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Correlation between blood glucose concentration in diabetics and noninvasively measured tissue optical scattering coefficient

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Received November 13, 1996

Diabetics would benefit greatly from a device capable of providing continuous noninvasive monitoring of their blood glucose levels. The optical scattering coefficient of tissue depends on the concentration of glucose in the extracellular fluid. A feasibility study was performed to evaluate the sensitivity of the tissue reduced scattering coefficient in response to step changes in the blood glucose levels of diabetic volunteers. Estimates of the scattering coefficient were based on measurements of the diffuse reflectance on the skin at distances of 1–10 mm from a point source. A correlation was observed between step changes in blood glucose concentration and tissue reduced scattering coefficient in 30 out of 41 subjects measured. © 1997 Optical Society of America

In 1993 the Diabetes Control and Complications Trial Research group reported the results of a long-term study that showed that tighter control of blood glucose in insulin-dependent diabetics reduced the severity of long-term complications such as retinopathy and nephropathy.[1] Many insulin-dependent diabetics rely on self-monitoring of blood glucose for the proper regulation of an intensive insulin therapy program. A small blood sample, which one obtains by lancing a finger, is placed on a reactive test strip, and the resulting enzymatic color change is either compared with a color chart or read by a meter. This procedure is inconvenient and unpleasant for diabetics, often leading to poor patient compliance and inadequate blood glucose monitoring and control.

Noninvasive monitoring by relation of the optical phenomenon of light scattering in tissue to the blood glucose concentration may be possible. The reduced scattering coefficient μ_s' of tissue is dependent on the refractive-index mismatch between the extracellular fluid and the cellular membranes. An increase in the glucose concentration of the extracellular fluid will increase its refractive index. If the refractive index of the scatterers remains the same and is higher than the refractive index of the extracellular fluid, the refractive-index mismatch is reduced, and the scattering coefficient is also reduced. Kohl *et al.*[2] observed this effect in tissue-simulating phantoms. Using mean values of refractive indices of selected human tissues, they predicted a decrease in μ_s' of 0.05% to 0.1%/mM change in glucose for adipose and muscle tissue. A larger effect was demonstrated by Maier *et al.*,[3] using a frequency-domain reflectance system on the thigh of a normal volunteer. During a standard glucose tolerance test they observed a decrease in μ_s' of 2.1% for an increase in blood glucose concentration of 3.6 mM. It should be noted that the glucose effect can be further complicated by changes in the intracellular refractive index and by changes in cell size induced by osmolarity changes. Liu *et al.*[4] published a theoretical analysis supported by experimental results in animal tissues demonstrating the influence of these variables. Their research showed that under certain conditions an increase in glucose concentration in the extracellular fluid can result in an increase in μ_s'.

65 mg/dl

In this Letter we describe another optical technique for measurement of μ_s' that potentially could be used for continuous, noninvasive monitoring of blood glucose levels. Spatially resolved diffuse reflectance has been used successfully to measure optical properties both in tissue-simulating phantoms and *in vivo*.[5–8] In this technique a narrow beam of light is directed through the tissue surface, and diffusely reflected light is collected at several distances from the entry point through

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the same surface. One can estimate the absorption and reduced scattering coefficients by fitting a diffusion model of light propagation to the reflectance-versus-distance data.[9,10]

A multichannel CCD-based detection system was used to measure the tissue reflectance. The surface probe housed a source fiber and 8 or 16 detection fibers with core diameters of 400 μm (N.A. 0.4) or 200 μm (N.A. 0.22), respectively, situated at distances between 1 and 10 mm from the source fiber. The probe face was constructed of black nylon that was polished after the fibers were epoxied in place. Light from a broadband quartz-tungsten-halogen light source (Oriel Instruments) was coupled to the source fiber, and an imaging spectrometer (Kaiser Systems) was used to form a spectrum from each detector fiber on a two-dimensional thermoelectrically cooled CCD (Princeton Instruments). In this way spectral and spatial information were obtained simultaneously. The useful wavelength range was limited by the CCD quantum efficiency and the spectrometer grating efficiency to approximately 600–900 nm. The data were collected with a P75 PC (Dell) that used a Windows based spectroscopy software package (Princeton Instruments). The response of each detector channel was corrected for differences in fiber transmission, CCD sensitivity, and spectrometer optics. We obtained the relative tissue reflectance by multiplying the measured signal by the appropriate calibration factor.

A neural network was used to extract optical properties from the reflectance data as described in detail in Refs. 9 and 10. A training set was obtained by use of the diffusion model to calculate the reflectance at the actual measurement distances for randomly selected combinations of absorption coefficient (μ_a) and μ_s' in the range appropriate for skin. The model assumed a matched refractive index at the tissue–probe boundary. The trained network provided a rapid data-reduction method, but similar results were also obtained by more conventional nonlinear least-squares fitting of the diffusion model[9] to the reflectance data.

We assessed the stability of the apparatus by performing reflectance measurements on a tissue-simulating phantom for several hours. The relative standard deviation in μ_s' over a 4-h period was typically 0.05%. *In vivo* stability measurements were also performed with healthy volunteers in which diffuse reflectance was measured continuously over a 4-h period. These results often showed a slow upward drift in μ_s' during the first 30 min of measurement of up to 5%. For 30 normal volunteers the relative standard deviation in μ_s' over the most stable 1-h period was 0.28%.

Individuals with insulin-dependent diabetes mellitus were selected for the study. Volunteers lay in a nearly horizontal supine position, and the probe was applied to the abdomen with a double-sided transparent medical adhesive (Adhesive Research, Inc.). The measurement location was usually shaved before the device was affixed, and regions of visible heterogeneity were avoided. During the measurement the volunteer remained as still as possible to avoid artifacts from movement, and food and drink were not permitted. Reflectance measurements were collected at 15-s intervals for ~5 h, and skin and room temperature were monitored throughout the course of the experiment. Informed consent was obtained from all volunteers in the study, and the protocol was approved by the hospital ethics committee.

For the diabetic study the blood glucose concentration of the volunteer was clamped at fixed levels with a Biostator[11] that also continuously recorded the blood glucose concentration. The clamping protocol consisted of a series of step changes in blood glucose concentration from nominal levels of 5 to 14 mM and back to 5 mM. We induced high blood glucose levels by administering a bolus of glucose, and those levels were held for approximately 45–60 min. A bolus of insulin was administered at the end of the elevated blood glucose step to reduce the blood glucose concentration quickly. The blood glucose was held at the initial concentration (5 mM) for at least 1 h before we began the clamping steps.

The time evolution of μ_s' was compared with the monitored blood glucose concentration measured for each individual. Figures 1–3 show the results at 650 nm for three clamping experiments on three individuals in which a series of 1, 2, or 3 blood glucose steps were induced. The scattering coefficient is plotted on a reversed scale to highlight the correlation. The only form of data smoothing applied to these results was integration of the reflectance over a wavelength interval of 4 nm.

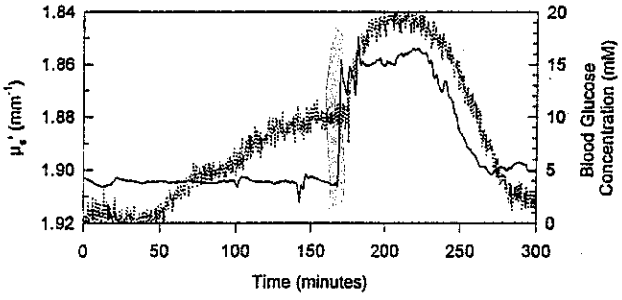

Fig. 1. Reduced scattering coefficient at 650 nm (dots) and blood glucose concentration (curve) measured on a diabetic volunteer during a single-step clamping experiment. The left ordinate scale is reversed to emphasize the correlation between the blood glucose concentration and the scattering coefficient.

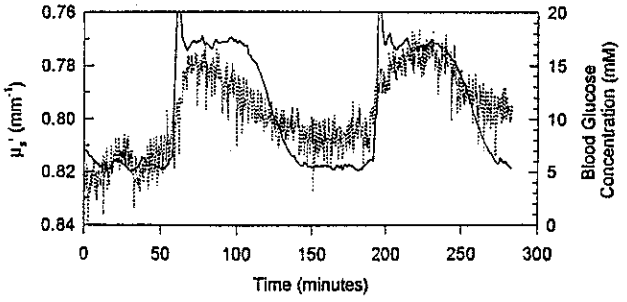

Fig. 2. Reduced scattering coefficient at 650 nm (dots) and blood glucose concentration (curve) measured on a diabetic volunteer during a double-step clamping experiment.