Rob Lindsay, M.D.

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Continuous Glucose Monitoring

Next we will get to some of the nitty gritty of the meetings. I need to emphasize in the beginning that there was nothing major and there were no significant breakthroughs at this session. Thus, if you want to stop reading now, you are certainly welcome to do so. The Saturday morning session was on continuous glucose monitoring. Dr. Jay Skyler gave an update on different continuous glucose monitoring devices. He pointed out that we are in about the same place now with continuous monitoring now as we were in the early 1980s with home blood glucose monitoring. *I can remember the fights we had with the first glucometers, trying to convince insurance companies that blood glucose monitoring was better than urine testing. It was the first time I ever appeared in court.* He pointed out that the Glucowatch was too inaccurate, too inconvenient and too irritating and thus is not a viable option. The Pendragon that I mentioned from earlier meetings is no longer being evaluated because its accuracy was too poor. The Orasense non-invasive meter is just being okayed now for study so it will be quite some time before we encounter that device. It boils down to three devices currently. MiniMed has the Guardian when it is used without the pump and the Paradigm when used in conjunction with their pump. DexCom has had a device out for almost two years now and Abbott is still working on getting the Navigator through the FDA. The Navigator will provide glucose every minute but has an ten hour warm-up period. The DexCom has been found to be stable for over seven days. The Guardian likewise has been used that long although it is not officially recommended for one week. He made a couple practical points. None of the machines should be calibrated except in a period of stable glucoses. If the blood sugar level is going up or down rapidly the calibration will be inaccurate. He also pointed out that the interstitial fluid lag (the time difference between blood & tissue fluid glucose levels) will delay the hypoglycemia alarm and will delay the evidence of recovery from hypoglycemia. Thus, blood testing still has a place acutely. He said that overall the studies showed that the Hgb A1c improved in patients using the CGM. One study showed the patients dropping from 8.6% to 8.3% and another from 9.5% to 8.5%. Patients who are very well controlled with SBGM remained well controlled with CGM. He felt that the meters gave insights into patients actions somewhat better, particularly their use of insulin and how they utilize food. He stated that he is having about 50% success with insurers after many letters are sent. *We have had less success than that, but I guess it goes to show that persistence is a virtue when new techniques are involved.*

Dr. Howard Wolpert gave a talk on practical experience with continuous glucose monitoring. He felt that CGM has several advantages: it allows the patient to fine tune their daily management, to detect and prevent hypoglycemia, to improve quality of life and can be used as a behavior modification tool. The real-time monitors reduced the

variability in blood sugars (both high and low) and the frequency of hypoglycemia. He emphasized the physiologic delay between interstitial fluid glucose and blood sugar glucose. A member in the audience pointed out that the true physiologic delay was the true lag time in interstitial fluid glucose plus the sensor lag (the time it takes the sensor to run a reading) plus the data processing lag. Thus the true lag is somewhat greater than just the difference between the interstitial fluid and blood glucose. He felt that the CGMs underestimate the rate of decline of glucose with exercise. He also pointed out that if the sensor shows the level to be low, the patient really should check a blood glucose level before making any decisions. If the glucose level is normal but the arrow on the meter shows that it is dropping, the blood glucose may in fact be low because of the lag. This would be a concern with patients driving. Finally the lag period could lead to over-treatment for hypoglycemia. The patient could eat in response to the hypoglycemia but the lag may show failure to respond so that the patient ends up eating even more. On the other hand, he expressed concerns about stacking boluses in response to high readings: if the patient does not leave sufficient time for the insulin to work and merely keeps giving insulin because the meter shows that he is high, it could lead to serious hypoglycemia. He has encountered more severe hypoglycemic events with real time monitoring because of this problem. He recommended that to minimize the risk, confirm that the bolus was in fact delivered, be sure to check the arrow before giving another bolus, remember that there is insulin on board when making decisions, and finally remember the type of carbohydrate eaten. Carbs with a high glycemic index (for instance a bagel) will cause a rapid rise in blood glucose level whereas a slow absorbing carbohydrate like spaghetti will cause a slower rise. He warned of alarm and numbers burnout just from having so much data available. He also recommended that these meters may not be helpful in patients whose Hgb A1c is greater than 9.0% because they have more significant issues than just monitoring. Dr. Boris Kovatchev gave a talk on mathematical models for proactive and reactive interpretation of CGM. It was all very interesting but is totally un-reproducible and will have its effects in years from now. The bottom line is that they are working on ways to forecast events rather than to respond to events. Dr. Geremia Bolli talked about interstitial glucose monitoring in general. He pointed out that the goals with self blood glucose monitoring were 1) a Hgb A1c of less than 7.0%, 2) minimalization of severe hypoglycemia and 3) maintenance of hypoglycemia awareness. But SMBG is inconvenient, embarrassing at times, painful and time consuming. In theory, the usefulness of CGM would be 1) improvement in Hgb A1c, 2) the detection of hypoglycemia and ultimately the prevention of hypoglycemia and 3) decreased variability in blood glucose day-to-day. He pointed out that CGM cannot substitute for intermittent blood glucose testing and it still cannot close the loop with the pump. After the presentations, there were several comments from the audience. One member mentioned that the lag really is about five minutes since the skin site has been perturbed so that there is more blood in the tissue. Another pointed out that seizures usually come after prolonged hypoglycemia and therefore CGM might well be able to pick up the problem before the seizure. Finally, Dr. Peter Chase commented that his experience with CGM showed that the Navigator was the most accurate machine currently with the DexCom coming in second and the Guardian third. On Monday, Dr. Larry Fox presented the DirecNet continuous glucose sensor experience. He spent much of his time comparing the old Mini-Med continuous glucose monitor with the Glucowatch. I am not going to bother going through that data because the Mini-Med system has been upgraded and the

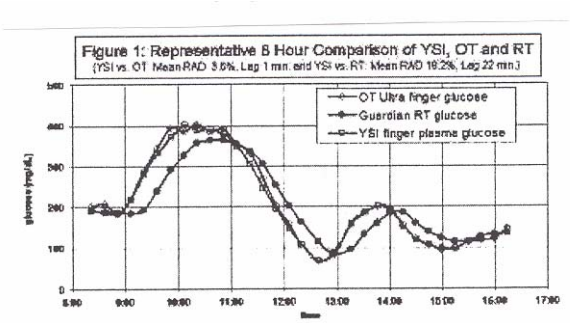
Glucowatch is simply not acceptable. I was interested, however, to find out that the Glucowatch, despite not even being displayed at the meetings, is still available. Seventy-six percent of the patients using the watch found that there was skin irritation, 56% found that it skipped too many tests, 47% found that it alarmed too frequently and 33% found that it simply was not accurate enough for them. Those are all good reasons as to why it is not being used. He did talk about the Paradigm Real Time and the Navigator, however. With the Paradigm, it will give glucose readings every five minutes. Sixty-eight percent of the readings were within the goal of 15% +/- of the blood glucose value by the lab. When the blood sugar was less than 70 mg/dL, however, it was within 15% only 30% of the time. Between 71 and 180 mg/dL it was within range 60% of the time and greater than 180 mg/dL it was within range 90% of the time. The Navigator gives glucose results every minute. The difficult part is that there is a ten hour warm-up before it can be used. In the study from DirecNet, the Hgb A1c of the patients using the Navigator dropped from 7.5% to 7.1%. They did find, however, that if the starting Hgb A1c was below 7% there was no change. There was no increase in glucose readings below 70 mg/dL so that the improvement in Hgb A1c was not the result of more frequent hypoglycemia but rather stabilization of the blood sugar. Both parents and patients gave high satisfaction ratings for the Navigator. His conclusion was that the technology has markedly improved and that short-term studies show that there can be significant improvement in diabetic control with both devices. They are also well liked and tolerated. The real need is for better algorithms and there must be team involvement to use the devices properly and safely.

I visited the booths of both Medtronic and DexCom at the commercial exhibits. The starter kit for the Medtronic sensor costs $999. That includes ten sensors. The sensors last three days and cost $35. There is a six month warranty for the transmitter. The transmitters will cost $649 when replaced. With the DexCom, the receiver costs $450 and has a one year warranty. The sensors cost $60 but last seven days as opposed to the three days for the Medtronic sensor. The DexCom people stated that at the moment, they have an indication for patients 18 years and older but they are working on a pediatric sensor. Their warm-up takes two hours. I talked to the Navigator people who, of course, could not demonstrate the device since it has not been approved by the FDA. They too will have an 18 year and older indication. Theirs warms up ten hours which is a problem. At the moment, it appears that it is somewhat larger than the Medtronic and the DexCom. They will have a two year warranty. I mentioned the physiologic lag earlier, and when I approached the representatives, the Medtronic reps felt that their machine had about a 20 minute lag, and the DexCom representative felt that there was about a seven minute lag.

Finally Dr. Robert Ratner summarized his feelings that he gleaned from the meetings at the highlight session the last day. He pointed out that in a study with adolescents, the percentage reaching a Hgb A1c of less than 7% increased from 9% to 35% with the use of a continuous monitor. He also warned, however, that Dr. Garg in Denver found that 33% of the patients stopped using the device and he felt that it was probably due to sensor fatigue. *Thus we probably will want to use these devices somewhat intermittently interspersed with blood glucose monitoring. The amount of data that one obtains with these devices can be somewhat overwhelming and we have to be careful that we really don't burn out our patients and our children. If you want more information about*

children and sensors, I would recommend going to www.childrenwithdiabetes.com. If you go through their index it has a good deal of information that will be useful for you.

Next I would like to go through some of the individual studies that were reported on CGM systems at the meetings. First, Dr. Clarke's group from Charlottesville, Virginia found that using CGM reduced the risk for hypo- and hyperglycemia. They used the Freestyle Navigator system and had a period when the meter was masked so that the patient could not have real time results and then compared it to another period where the patients could immediately use their meter results. They found that the percent of subjects in the high-risk category for hypoglycemia was reduced more than three-fold, dropping from 9.8% during the masked phase to 2.9% during the un-masked phase. Likewise the percentage of subjects at high risk for extreme hyperglycemia was reduced three fold from 7.9% to 2.5%. They felt that the overall blood glucose variability was significantly reduced and at the time in the target range increased from 55 to 59% of the time. A group from Northridge, California did a large study using the Paradigm real time system in which there were over 60,000 paired sensor/meter readings. Only 1% of the 7,115 sensors failed their initial start-up following the two-hour warm-up time. They found that 76.8% of the readings were within +/- 20% agreement with the glucose meter. In adolescence, the percent was 71.2%. They concluded that the sensor glucose values are accurate and may provide meaningful information to improve diabetes management. Another group from Salinas, California agreed that the meters showed agreement in glucose values but when they used multiple Paradigm sensors in the same patient there was quite a bit of disagreement in the direction and rates in the change arrows on the meters. Thus they felt that these parameters should not be used to adjust insulin doses. *This was interesting because most of the people using the sensors feel that the direction arrows are more helpful than the absolute numbers. I am not quite sure what to make of this since these problems were not reported in the general sessions.* A group from the Czech Republic looked at the relationship between Hgb A1c values and the average one-month interstitial glucose concentrations as determined with the Paradigm sensor. They found that the CGM appeared to be helpful in establishing precise relations between the concentration of Hgb A1c and the mean interstitial fluid glucose over several preceding weeks. There was a significant correlation between the two. I have included a graph from another report from Minneapolis.



They did simultaneous testing with a continuous monitor (The Guardian), the One Touch Ultra Glucose meter and the lab. I just included this graph to show the general agreement between all three methods. They did find that the continuous monitoring lag time was about 22 minutes. Another study looked at post-meal blood sugar excursions. They

compared the continuous glucose monitoring information with standard blood glucose monitoring that patients did to determine their degree post-meal hyperglycemia. The mean post-meal hyperglycemic value by CGM was 219 mg/dL and the mean value recorded by the One-Touch meter was 163 mg/dL. They concluded that the spikes in post-prandial blood sugar measured by continuous glucose monitoring, and at times missed by the One-Touch meter, can be an important piece of information in the management of diabetes and strict glycemic control. *They were not saying that the continuous glucose monitoring was more accurate than the meter, it is just that there is much more information with the continuous monitor than there is with a single post-prandial blood sugar determination. We don't really know with each patient when they reach their peak after eating and the CGM system picks up this peak with its frequent readings whereas doing a single post-meal blood sugar level may oftentimes miss the peak. Since many reports show how important the post-meal tests are, this may be a distinct advantage for CGM.*