral intake of different sugars. Further studies with a larger number of subjects including diabetic subjects are planned to validate these preliminary results.

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