Noninvasive monitoring of glucose concentration with optical coherence tomography

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We have proposed a tested in tissue phantoms and *in vivo* a novel sensor based on optical coherence tomography (OCT) for noninvasive and continuous monitoring of blood glucose concentration. OCT images were obtained from pig and rabbit skin before and after glucose administration. Slopes of OCT signals decreased substantially (~40% in tissues *in vivo*) and linearly with the increase of blood glucose concentration from 4 to 30 mM, typical for normal and diabetic subjects. Phantom studies demonstrated 1% accuracy of scattering-coefficient measurement. Our theoretical and experimental studies suggest that glucose concentration can potentially be measured noninvasively with high sensitivity and accuracy with OCT systems. © 2001 Optical Society of America

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Approximately 14 million people in the United States (5% of the population) and more than 140 million people worldwide suffer from diabetes mellitus,[1] a chronic systemic metabolic disease. Control of this disease includes daily self-monitoring of blood glucose by use of a finger puncture several times a day to obtain a droplet of blood for further chemical analysis. This procedure is invasive, inconvenient, and unpleasant for diabetics, often leading to poor patient compliance. In the past two decades, significant efforts have been devoted to develop noninvasive techniques to monitor blood glucose concentration by use of various optical approaches,[2] including near-infrared and mid-infrared absorption spectroscopy, near-infrared scattering measurements, polarimetry, Raman spectroscopy, and photoacoustics. At present, the sensitivity and specificity of glucose-concentration measurements with these techniques are limited at clinically relevant levels.

It is well known that an increase of glucose concentration decreases the scattering coefficient of tissues and tissue phantoms.[3–5] The scattering coefficient, μ_s, and the reduced scattering coefficient, μ_s', are dependent on the mismatch of the refractive index, n, of the extracellular fluid (ECF) and the cellular membranes. In the near-infrared spectral range the refractive index of the ECF is 1.348–1.352,[6,7] whereas the refractive index of the cellular membranes and protein aggregates is in the range 1.350–1.460.[7,8] Adding glucose to blood will raise the refractive index of the ECF and will consequently decrease the scattering coefficient of the tissue as a whole. This effect was demonstrated in tissue-simulating phantoms[3] and *in vivo* by use of reflectance-measurement systems.[4] Although the results of these studies are encouraging, detection of diffusively scattered photons results in low sensitivity and accuracy of glucose-concentration measurements because of integration of the signal over the entire optical path in optically thick structures such as human skin.

A novel technique for high-resolution imaging of tissues, optical coherence tomography (OCT), was proposed by Fujimoto and co-workers in 1991[9] and is being actively developed by several research groups.[10] OCT systems use an interferometer in which light in one arm is aimed into the objects that are to be imaged. Light that is coherently backscattered from structures within the tissue is collected and interfered with the light from the reference arm. The systems use a superluminescent diode, a light source with low coherence that allows in-depth resolution of ~10 μm or even less at a depth of as much as 1 mm.

We propose using OCT for noninvasive glucose monitoring based on measurement and analysis of coherently scattered light from specific layers of tissues (e.g., skin, mucosa, eye tissues). The high resolution of the OCT technique may allow high sensitivity, accuracy, and specificity of glucose-concentration monitoring because the technique permits precise measurements of glucose-induced changes in the scattering coefficient from the layer of interest. Coherent detection of the backscattered light may eliminate the influence of changes in the optical properties of surrounding layers of tissue. The aims of the study reported in this Letter were (1) to determine the sensitivity of the OCT technique to changes in glucose concentration in tissue phantoms and (2) to estimate changes in OCT signals as a result of blood glucose fluctuations *in vivo* in animal models.

Two OCT systems (output power, 0.5 mW) with wavelengths of 830 and 1300 nm were used in this study. $X-Z$ transverse scanning was ~1 cm and was performed every 3 s. Positions of the infrared beams were tracked by use of a 640-nm cw diode beam, which travels together with the infrared beams. The operation of the OCT scanner was completely

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automated and controlled by a portable personal computer. We averaged two-dimensional intensity distributions from each image into a single curve to obtain a one-dimensional distribution (OCT signals) of light in depth on a logarithmic scale. The linear fit of the slope of this distribution is proportional to the attenuation coefficient of ballistic photons, $\mu_t = \mu_a + \mu_s$ in the samples, where μ_a is the absorption coefficient and μ_s is the scattering coefficient. Since $\mu_a \ll \mu_s$ in the near-infrared spectral range, the change in the slope is proportional to the change in the scattering coefficient and, therefore, to the change in the refractive index. At least five OCT signals were obtained for each data point. Polystyrene microspheres ($n = 1.57$; diameter, 0.76 μm) and naphthol green were used as scatterers and absorbers, respectively, in aqueous solutions for the phantom studies to provide scattering ($\mu_s = 100\ \mathrm{cm}^{-1}$) and absorption ($\mu_a = 1\ \mathrm{cm}^{-1}$) coefficients that are typical for tissues in the near-infrared spectral range. Six phantoms with the same concentration of polystyrene microspheres and naphthol green and different concentrations of D-glucose (0, 20, 40, 60, 80, and 100 mM) were measured in a quartz cuvette with a thickness of 5 mm.

Bolus (rapid) glucose-injection and glucose-clamping experiments were performed in four hairless Yucatan micropigs (best model for human skin[11]) and six New Zealand rabbits. All procedures with animals were performed according to a protocol approved by the Institutional Animal Use and Care Committee of the University of Texas Medical Branch. OCT images were taken from the dorsal area (micropigs) or the inner area of the right ear (rabbits). Blood glucose concentration was monitored with a Beckman glucose analyzer or with a standard glucometer (One touch, Johnson&Johnson). Blood samples were taken from the right femoral vein, and glucose solutions were injected in a left ear vein. We positioned OCT probes directly on the surface of the skin with a special holder to minimize motion artifacts.

Mie theory[12] was applied to predict changes in scattering coefficient, μ_s, and scattering efficiency, Q_{sca}, as a function of glucose concentration for the phantoms and tissues. An algorithm given by Bohren and Huffman[13] was applied to polystyrene microspheres (diameter, 0.76 μm) in aqueous media and cells (diameter, 15 μm) in the ECF. The wavelength dependence of the refractive index of water, n, is $n(\lambda) = n_0 + (n_2/\lambda^2) + (n_4/\lambda^4) + (n_6/\lambda^6)$, where λ is in nanometers. The following fitting parameters were used: $n_0 = 1.3199$, $n_2 = 6.878 \times 10^3$, $n_4 = -1.132 \times 10^9$, $n_6 = 1.11 \times 10^{14}$, and $n_0 = 1.5626$ for water microspheres and $n_2 = 1.169 \times 10^4$, $n_4 = -1.125 \times 10^9$, $n_6 = 1.72 \times 10^4$ for polystyrene microspheres.[7] The relative change of refractive index as a function of glucose concentration is $\Delta n = 2.73 \times 10^{-5}$ per 1 mM glucose.[5]

The slope of the OCT signal as a function of glucose concentration in the phantoms is presented in Fig. 1. The figure also shows calculations of the scattering coefficient that were performed by use of Mie theory. This figure demonstrates that the decrease of the OCT slope is equal to 4.5% in the range of glucose concentration from 0 to 100 mM and is in good agreement with calculations performed with Mie theory. The error bars show the calculated standard deviation of the OCT slope in these experiments. The data demonstrate that the OCT systems are capable of measurement of scattering coefficient with high accuracy of ~1% and detect small changes in the scattering coefficient of a turbid medium that are induced by fluctuations in glucose concentration.

Inverted slope (1/slope) of the OCT signal recorded from the rabbit skin and corresponding blood glucose concentrations measured at different time during the bolus injection experiment are shown in Fig. 2. The best correlation between actual blood glucose concentration and the inverted slope of the OCT signal was found at a depth of 150 to 200 μm. Our OCT systems provided reliable slope determination in this range. Bolus glucose injection can induce a physiological response in animals as a result of rapid changes in blood glucose concentration (changes in, e.g., cell volume, blood vessel diameter). In another study we

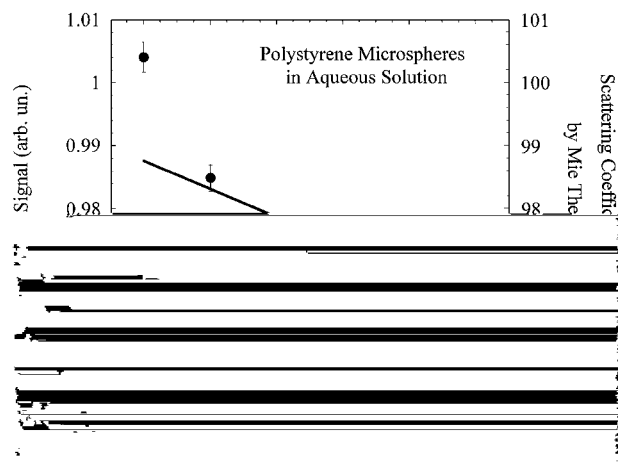

Fig. 1. Slope of OCT signal (mean ± standard deviation) and scattering coefficient (line) as a function of glucose concentration in the aqueous solution of polystyrene microspheres.

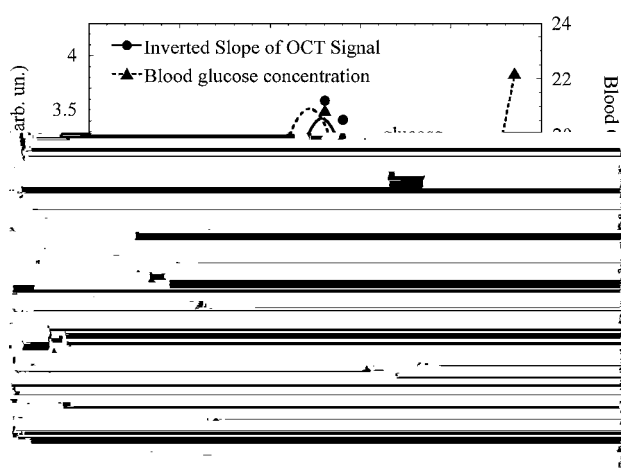

Fig. 2. Inverted slope of OCT signals (recorded from rabbit ears) and blood glucose concentration measured at different times after bolus glucose injections.