Significance of research

Frequent measurement of blood glucose is essential for intensive glycaemic control. Fingerstick blood glucose measurement is the gold standard at that time. However, it may miss too many hypo- and hyperglycaemic episodes. The pain, inconvenience, and cost of fingerstick measurement limit the testing frequency.

There were some technologies proposed at that time to address these issues. One was to apply Near infrared (NIR) spectroscopy. ~~It allows blood glucose measurement in tissues by variations of light intensity, based on transmittance and reflectance.~~ However, detecting the spectroscopic signature of glucose in a complex overlapping spectrum of water, proteins, and other biomolecules is a challenging task. ~~The low sensitivity of glucose signal posed high demands on signaling processing algorithms and hardware sensitivity, inhibiting the commercialization of the technology in the early days.~~

The other type is implantable subcutaneous sensor. One product at that time could be inserted subcutaneously for up to 3 days and provide reading every 5 min. But the readings were not available to the patients in real time and ~~calibration needed to be done by physician using a profile of glucose level in last 3 days~~.

In this study, cygnus company developed a non-invasive glucose monitoring device called GlucoWatch for frequent measurement of blood glucose. The efficient data collected enables detection of patterns in glucose level for better glycaemic control. ~~Then, physicians could tailor a better insulin dosing scheme suitable for the patient's lifestyle.~~

Methods - principle

The GlucoWatch biographer is a wrist-watch device. The right photo shows what it looks like. The device has multiple layers from outside to inside. The front panel of the device is a display. Then the electronics include circuits to operate the amperometric biosensors and the iontophoresis function, a microprocessor to control the operation and process the signals. It has data memory to save glucose readings and a serial port for uploading the data to a PC. The next layer contains temperature and skin conductivity sensors to detect skin temperature fluctuations and perspiration, respectively and the disposable portion of the device called autosensor. The auto-sensor fits into the skin-side and comprises two identical sets of biosensor and iontophoresis electrodes, and two hydrogel discs. These hydrogel discs where glucose oxidase is dissolved into are to collect the glucose and catalyze the oxidation reaction. ~~serve as the biosensor electrolyte as well as the reservoirs where the glucose is collected. The glucose oxidase is dissolved into these hydrogel discs to catalyze the glucose oxidation reaction.~~ ~~at a concentration sufficient to eliminate glucose to produce an electric current signal on the biosensor~~.

Principle

The design of the biographer is shown in the figure. There are 3 technologies or steps integrated into the device for measuring glucose. 1) glucose sample extraction through reverse iontophoresis, 2) glucose sample measurement by amperometric biosensor and 3) data processing leading to display of the glucose reading. Overall, the 1st step uses iontophoresis electronics. The 2nd step involves both hydrogels and biosensor electronics, The 3rd needs the rest of things. ~~Note that there are two identical sets of biosensor and iontophoresis electrodes in each hydrogel for improving measurement which will be discussed later.~~

Principle (continue)

Let's dive into technologies step by step. First, the reverse iontophoresis for extracting blood glucose. A constant, low-level electrical current between two electrodes is applied onto the surface of the skin. The ions in the body can act as the charge carriers for this current to extract substances from within the body outward through the skin. Because the skin has negative charges at physiological pH, positively charged sodium ions are the major current carriers. The migration of sodium ions toward the iontophoretic cathode induces an electro-osmotic flow toward this electrode. Uncharged molecules, like glucose, are carried along by this electro-osmotic flow. In this way, glucose is preferentially extracted at the cathode. ~~Glucose transport correlated well with BG in a linear manner; however, the sensitivity varied among individuals and skin sites. A single-point calibration was used to compensate for this variability.~~

The next step is to accurately measure this small amount of glucose by using an amperometric biosensor. The GOx enzyme in the hydrogel discs reacts selectively with glucose via this reaction: Glucose + 02-> Gluconic Acid + H2O2. The hydrogen peroxide is detected at a platinum-containing working electrode via an electro-catalytic oxidation reaction producing an electric current that is measured.

The last step is to process the electric current signal. Here is the iontophoresis and biosensor duty cycle for measurement. ~~There are two identical sets of biosensor and iontophoresis electrodes in each hydrogel.~~ In order to produce a glucose measurement, the biographer first passes a low-level iontophoretic current for 3 min and during the time the glucose is extracted into the hydrogel at the iontophoretic cathode. After that, the biosensors are activated and the glucose-derived current from the biosensor at the cathode is mathematically integrated over 7 min. Then the polarity of the iontophoresis current is reversed and repeat the previous 2 steps. The total length of the measurement cycle is 20 min. The reverse operation is to diminish the effect caused by variability of application sites and amplify the signal.

~~Because the biosensors are worn on the wrist, they are subject to environmental conditions that could affect the sensor signal. Before calculation, we need to check parameters include low or rapidly changing temperature, the presence of excess perspiration, excess noise in the data. If the presence of any of these parameters is~~

~~detected, individual readings are skipped to ensure the accuracy of the remaining glucose measurements.~~

Experiment results

The performance of the biographer was evaluated in 3 different clinical trials: a clinic setting, a simulated home environment, and the actual home environment. ~~Additional 3 studies evaluated the accuracy of the biographer vs a laboratory standard method the precision of the biographer in a simulated home environment, and the effect of acetaminophen on biographer accuracy, which is a potential interference for home glucose monitors.~~

Accuracy assessments were based on comparisons with serial fingerstick BG measurements performed every 1 or 2-h. ~~In these studies, subjects wore the biographer for 15-h sessions (3-h of warm-up and 12 h of measurements).~~ In the clinic setting, subject movement was limited; greater freedom of movement was allowed in the simulated home environment studies. In the actual home environment study, subjects were instructed to go about their daily activities, and the only restriction was not to get the biographer wet.

Overall, the demographic distribution of subjects was equally divided between male and female, their mean age was about 48 years old, approximately two-thirds had type 1 diabetes with a mean duration of 17 years. The ethnic distribution was approximately 75 % Caucasian, 10% African American and 15% Asian, Latino, and others.

GlucoWatch could measure glucose accurately

The accuracy measures from the clinical trials are shown in the table. We found the correlation coefficients between biographer readings and BG measurements are around 0.8. The Deming regression slopes were near 1 unity. In Clarke error grid analysis, the distribution of points in the clinically acceptable (A+B) regions ranged from 94% to 98%, ~~with 0.1% in the E region that could confuse the treatment. The mean difference (MD) was less than 0.3 mmol/L.~~ The small values for MD and MRD and a Deming slope near unity indicate the overall bias in the biographer measurements was small. The values for SD, MARD, RMSE and correlation coefficient show an acceptable amount of noise in the data set. Based on these results, we can say that the measurement of GlucoWatch could accurately reflect the real BG.

Factors that affect measurement accuracy

Also, experiments about what factors could affect the biographer measurement were performed. The first factor was BG range. By assessing the biographer accuracy in different BG ranges, ~~MD, MRD, and MARD were calculated for all the paired points in four ranges,~~ <=5.56 mmol/L, 5.56-10, 10-13.33, > 13.33. ~~The ranges represent low level to high level of BG.~~ We could find that there is a slight positive bias at low glucose levels and a slight negative bias at high glucose levels. ~~As for the MARD, lower BG level seemed to have higher bias.~~ As we can see in the right figure about

the BG profile of individual subject, when glucose levels are low and relatively unchanging, the correlation will be low and the MARD will be large because the denominator (BG) is small. The results indicate that the probability of missing alert of hypo- and hyperglycemia couldn't be ignored which may cause severe outcomes.

continue

The second factor investigated was the rate and direction of BG changes. Throughout most of the range, there was a slight trend for MRD to go from positive to negative as the rate of change of BG went from negative to positive. For very rapidly decreasing BG levels, ~~more than -6.67 mmol/ L/h,~~ the MRD exceeded 22%~~ in the home environment study~~, indicating that the biographer read high in those cases and vice versa in the rapidly increasing situation. The other two factors that could affect GlucoWatch performance were ethnicity and body mass index. Specifically, African-Americans tend to have negative values for mean difference. Other factors such as age, gender, and acetaminophen have no impact on the performance of the GlucoWatch statistically.

Conclusion

~~For example, when the low glucose alert level was set to 5.6 mmol/L, 75% hypoglycaemic points could be correctly identified with 10% false alerts. Similarly, when the high glucose alert level was set to 15 mmol/L, the biographer correctly identified 79% of hyperglycaemic points with 8% false alerts.~~

Critique

First before comment, I need to say in advance that it's a technique and business failure example. ~~Its sales were much lower than expected even it was the first generation of non-invasive glucose monitoring device approved by FDA.~~

Although the alert rate seems to be much higher than traditional fingerstick BG, the accuracy is not high enough for a frequently used device in the field of the clinic.

Safety is a critical factor to consider when designing clinical biosensors. Dermatology assessments showed that mild skin irritation was present in most subjects and strong oedema was observed in about 1% cases. This is a big problem!

So the poor performance, safety problem, togther with other reasons like failing to educate the end-user properly ~~and failing to meet well with existing glucose monitoring standard,~~ lead to the failure of the product.

I think a typical failure example could help us learn a lot of experience. Here are some thinkings about blood glucose measurement. It's much easier to get uncharged molecules into the skin than out of it. Attempts to force glucose across the skin may alter the local concentration of glucose, perhaps due to the immune response. I

suppose when designing a measuring system, keeping the status of the target substance and its surrounding environment unchanged are critical for the accuracy and validity of the system. In addition, simpler detection principles and system designs should be more preferred rules.