Noninvasive Photonic-Crystal Material for Sensing Glucose in Tears

Most noninvasive (NI) methods for the determination of glucose either detect a small specific glucose signal or measure the effect of glucose on a tissue optical property (1, 2). A recent review identified the three main issues in NI glucose measurements as specificity, compartmentalization of glucose values, and calibration (1). This editorial discusses a photonic crystal method (3), with respect to these issues.

Asher’s group have developed a novel photonic sensing material that responds to glucose concentrations via diffraction of visible light. Polymerized crystalline colloidal arrays (PCCAs) are periodic crystalline lattices of polystyrene microspheres polymerized within thin hydrogel films (3–7). The arrays are brightly colored and act as diffraction gratings for white light according to the Bragg diffraction equation (4, 5):

\[ \Delta \lambda = \frac{n \times d}{\sin \theta} \]  

In Eq. 1, \( n \) is the refractive index of the system (medium, hydrogel, and colloids), \( d \) is the spacing between the diffracting planes, \( \lambda \) is the diffracted wavelength, and \( \theta \) is the glancing angle between the incident light and the diffracting planes. A change in electric charge in the glancing angle between the incident light and the diffracting planes. A change in electric charge in the polymer film can cause changes in the spacing, \( d \), and there is a subsequent wavelength shift, \( \Delta \lambda \), of the light reflected off the array.

Asher’s group have constructed a photonic glucose sensor in the form of thin acrylamide PCCA hydrogel films that contain glucose molecular recognition elements (3, 6, 7). Phenylboronic acid derivatives in the lattice bind glucose, causing a change in charge distribution and a blue shift, \( -\Delta \lambda \), in the diffracted light (3). In vitro experiments showed that \( \Delta \lambda \) responded to changes in glucose concentration with highest sensitivity at glucose concentrations <10 mmol/L (3, 6, 7). The magnitude of the blue shift decreased as a function of glucose concentration when glucose approached 20 mmol/L (3). This made the PCCAs suitable only for detection of the tear-glucose concentration, which is considerably lower than that of blood. The PCCA lattice shrinks as the glucose concentration increases (3) and possibly reaches a lower limit where minimal \( \Delta \lambda \) is observed. The authors conceive using the polymer film sensor as a contact lens that changes color according to the glucose concentration in tears.

Boronic acid fluorophores embedded in a commercial contact lens and immersed in glucose solutions undergo changes in fluorescence intensity and wavelength on binding to glucose (8). The fluorescent contact lens film has the highest sensitivity at low glucose concentrations, which correspond to those in tear fluid.

The novelty and the sensitivity of PCCAs at low glucose concentrations are the impetus for this editorial, in which I examine the contact lens construct as a NI glucose testing modality.

The detection method depends on interaction between glucose and a specific binding molecule. It will have a specificity advantage over near-infrared absorption and scattering methods, but successful application in vivo is awaited. The dynamic range is limited to the glucose concentration in tears (3). The reversibility of the \( \Delta \lambda \) change on a reverse in the change in glucose concentration must be demonstrated in animal models and in human volunteers.

Current patient care is based on measurement of glucose in venous blood or arterialized venous blood. NI methods attempt to determine glucose in other body fluids, such as in tissue interstitial fluid, eye vitreous fluid, or tears, as substitutes for venous or capillary blood glucose. NI-determined glucose values in any body compartment must track changes in blood glucose without a lag time (9). This may not be the case when changes in blood glucose concentrations are sudden and are of too large a magnitude to allow for equilibration between the vascular compartment and other body compartments (1, 9, 10). Even for blood glucose measurements, there are site-specific rates of increase and decrease in blood glucose values (10). Equilibration between glucose in the blood and in other body fluids is a controversial issue with widely different reported lag times (1). Alexeev et al. (3) propose using photonic contact lens sensors with tears as the body fluid. The relative concentrations and lag times between glucose concentrations in tears and in the vascular system will require detailed studies.

Tears are generated in the lachrymal glands, and external stimuli affect the rate of tear generation. There are limited reports on the relationship between tear and blood glucose concentrations. The relationship seems to depend on the sampling method for tears and the extent of eye irritation during sampling (11). Earlier tear-glucose studies were semiquantitative because the investigators used color strips, and they did not include glucose surge experiments.

Gassett et al. (12) showed that in an oral glucose tolerance test (OGTT), tear-glucose concentrations tracked blood glucose with a time lag (from graph) of ~20 min. The mean (SD) tear glucose value for 30 nondiabetic individuals was 0.24 (0.17) mmol/L, and that of blood was 4.4 (1.7) mmol/L (12).

Citing earlier studies, Van Haeringen (11) concluded that there was no significant increase in tear-glucose concentrations when blood glucose concentrations were >20 mmol/L, which he considered to indicate that the corneal and conjunctival epithelium acted as a barrier against glucose transfer from tissues into the tear fluid. Tissue fluid, and not the lachrymal gland fluid, contributed to the “tear glucose” after mechanically stimulated methods of collection, making the relationship between
tear glucose and blood glucose concentrations similar to that between blood glucose and tissue fluid (11).

Daum and Hill (13) reported a mean tear-glucose concentration of 0.42 (0.36) mmol/L for 12 nondiabetic individuals. The tear-glucose concentration generally tracked blood glucose during the day. Tear-glucose concentrations can be increased by mild abrasion of the conjunctival epithelium and exposure to hypotonic solutions. Nonmechanical stimuli that cause reflex tears, such as light flashes and noxious vapors, decrease tear-glucose concentrations (13). The authors of a recent study reported the result of an OGTT, without showing correlation data, as “the tear glucose levels maintained a more or less steady relationship with blood glucose level” (14).

With these limited reports on the relationship between tear and blood glucose, the critical test is measurement of ∆Λ for a PCCA as a function of blood glucose concentration in an animal model and/or human volunteers.

The presented PCCA data suggest a simple in vitro calibration of ∆Λ vs tear-glucose concentration in artificial tear fluid (3), but in vivo calibration must correlate ∆Λ with the blood glucose concentration. If lag times or other confounding factors are found, algorithms that account for these factors will be needed. The effects of eye irritation, lachrymating agents, and environment must be studied. It is important to decide whether the readout will be visual and semiquantitative, using color charts, or quantitative, using a spectrometric device. Although the simplicity of the calibration is quite encouraging, in vivo animal and human experiments are needed to address calibration issues, some of which are: How is the contact lens testing device to be calibrated? Is it a single-person calibration or multiple-person calibration? Will the readout device be calibrated by the manufacturer, or can the user calibrate it? What other inputs are required for the calibration?

The simplicity and novelty of this method are quite striking. In vivo animal and human experiments are needed to delineate the potential and the limitations of this interesting technology.

References

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