Overview of Non-Invasive Optical Glucose Monitoring Techniques

Overview of Non-Invasive Fluid Glucose Measurement Using Optical Techniques to Maintain Glucose Control in Diabetes Mellitus

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Background

Diabetes mellitus is a medical condition in which the body does not adequately produce the quantity or quality of insulin needed to maintain a normal circulating blood glucose. Insulin is a hormone that enables glucose (sugar) to enter the body's cells to be used for energy. Two types of diabetes are common. Type I is also known as Insulin Dependent Diabetes Mellitus (IDDM) and accounts for 5-10% of all cases. Type II or Non-Insulin Dependent Diabetes Mellitus (NIDDM) occurs in 90-95% of the diabetic population. In IDDM, the disease occurs in childhood and requires insulin doses to maintain life, in addition to healthy eating and exercise. NIDDM occurs later in life - perhaps after 40 years of age and may require insulin or be controllable with oral medication, weight loss, a nutritious diet and a regular exercise program.

It is estimated that diabetes afflicts nearly 16 million people in the United States and over 100 million people worldwide. Diabetes is the fourth leading cause of death by disease in the United States, killing more than 169,000 people each year [1]. Frequent self-monitoring of blood glucose is crucial for effective treatment and reduction of the morbidity and mortality of diabetes.

Diabetes can lead to severe complications over time, including blindness, kidney failure, heart failure, and peripheral neuropathy associated with limb pain, poor circulation, gangrene and subsequent amputation [2]. According to the American Diabetes Association (ADA) complications arising from diabetes cost the US health care system in excess of $45 billion. These complications are largely due to years of poor glucose control. The Diabetes Care and Complications Trial (DCCT) demonstrated that more frequent monitoring of blood glucose and insulin levels could prevent many of the long term complications of diabetes [3]. However, current blood (fingerstick) glucose tests are painful, inconvenient due to disruption of daily life, cause fear of hypoglycemia resulting from tighter glucose control and maybe difficult to perform in long term diabetic patients due to calluses on the fingers and poor circulation.

Thus, the average diabetic patient tests his/her blood glucose levels less than twice a day versus the recommended 4-7 times per day. A non-invasive method (fast, painless and convenient) for glucose monitoring could provide adequate control and greatly reduce the complications seen in these patients and consequently reduce health care costs.

Currently glucose measurements are done by pricking a finger and extracting a drop of blood which is applied to a test strip composed of chemicals sensitive to the glucose in the blood sample. An optical meter (glucometer) is
used to analyze the blood sample and gives a numerical glucose reading. The various types of glucometers sold usually cost less than $100 dollars or have been discounted greatly because of the purchase of expendable, one-use-only test strips. These strips cost 50 cents ($0.50), a modest cost if only a small use rate is required. A strip used every day costs about $183.00 per year for the diabetic that tests only one time a day. Those requiring multiple measurements (the elderly and children etc.) would easily have much higher yearly costs. The worldwide market for glucose monitoring products is expected to exceed 3 billion dollars by the year 2000. These figures and the revenue potential make development of the non-invasive glucose sensor a most sought after device.

But many technological and financial challenges and questions remain.

Ultimately, can the devices developed provide clinically meaningful and accurate measurements for all diabetics at a reasonable cost with sufficient financial return to the manufacturer?

**Types of Measurement Techniques**

Non-invasive glucose monitoring techniques can be grouped as subcutaneous, dermal, epidermal and combined dermal and epidermal glucose measurements.

Matrices other than blood under investigation include interstitial fluid, ocular fluids and sweat. Test sites being explored include finger tips, cuticle, finger web, forearm and ear lobe. Subcutaneous measurements include microdialysis, wick extraction, and implanted electrochemical or competitive fluorescence sensors. Microdialysis is also an investigational dermal and epidermal glucose measurement technique. Epidermal measurements can be obtained via infrared spectroscopy, as well. Combined dermal and epidermal fluid glucose measurements include extraction fluid techniques (iontophoresis, skin suction and suction effusion techniques) and optical techniques. The optical techniques include near infrared spectroscopy, infrared spectroscopy, raman spectroscopy, photoacoustic spectroscopy, scatter and polarization changes [4]. This overview is focused on a description of the optical techniques (Table 1) currently under development by diagnostic equipment manufacturers for glucose monitoring in diabetics- the fastest growing segment of diagnostic testing.

**Common Features of Non-Invasive Optical Techniques**

Non-invasive optical measurement of glucose is performed by focusing a beam of light onto the body. The light is modified by the tissue after transmission through the target area. An optical signature or fingerprint of the tissue content is produced by the diffuse light that escapes the tissue it has penetrated. The absorbance of light by the skin is due to its chemical components (i.e., water, hemoglobin, melanin, fat and glucose). The transmission of light at each wavelength is a function of thickness, color and structure of the skin, bone, blood and other material through which the light passes [4].

The glucose concentration can be determined by analyzing the optical signal changes in wavelength, polarization or intensity of light. The sample volume measured by these methods depends on the measurement site. The correlation with blood glucose is based on the percent of fluid sample that is interstitial, intracellular or capillary blood. Drs. Roe and Smoller [4] have devised the following example. The fluid viewed through the limb is 63% intracellular and 37% extracellular, of which 27% is interstitial and 10% plasma. A blood glucose value of 100mg/dl is equivalent to a tissue sample glucose average of 38mg/dl of which 26% is due to blood, 58% is due to interstitial fluid and 16% is due to intracellular fluid. What the tissue sample glucose means clinically in respect, to therapy is still under investigation.

Not only is the optical measurement dependent on concentration changes in all body compartments measured, but changes in the ratio of tissue fluids (as altered by activity level, diet or hormone fluctuations) and this, in turn, effects the glucose measurement. Problems also occur due to changes in the tissue after the original calibration and the lack of transferability of calibration from one part of the body to another. Tissue changes include: body fluid source of the blood supply for the body fluid being measured, medications that affect the ratio of tissue fluids, day-to-day changes in the vasculature, the aging process, diseases and the person’s metabolic activity.
<table>
<thead>
<tr>
<th>Technique</th>
<th>Definition</th>
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<tr>
<td>Near Infrared Spectroscopy (NIR)</td>
<td>Absorption or emission data in the 0.7 to 2.5 µm region of the spectrum are compared to known data for glucose.</td>
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<tr>
<td>Raman Spectroscopy</td>
<td>Laser light is used to induce emission from transitions near the level excited.</td>
</tr>
<tr>
<td>Photoacoustic Spectroscopy</td>
<td>Laser excitation of fluids is used to generate an acoustic response and a spectrum as the laser is tuned.</td>
</tr>
<tr>
<td>Scatter Changes</td>
<td>The scattering of light can be used to indicate a change in the material being examined.</td>
</tr>
<tr>
<td>Polarization Changes</td>
<td>The presence of glucose in a fluid is known to cause a polarization preference in the light transmitted.</td>
</tr>
<tr>
<td>Mid-Infrared Spectroscopy</td>
<td>Absorption or emission data in the 2.5 µm - 25 µm region are examined and used to quantitate glucose in a fluid.</td>
</tr>
</tbody>
</table>

*Limited to epidermal surface.

**Fluid Glucose Optical Measurement Strategies**

**Near Infrared Spectroscopy (NIR)**

Glucose produces one of the weakest NIR absorption signals per concentration unit of the body's major components. NIR spectroscopy glucose measurement enables investigation of tissue depths in the range of 1 to 100 millimeters with a general decrease in penetration depth as the wavelength value is increased. NIR transmission through an ear lobe, finger web and finger cuticle or reflected from the skin of the forearm and lip mucosa has been attempted in the NIR region between 1000nm to 2500nm. NIR diffuse reflectance measurements have been performed on the finger and cuticle have shown good correlation with blood glucose but 10% of the predictions are not clinically acceptable [5].

Diffuse reflectance studies of the inner lip also have shown good correlation with blood glucose and indicated a time lag of 10 minutes between blood glucose and the measurement signal [6]. Salivary glucose levels (a component of lip measurements) did not reflect blood glucose levels. Physical and chemical parameters such as variation in pressure, temperature, triglyceride and albumin interfere with glucose measurement. Errors can also occur due to environmental variations such as changes in temperature, humidity, skin hydration, carbon dioxide, and atmospheric pressure [4]. Extensive validation and testing of the glucose prediction equation is needed to determine if the glucose correlation is consistent in all clinically important conditions in all types of patients.

**Infrared Spectroscopy (IR)**

The IR glucose measurement systems at the epidermal surface enables investigation of tissue depths in the range of 10 to 50 micrometers at using a wavelength band in the IR region from 700 to 1000nm [7]. These systems do not measure glucose in the blood containing tissues. An attenuated total reflection technique has been used for oral mucosa, however, the drawbacks include glucose contamination of the measurement site by food and a highly variable saliva of low rate [8]. Assays using used whole blood as the sample matrix, are subject to interferences due to albumin, red cells and gamma globulin and changes in temperature and pH. Further, saliva glucose varies considerably and does not reflect blood glucose methods [4].

**Raman Spectroscopy**

Raman spectroscopy measures scattered light that has been influenced by the oscillation and rotation of the scatter. Various raman techniques have been attempted in blood, water, serum, and plasma solutions and the eye, but multiple problems remain before human studies can be performed. Analytical problems include, instability in
the laser wavelength and intensity, errors due to other chemicals in the tissue sample and long spectral acquisition times [4].

**Photoacoustic Spectroscopy**

Photoacoustic spectroscopy uses an optical beam to rapidly heat the sample and generate an acoustic pressure wave that can be measured by a microphone. The determination of glucose in blood [9], tissue phantoms [10] and humans [11] can provide greater sensitivity than conventional spectroscopy when specific physical parameters are favorable. Excellent correlation between the photoacoustic signal and blood glucose levels have been shown on index fingers of healthy and diabetic patients. The instrumentation is currently custom made, expensive and sensitive to environmental parameters. The technique is also subject to chemical interferences from biological molecules as well as physical interference from temperature and pressure changes.

**Scatter Changes**

Scatter measurement monitors the changes in tissue reduced scattering coefficient and is used for the determination of glucose in tissue phantoms and humans.

Increased glucose in the sample is proportional to an increase in the refractive index of the sample and thus the particle scattering properties of the sample are changed. Measurements on the abdomen of the diabetic patients showed excellent correlation between the scatter signal and blood glucose levels [12]. Many parameters contribute to a natural physiological drift of the scattering parameter. Methods are needed to compensate for the signal drift.

**Polarization Changes**

Although the change in optical signal by glucose is small, glucose is a good optical rotator. This characteristic has been used to conduct in-vitro glucose assays [13]. The intensity of light corresponds to the amount of light present. Skin is not a feasible site due to its high light scattering properties. The eye's aqueous humor has been suggested and solution measurements have been published. Use of multiple wavelengths have been shown to minimize the poor specificity of this technique. Other optically active substances will interfere, with the analysis as will variations in the temperature and pH of the sample.

**Conclusions, Challenges and Issues Requiring Further Study**

Diabetes mellitus is a complex group of syndromes that have in common a disturbance in the body's use of glucose, resulting in an elevated blood sugar. Once detected, “sugar diabetes” can be controlled by an appropriate regimen that should include diet therapy, a weight reduction program for those persons who are overweight, a program of exercise and insulin injections or oral drugs to lower blood glucose. Blood glucose monitoring by the patient and the physician is an important aspect in the control of the devastating complications (heart disease, blindness, kidney failure or amputations) due to the disease. There is no cure.

Intensive therapy and frequent glucose testing has numerous benefits. Dr. William Herman and his colleagues have determined that intensive therapy delays the time to first complication by about 15 years, blindness by about eight years and end-stage renal disease and lower extremity amputation by about six years. Further, intensive therapy prolongs the life of the diabetic by about five years at a cost of about $30,000 per life year gained [3].

With ever improving advances in diagnostic technology, the race for the next generation of bloodless, painless, accurate glucose instruments has begun.

However, many hurdles remain before these products reach the commercial marketplace.

Calibration of the instruments and validation of the results obtained by the optical methods under different environmental conditions and used by different patient populations (i.e., different ages, sizes and ethnic origins) must be performed. The devices may have to be calibrated to individual users.
Current instrumentation lacks specificity due to substantial chemical and physical interferences. The devices use multivariate regression analyses that convert the optical signal to a glucose concentration. Large amounts of data are used to build the glucose model and must take into consideration the concentration range, sampling environment and other factors involved in the analysis. First an instrument must be designed that accurately detects glucose concentration. Correlation and clinical interpretation of this value, in respect to the patient’s “true glucose” value, is imperative for optimum therapy and disease management.

Considerable progress has been made in the development of non-invasive glucose devices however, at this time, frequent testing using invasive blood glucose determination via fingerstick provides the best information for diabetes disease management. Industry spokespersons have said: “… anyone who can come up with a viable noninvasive or painless technique is going to make a lot of money. People’s lives are involved … and we don’t want to suggest that this technology is right around the corner. This is very tricky, difficult work.”[14].

References


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