Possible correlation between blood glucose concentration and the reduced scattering coefficient of tissues in the near infrared

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Received September 29, 1994

Tissue glucose levels affect the refractive index of the extracellular fluid. The difference in refractive index between the extracellular fluid and the cellular components plays a role in determining the reduced scattering coefficient ($\mu_r'$) of tissue. Hence a physical correlation may exist between the reduced scattering coefficient and glucose concentration. We have designed and constructed a frequency-domain near-infrared tissue spectrometer capable of measuring the reduced scattering coefficient of tissue with enough precision to detect changes in glucose levels in the physiological and pathological range.

In this Letter we investigate modifications of light transport through tissues as a result of changes in glucose concentration. We focus our attention on near-infrared light because tissue absorption in this spectral region is low, leading to harmless penetration of light deep into the tissue. Recently we developed a sensitive frequency-domain near-infrared tissue spectrometer capable of separately measuring reduced scattering ($\mu_r'$) and absorption ($\mu_a$) coefficients in tissues. We can independently assess the effect of glucose concentration on the absorption and scattering properties of tissues. The method is based on measurement of the product of the reduced scattering coefficient and the mean index of refraction of tissue ($n$) at a single wavelength (850 nm). We propose a model that correlates this product ($n\mu_r'$) to changes in the refractive index of the blood plasma and interstitial fluid (together known as the extracellular fluid (ECF)).

Light scattering occurs in tissues because of the mismatch of index of refraction between the ECF and the membranes of the cells composing the tissue. The index of refraction of ECF ($n_{ECF}$) varies with dissolved sugar concentration, whereas the index of the cellular membranes ($n_{cell}$) is assumed to remain relatively constant. In the near infrared the index of refraction of the ECF is $n_{ECF} \approx 1.348-1.352$, whereas the index of refraction of the cellular membranes and protein aggregates is in the range $n_{cell} \approx 1.350-1.460$. Adding glucose to blood will raise the refractive index of the ECF, which will cause a change in the scattering characteristic of the tissue as a whole. Our approach is based on the principle that physiological changes in the glucose concentration in the ECF can cause measurable changes in the product of the reduced scattering coefficient of the tissue and the mean refractive index of the tissue ($n\mu_r'$).

The in vitro experiment is described as follows: we measured the product $n\mu_r'$ at 850 nm of a Liposyn–glucose suspension (1.5% lipid solid content) as a function of glucose concentration, using a previously described frequency-domain technique. Briefly, this technique involves placing an intensity-modulated light source deep in the medium to be studied. The phase and the intensity of the photon-density wave generated by this source are measured with high precision at several source–detector separations. These measurements are combined with equations analytically derived from linear transport theory to yield the ratio of the absorption coefficient to the mean refractive index ($\mu_a/n$) and the product of the mean refractive index and the reduced scattering coefficient ($n\mu_r'$) characteristic of the medium.

The light source was a light-emitting diode with a peak wavelength of 850 nm. Its intensity was modulated at a frequency of 120 MHz. Over the course of the experiment we incrementally added to the Liposyn suspension a previously prepared solution with a glucose concentration of 140 g/L and the same Liposyn concentration as the suspension. The results are shown in Fig. 1, in which the experimental data are plotted against glucose concentration (lower axis) and the refractive index of the water–glucose mixture (upper axis).

To compare the above experimental results with an appropriate model, we consider the reduced scattering coefficient $\mu_r' = \mu_s(1 - g)$, where $\mu_s$ is the microscopically derived scattering coefficient and $g$...

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Millions of diabetics around the world measure their blood glucose concentration several times a day. Essentially, all the current methods for glucose determination require patients to obtain blood by lancing a finger. They then perform a quantitative analysis of blood sugar by monitoring a chemical reaction with the blood sample. Reference 1 provides a brief review of the diverse minimally invasive approaches to monitoring blood glucose. Other ideas include sensors implanted subcutaneously, direct measurement of plasma index of refraction, and noninvasive chemometric analysis of tissue effective absorption spectra.

In this Letter we investigate modifications of light transport through tissues as a result of changes in glucose concentration. We focus our attention on near-infrared light because tissue absorption in this spectral region is low, leading to harmless penetration of light deep into the tissue. Recently we developed a sensitive frequency-domain near-infrared tissue spectrometer capable of separately measuring reduced scattering ($\mu_r'$) and absorption ($\mu_a$) coefficients in tissues. Using this instrument, we can independently assess the effect of glucose concentration on the absorption and scattering properties of tissues. The method is based on measurement of the product of the reduced scattering coefficient and the mean index of refraction of tissue ($n$) at a single wavelength (850 nm). We propose a model that correlates this product ($n\mu_r'$) to changes in the refractive index of the blood plasma and interstitial fluid (together known as the extracellular fluid (ECF)).

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To compare the above experimental results with an appropriate model, we consider the reduced scattering coefficient $\mu_r' = \mu_s(1 - g)$, where $\mu_s$ is the microscopically derived scattering coefficient and $g$...
is the average of the cosine of the scattering angle. Microscopically, Mie theory rigorously treats scattering by spherical scatterers of index of refraction \( n_1 \) suspended in a medium of index of refraction \( n_0 \). We employ the Rayleigh–Gans theory as an approximation to Mie theory to find the dependence of the reduced scattering coefficient on the indices of refraction \( n_1 \) and \( n_0 \). With this theory, which is appropriate when \( |n_1/n_0 - 1| \ll 1 \), the reduced scattering coefficient has the following dependence on the indices of refraction\(^{11,12} \):

\[
\mu_s' = K \left( \frac{n_1 - n_0}{n_0} \right)^2,
\]

where \( K \) is a proportionality factor related to particle size, wavelength, and particle density and includes \( g \).

The curve in Fig. 1 corresponds to a plot of this model for \( n \mu_s' \) (we assume that \( n \approx n_0 \)), where \( n_1 \) and \( n_0 \) are obtained from the CRC Handbook of Chemistry and Physics and are based on the type of fat in the suspension (soybean oil) and on the known glucose concentration, respectively\(^2 \).

We set \( n_1 = 1.465 \) and \( n_0 = 1.325 + 1.515 \times 10^{-6} \times [C] \), where \([C]\) is the concentration of glucose in milligrams per deciliter. For the curve in Fig. 1, \( K \) is equal to \( 1.30 \times 10^9 \) cm\(^{-1} \)

We stress that \( K \) is the only adjustable parameter in our application of Eq. (1). For a lipid emulsion similar to the one that we employed and in the absence of glucose, an experimentally derived formula verified by Mie theory calculations\(^{13} \) leads to a similar value for \( K \) of \( 1.25 \times 10^9 \) cm\(^{-1} \).

For the noninvasive in vivo measurement we used a previously described frequency-domain tissue spectrometer\(^5 \). Four light sources (light-emitting diodes with a peak wavelength of 850 nm) are placed at the skin surface to obtain measurements at several source–detector separations. We measured the response of a nondiabetic male subject to a glucose load of 1.75 g/kg body weight, as in a standard glucose tolerance test\(^{10} \) by continuously monitoring the product \( n \mu_s' \) measured on muscle tissue of the subject’s thigh. Instrument acquisition time was 30 s per data point. Informed consent of the subject and institutional review board approval were obtained before the experiment.

Simultaneously, we measured the subject’s blood glucose, using a home blood glucose monitor (One Touch, Johnson & Johnson) periodically throughout the experiment. The results of the optical measurement and of the home blood glucose monitor test are shown in Fig. 2. As the subject’s blood glucose rose, the reduced scattering coefficient decreased. Figure 3 shows the correlation plot obtained from the data of Fig. 2. A complete explanation of the results in the physiological system requires a sophisticated physical model. However, the simple Rayleigh–Gans model, which explains the in vitro experiment, can be used as a first step in the explanation of the in vivo results.

To this end we assume a suspending medium with refractive index \( n_{ECF} \) that is close to the refractive index of the suspended scatterers, \( n_{cell} \). The index of refraction of the fluid changes only slightly [less than 0.05% (Ref. 3)] as a result of physiological changes in glucose concentration. If we let \( n_{ECF}(0) \) be the index of refraction of the ECF at a baseline physiological glucose concentration, we can write \( n_{ECF} = n_{ECF}(0) + \delta n \), with \( \delta n \ll n_{ECF}(0) \). By replacement of the Rayleigh–Gans parameters \( K, n_0, \) and \( n_1 \) with the corresponding tissue parameters \( K_T, n_{ECF}, \) and \( n_{cell} \), respectively, Eq. (1) becomes

\[
\frac{n \mu_s'}{n_{ECF}(0)} = \frac{K_T(n_{cell} - n_{ECF}(0) - \delta n)}{n_{ECF}(0)},
\]

where \( \delta n \) is neglected in the denominator because it is much less than \( n_{ECF}(0) \) and we assume \( n \approx n_{ECF}(0) \).
Our claims for the correlation between blood glucose concentration and reduced scattering coefficient are based on a simple physical model for light transport in tissues. This model accounts for the changes of reduced scattering coefficient to changes in the refractive index of ECF. The novelty of our method lies in exploiting the better match of index of refraction between ECF and cellular materials caused by an increase in glucose concentration. An increase of glucose concentration in the physiological range decreases the total amount of tissue scattering. Clearly our approach assumes a value for the baseline and, in this sense, can provide only a relative measurement that permits monitoring glucose levels over an extended period of time. Key factors for the success of this approach are the precision of the measurement of the reduced scattering coefficient and the separation of scattering changes from absorption changes, as obtained with our frequency-domain spectrometer. However, we observe that the physical model that we propose is only a possible explanation of the glucose-induced scattering effect.

Other physiological effects related to glucose concentration could account for the observed variations of the reduced scattering coefficient with time. Because glucose has low absorption at 850 nm relative to other tissue constituents the absorption coefficient is negligibly affected by glucose concentration. This was borne out in both the in vitro and the in vivo experiments that we conducted. Because the reduced scattering coefficient is more affected by changes of glucose concentration, the fact that scattering dominates the transport properties of near-infrared light in tissues is actually advantageous in refractive-index-based glucose monitoring. Provided that one can separate absorption and scattering effects, the highly scattered slightly absorbed near-infrared light employed in this technique is actually in the spectral region of choice.

During the course of our study we learned that other researchers are developing a similar approach to noninvasive glucose monitoring. Our research is supported by National Institutes of Health grants RR03155 and CA57092 and by the University of Illinois at Urbana-Champaign. We thank Albert Cerussi for help in performing the in vitro experiment.

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