Noninvasive Blood Glucose Monitoring With Optical Coherence Tomography

A pilot study in human subjects

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OBJECTIVE — To study the feasibility of noninvasive blood glucose monitoring using optical coherence tomography (OCT) technique in healthy volunteers.

RESEARCH DESIGN AND METHODS — An OCT system with the wavelength of 1,300 nm was used in 15 healthy subjects in 18 clinical experiments. Standard oral glucose tolerance tests were performed to induce changes in blood glucose concentration. Blood samples were taken from the right arm vein every 5 or 15 min. OCT images were taken every 10–20 s from the left forearm over a total period of 3 h. The slope of the signals was calculated at the depth of 200–600 μm from the skin surface.

RESULTS — A total of 426 blood samples and 8,437 OCT images and signals were collected and analyzed in these experiments. There was a good correlation between changes in the slope of noninvasively measured OCT signals and blood glucose concentrations throughout the duration of the experiments. The slope of OCT signals changed significantly (up to 2.8% per 10 mg/dl) with variation of plasma glucose values. The good correlation obtained between the OCT signal slope and blood glucose concentration is due to the coherent detection of backscattered photons, which allows measurements of OCT signal from a specific tissue layer without unwanted signal from other tissue layers.

CONCLUSIONS — This pilot study demonstrated the capability of the OCT technique to monitor blood glucose concentration noninvasively in human subjects. Further studies with a larger number of subjects including diabetic subjects are planned to validate these preliminary results.

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Monitoring of glycemic status in patients with diabetes is considered a cornerstone of their care. Results of monitoring are used to assess the efficacy of therapy and to guide adjustments in medical nutrition therapy, exercise, and medications to achieve the best possible glucose control (1,2).

At present, the widely used method of self-monitoring of blood glucose (SMBG) involves determination of blood glucose concentration with specific devices using chemical analysis of blood samples taken by puncturing the finger or the forearm. Although SMBG has revolutionized the management of diabetes, discomfort and inconvenience of this invasive technique are frequent barriers for effective compliance and, therefore, optimum management (3,4). These drawbacks limit the number of blood glucose measurements performed by patients with diabetes and thus may result in poor management of the disease. A noninvasive technique capable of continuous monitoring of blood glucose concentration with accuracy equal to or better than the current chemical glucose meters may improve compliance for glucose monitoring.

Significant efforts have been made by several scientific groups and companies in the past few decades to develop a biosensor for noninvasive blood glucose analysis. Different optical approaches were proposed to achieve this goal (rev. in 5). These approaches include polarimetry (6,7), Raman spectroscopy (8), near-infrared (NIR) absorption and scattering (9–12), and photoacoustics (13). Although these techniques are promising, they have limitations associated with low sensitivity and accuracy and insufficient specificity of glucose measurements at physiologically relevant levels.

In this article we tested the novel optical coherence tomography (OCT) technique for noninvasive blood glucose monitoring in pilot clinical studies on healthy volunteers. The OCT technique was first introduced by Fujimoto and colleagues in 1991 (14), and since then, it has been widely applied for medical imaging and diagnostics. The OCT system uses an interferometer with a low coherent light source (coherence length: l_c = 10–15 μm), a moving mirror in a reference arm, a sample arm, and a photodetector to measure the interferometric signal. Light backscattered from tissues is combined with light returned from the reference arm of the interferometer, and the resulting interferometric signal is detected by the photodetector. The inter-

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Abbreviations: 1-D, one-dimensional; 2-D, two-dimensional; ISF, interstitial fluid; NIR, near-infrared; OCT, optical coherence tomography; OGTT, oral glucose tolerance test; PC, personal computer; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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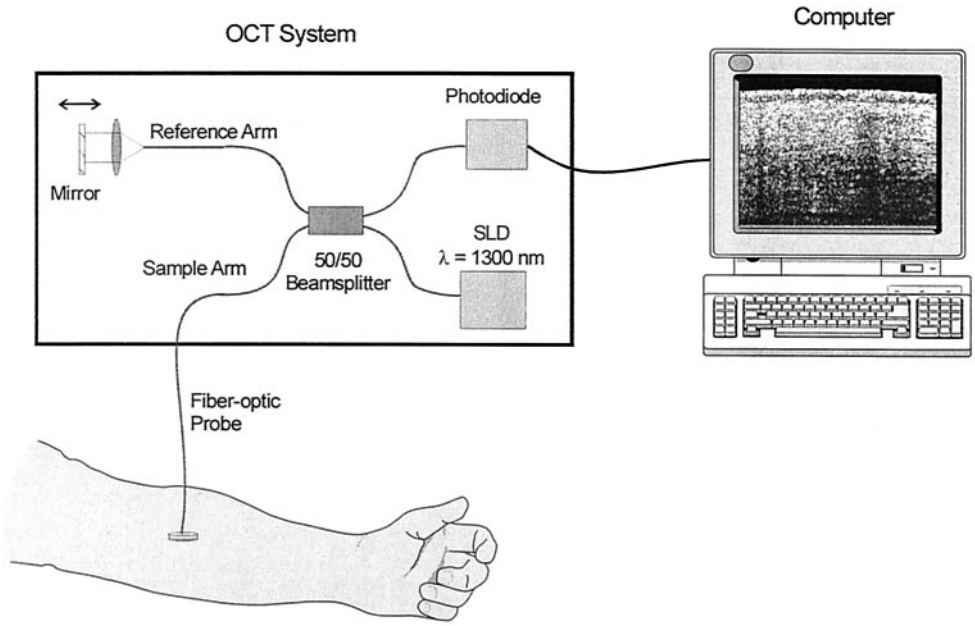

Figure 1—*Schematics of the experimental setup used in the clinical studies. SLD, superluminescent diode.*

ferometric signal can effectively be formed only within the coherence length of the source; therefore, high in-depth resolution (~10 μm) of the OCT system can be achieved. Moving the mirror in the reference arm of the interferometer allows scanning in the tissues up to a depth of ~1 mm. Introducing a second moving mirror into the sample arm allows scanning of the probing beam along the tissue surface. Therefore, the new OCT technique has unique capability of in-depth and lateral scanning to obtain two-dimensional (2-D) images with high resolution.

According to the Beer-Lambert law, light attenuation inside tissues is exponential. The slope of this exponential attenuation is proportional to the total attenuation coefficient of ballistic photons ($\mu_t = \mu_s + \mu_a$, where μ_s is the scattering and μ_a is the absorption coefficients, respectively). Because $\mu_a \ll \mu_s$ for tissues in the NIR (15), the exponential attenuation is proportional to the scattering coefficient. Only ballistic photons backscattered to the OCT system contribute to the OCT image; therefore, by analyzing the exponential profile of light attenuation detected by the OCT system, one can obtain information on tissue scattering properties.

Tissue scattering properties are highly dependent on the ratio of the refractive index of scattering centers (cell membranes, cellular components, and protein aggregates), n_s, to the refractive index of the interstitial fluid (ISF), n_{ISF}:

$$\Delta n \equiv \frac{n_s}{n_{ISF}}$$

Raising the tissue glucose concentration increases n_{ISF} by 1.52×10^{-5} per each 10 mg/dl (16), decreases the scattering coefficient (μ_s) of tissues, and decreases the refractive index mismatch:

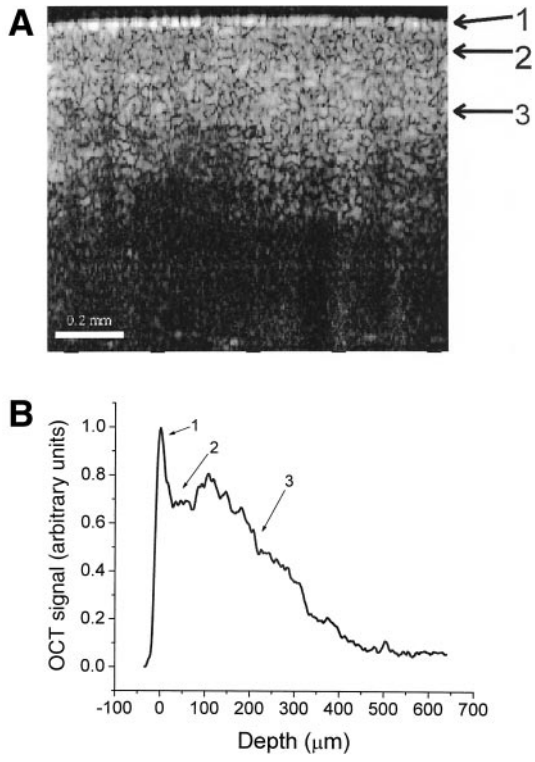

Figure 2—A*: Typical OCT image obtained from skin of a volunteer.* B*: Corresponding 1-D OCT signal. 1, stratum corneum; 2, prickle-cells layer; 3, dermis.*

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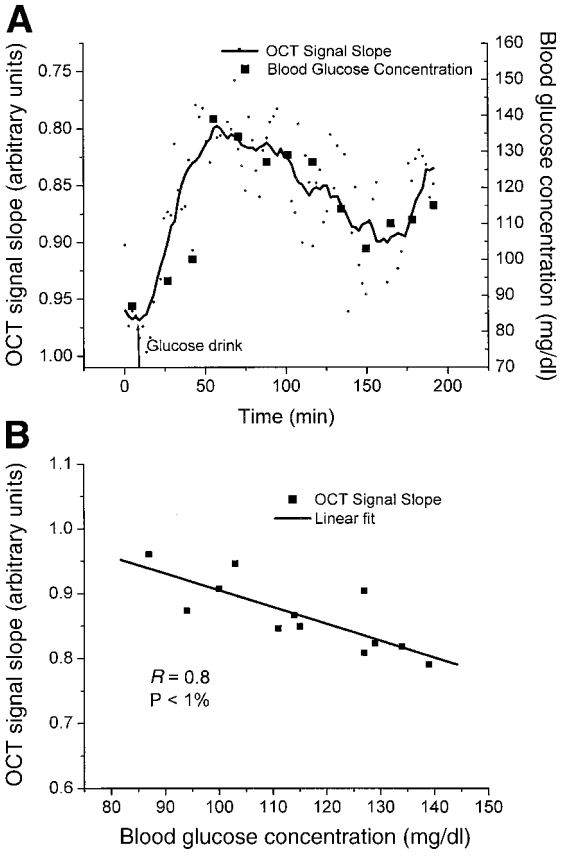

Figure 3—A*: Slope of OCT signals (plotted in the inverted scale) and corresponding blood glucose concentrations obtained from a healthy volunteer. The blood glucose concentration was measured every 15 min. Dots represent the OCT signal slope (in arbitrary units), and the black line represents the fit of the data points.* ■*, actual blood glucose concentrations.* B*: Slope of OCT signals versus blood glucose concentration for the data shown in* A. R*, correlation coefficient. Dots represent the OCT signal slope, and the line represents the linear fit of the OCT data points.*

$$\Delta n \equiv \frac{n_s}{n_{ISF} + 1.52 \times 10^{-5}/10\ mg/dl}$$

These glucose-induced changes in the tissue scattering coefficient can potentially be detected with the OCT system.

High resolution of the OCT technique and scanning depth up to 1 mm allow for measurement of tissue scattering properties from a specific layer in skin. For example, the human skin has three major layers: a dead keratinized layer of squames (stratum corneum of the epidermis), a prickle-cells layer (epidermis), and a connective tissue of dermis, which is the only layer containing a developed blood microvessel network. Because glucose concentration in the ISF is closely related to the blood glucose concentration, one can expect glucose-induced changes in OCT signal detected from the dermis area of the skin. High resolution and coherent light detection in the OCT technique allows sensitive and direct probing of a tissue layer in dermis without influence of other tissue layers on the OCT signal. In contrast, signals obtained by standard optical techniques (such as diffuse reflectance spectroscopy) are integrated over the entire photon path, which includes many tissue layers.

Our previous studies performed in tissue phantoms and animals in vivo with an OCT system showed high accuracy of measurements of changes in the scattering coefficient in tissue phantoms and a good correlation between changes in glucose concentration and the OCT signal slope in animals (17, 18). In this pilot study, we tested the feasibility of noninvasive glucose monitoring with this OCT system in healthy human subjects.

RESEARCH DESIGN AND METHODS

Experimental setup

In these studies, we used an OCT system with a wavelength of 1,300 nm, output power of ~0.3 mW, and in-depth and lateral resolution of 10 and 14 μm, respectively. Schematics of our experimental setup used in this study is depicted in Fig. 1. Light from the OCT system was delivered to the skin using a single-mode optical fiber. A specially designed optical fiber holder was attached to the subject's forearm using medical double-sided adhesive tape. Lateral and in-depth scanning was ~5 and 1 mm, respectively. In-depth scans were averaged five to seven times. Single lateral scans were accomplished every 15–25 s. The operation of the OCT scanner was completely automated and controlled by a portable personal computer (PC). Altogether, ~500 2-D OCT images were obtained in each experiment and stored in the PC for further processing.

Study subjects

A total of 15 healthy subjects (8 men and 7 women) aged 18 years or older (mean age 49 years) were studied in 18 clinical experiments. The subjects were in good health, took no medication, and were randomly selected from different racial groups. The study protocol was approved by the institutional review board of the University of Texas Medical Branch. A signed informed consent was obtained from all subjects.

Experimental protocol

Standard oral glucose tolerance test (OGTT) using 75 g of glucose was performed in all volunteers starting at 8:00 A.M. (time = 0) after overnight fast. The duration of each experiment was ~190–200 min (10–20 min for baseline recording and 180 min after administration of the glucose solution). OCT images were taken from the left forearm. During the measurement, the volunteers were asked to remain still to minimize motion artifacts, and food and drinks were not permitted. Two subjects were excluded from the study because they were not able to complete the experiment without a break. Whole-blood samples were serially drawn at 5- or 15-min intervals during the experiment from the right forearm using a catheter inserted into the subject's

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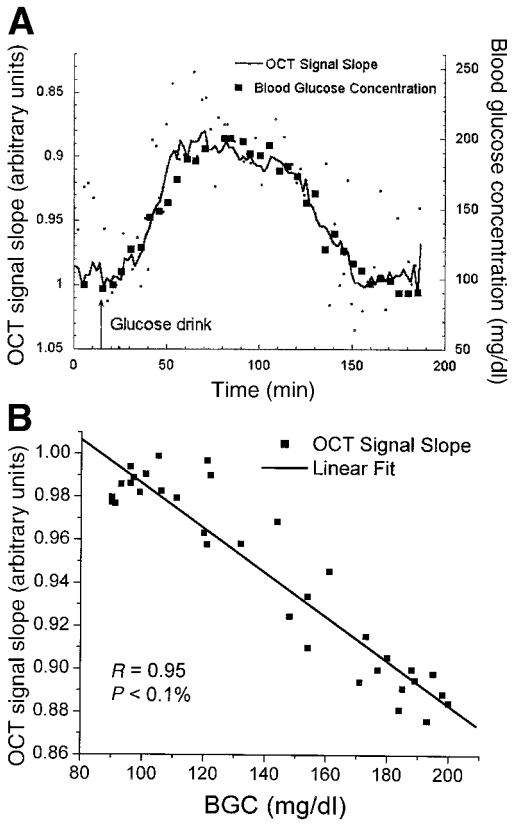

Figure 4—A*: Slope of OCT signals (plotted in the inverted scale) and corresponding blood glucose concentrations obtained from another healthy volunteer. The blood glucose concentration was measured every 5 min. Dots represent the OCT signal slope (in arbitrary units), and the black line represents the fit of the data points.* ■*, actual blood glucose concentrations.* B*: Slope of OCT signals versus blood glucose concentration (BGC) for the data shown in* A. R*, correlation coefficient. Dots represent the OCT signal slope, and the line represents the linear fit of the OCT data points.*

vein. The plasma glucose concentration was measured using a laboratory blood glucose meter (Vitros 950; Ortho-Clinical Diagnostics, Raritan, NJ).

Analytical procedures

All data processing was performed using a specially designed program written in Microsoft Visual C++ 6.0. After each experiment, the 2-D images were averaged into a single curve to obtain a one-dimensional (1-D) distribution of light in depth. The 1-D distributions were plotted in a logarithmic scale as a function of depth for further analysis. A linear fit of the slope of this distribution at different depths was performed by using the least-squares method. The OCT signal slope was calculated at different depths to obtain the best correlation between the actual blood glucose concentration and the slope of the OCT signal. The best correlation was obtained in the range from 200 to 600 μm. Slopes of four consecutive OCT signals were averaged, normalized, and plotted as a function of time or as a function of actual blood glucose concentration.

RESULTS — A total of 426 blood glucose measurements were performed using blood chemical analysis, and 8,437 OCT images and corresponding signals were recorded and processed in all of these experiments.

Figure 2 shows a typical OCT 2-D image obtained from the skin of a volunteer (Fig. 2*A*) and a corresponding OCT signal in logarithmic scale as a function of depth (Fig. 2*B*). Major skin layers are easily distinguishable and marked on both the image and the OCT signal. Two representative results of our study are shown in Figs. 3 and 4. The slope of OCT signals is plotted in the inverse scale. The blood glucose concentration was measured every 15 and 5 min (Figs. 3*A* and 4*A*, respectively) during the experiments. The decrease and increase of the OCT signal slope followed changes in the blood glucose concentration. The slope was calculated at a depth of 550–600 μm (Fig. 3) and 380–500 μm (Fig. 4). The slope changed significantly ~17% with the changes in glucose concentration, from 90 to 140 mg/dl, in one volunteer and ~15% with the changes in glucose concentration, from 100 to 200 mg/dl, in the other volunteer.

Corresponding dependencies of the OCT signal slope on measured blood glucose concentration are presented in Figs. 3*B* and 4*B*, respectively. The blood glucose concentration was measured 12 times (Fig. 3*B*) and 35 times (Fig. 4*B*) during 3 h, and corresponding slopes of OCT signals were calculated. Changes of 2 and 1.2% in the OCT slope per 10 mg/dl were observed in these experiments (Figs. 3*B* and 4*B*, respectively). The correlation coefficients were equal to 0.8 and 0.95, and calculated *P* values were <1 and 0.1% in Figs. 3*B* and 4*B*, respectively. Data obtained from other volunteers (not shown) demonstrated an average 1.9% change in the OCT slope per 10 mg/dl.

CONCLUSIONS — Results of our first clinical studies performed on healthy volunteers demonstrated good correlation between changes in the slope of noninvasively measured OCT signals and actual blood glucose concentration in normal subjects during an OGTT. On average, the slope changed 1.9% per 10 mg/dl in these studies. The results of these tests are in good agreement with those obtained in our animal studies (17,18).

The major advantages of the OCT technique for blood glucose monitoring in comparison with previously proposed optical techniques are: *1*) the high resolution, and *2*) coherent detection of backscattered photons. These unique characteristics permit measurements of tissue optical properties with high accuracy, sensitivity, and resolution. The glucose-induced changes in the OCT signal slope obtained in our experiments were due to: *1*) the capability of the OCT technique to monitor tissue optical properties of specific layers in tissues without unwanted signal from other layers and *2*) small refractive index mismatch between the cell membranes and components and the ISF in the dermis at the wavelength of 1.3 μm.

Our clinical studies in normal subjects demonstrated correlation of the

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OCT signal slope with blood glucose concentration at the depth of 200–600 μm during OGTT. For measurements performed in layers of epidermis and upper dermis, either they did not show changes in the OCT signal slope at variations of blood glucose concentration, or the changes were very weak (data not shown). Most likely, this is due to a gradient of glucose concentration from dermal blood microvessels to the stratum corneum. Thus, sensitivity and accuracy of the OCT measurements of blood glucose concentration would be maximal in lower dermis area.

Fluctuation of data points obtained in our experiments is mostly caused by motion artifacts and the tissue inheterogeneity. Our next studies will be focused on development of new algorithms of OCT image recording, averaging, and signal processing in order to improve accuracy of noninvasive glucose monitoring with the OCT technique. Different physiological and environmental conditions could alter tissue scattering properties and, therefore, slope of OCT signals. Influence of glucose as an osmolyte capable of changing the size of tissue components, tissue heterogeneity, motion artifacts, temperature drift, blood pressure, and heart rate on OCT signal slope will be evaluated in our future studies. Our preliminary studies on influence of other meal-derived osmolytes on specificity of OCT-based glucose sensor indicate that the maximal possible changes in scattering coefficient induced by these substances are much less than that produced by glucose. Although OCT systems are likely to need calibration with invasive glucose sensors, they may dramatically reduce the number of invasive measurements and provide continuous monitoring of the blood glucose concentration.

The results of our pilot study showed that the OCT technique is capable of noninvasive, real-time, and sensitive monitoring of the blood glucose concentration in human subjects during an OGTT. Further studies with a larger number of subjects including diabetic subjects are planned to validate these preliminary results.

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