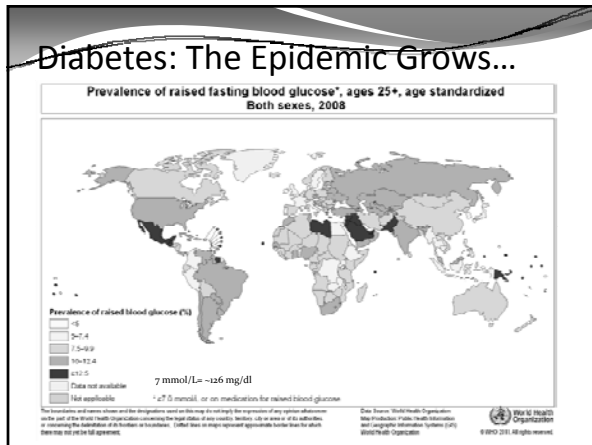


Continuous Glucose Monitoring:
Improving patient outcome through clinical application

Tomas C. Walker, MSN, APN, CDE, BC-ADM
 Nurse Practitioner
 Desert Endocrinology



Diabetes: A Costly Epidemic

- 26 Million have DM in the U.S. (~8.3% of pop.)
- 79 Million have Pre-Diabetes
- In 2050 1 in 3 in the U.S. will have DM
- 1 in 2 AA and Hispanic children will develop during their life

- Costs (\$U.S.Billions)
- Direct Medical \$116
- Indirect: \$58
- Total: \$174 B

CDC, 2011 Diabetes Fact Sheet.

What is the Importance of Glycemic Control?

- Only 37% of patients with diabetes obtain levels of glucose control recommended by the American Diabetes Association
- The AVERAGE A_{1c} on an insulin pump is >8%
- Today tight glucose control is a standard of care
 - Most challenging for patients on insulin therapy

Age-specific advantages of Cont. Subcutaneous insulin infusion... Kordonouri, O. Diabetes Care, 29:133-134, 2006

Insulin pump therapy a meta-analysis, Weisber-Benchell, J. Diabetes Care 26:1079-1087, 2003

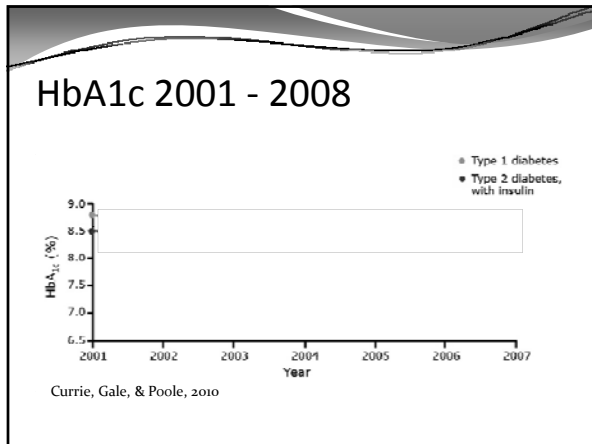
Tight Glycemic Control Prevents Microvascular & Macrovascular Complications

HbA _{1c}	DCCT ¹ 9 to >7%	Kumamoto ² 9 to >7%	UKPDS ³ 8 to >7%
Retinopathy	63%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	—	—
Macrovascular disease	41%	—	16%*

*NS
HbA_{1c}=glycosylated hemoglobin A.
1. Diabetes Control & Complications Trial Research Group. *N Engl J Med.* 1993;329:977.
2. Okubo, et al. *Diabetes Res Clin Pract.* 1995;28:103.
3. United Kingdom Prospective Diabetes Study Group 33. *Lancet.* 1996;352:837.


What has the last 10-years brought Diabetes Care ??

- Insulin Analogues
 - Long-acting basal
 - Rapid-acting meal
- GLP-1 Receptor Agonists
 - Exenatide / Liraglutide
- Amylinomimetics
 - Pramlintide
- New pumps/meters



Problems with insulin delivery?


- Variable absorption
- Dosing Errors
- Poor adherence to dosing
- Balancing complex issues
 - Activity
 - Meals
 - Stress
- Can you predict the future?



The Problem: Is it Therapies or Information?

- 2 insulin injections a day extended life by decades starting in 1922.
- Insulin/Pharmaceutical options & delivery methods are sufficient today
- Fingerstick data - only as good as the number done each day - Gives NO trending information-Going up? Going down? Who knows?
- Glucose is NOT static
- **Less than 25% of patients have acceptable glucose control across the day***

*Hirsch, I.B. (2004). Blood glucose monitoring technology: translating data into practice. *Endocrine Practice*, 10, 67-76.



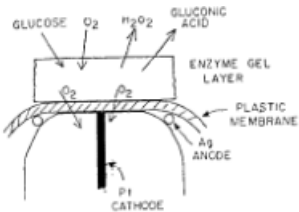
The search for a solution....

- Home SMBG is providing inadequate information
- We need a new tool that lets us view glucose as a changing dynamic
- Continuous Glucose Monitoring is that long sought after solution



Continuous Glucose Monitoring:

First proposed in 1967...

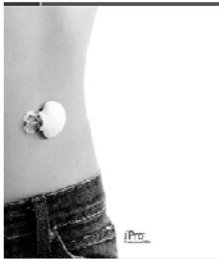


- ⊙ Resistance layer reduces the amount of glucose penetrating to the electrode, making glucose levels the limiting factor in the reaction
- ⊙ Glucoseoxidase reacts with glucose to create an electric current related to the amount of glucose
- ⊙ 40 years to get to clinical use.

Udlike SJ, Hick GP. Nature. 1967. (214) 986-988.

Medtronic iPRO

- Blinded r-CGM
- Collects data for 72 hours
 - Every 5 minutes/288 readings per 24h period
- Startup and download are done in the clinician's office
- Minimal patient involvement
- No hypo- or hyper-glycemia alerts
- Reusable transmitter, rechargeable, disposable sensor



Retrospective CGM Cont.

- Benefits of r-CGM
 - Fairly accurate,
 - Always easier to correct in retrospective analysis
 - Reimbursable
 - Most insurances cover twice a year
 - Minimal Patient training
 - Ability to review glucose patterns
 - Patient data is blinded
- Problems with r-CGM
 - No failure alert
 - Patient has no hypo- or hyperglycemia warnings
 - Designed to benefit clinicians
 - Patient data is blinded
 - No direct benefit to the patient

1. Sachedina & Pickup, 2003, Diabetes Medicine, 20, 1012-15.

Retrospective CGM: Is it effective in long-term improvements in glucose control?

- In a word. NO.
- Meta-analysis of 31 Trials
- Type-1 and Type-2 Patients
 - HbA1c Improved by 0.2% compared to the control group
 - There was an un-sustained reduction of Hypoglycemic Events
 - 29 of the 31 Studies found NO significant ($P < .001$) difference between the Experimental and Control groups.
- Retrospective should be reserved for when blinding is medically necessary.

Currie, Poole & Pope (2009), Current Medical Research and Opinion


When is CGM blinding needed?

- Clinical/Research Trials when the subject should not know what their glucose is doing
- When constant awareness of glucose levels may have a negative influence on the data being collected.
- When the clinician believes that access to the data may be detrimental to the patient.
- However – the patient will get NO WARNINGS about hypo- or hyper-glycemic events.

Real-time Continuous Glucose Monitoring (rt-CGM)

- Two devices released in 2006.
 - Medtronic Paradigm RT
 - Dexcom STS
- One released in 2007 and now is off the market
 - Abbott Navigator

Discontinued in US market in Sept 2011 ->



Indications for Using the CGM


- These devices:
 - Aid in the detection of episodes of hyperglycemia and hypoglycemia
 - Facilitate both acute and long-term therapy adjustments
 - Assist in minimizing glucose excursions
 - Can be safely used for type 1 or type 2 diabetes mellitus, age 18 and older (DEXCOM), age 7 or older for MDT
 - Are adjunctive therapy
 - DO NOT replace Fingersticks

rt-CGM Benefits

- Glucose readings every 5 minutes - 288 readings/24h.
- High and Low Alerts
 - Audio/Vibratory alarms
- Trending information
 - Looking at the last hour, 3-hours, 6, 12 and 24 hours.
 - Ability to download and manipulate the data to establish patterns
- Provide a constant awareness of glucose levels
- Offer improved understanding to the patient of THEIR glucose
- Patients provide us with feedback about their glucose control.

Dexcom 7-Plus


- Glucose value reported every 5 minutes
- Low and High alerts to increase awareness of glucose excursions.
- User definable points for hypo- and hyperglycemia alarms
- User adjustable audio and vibratory alert
- Stand alone device can be used for patient on CSII or MDI



www.dexcom.com

Medtronic Minimed Revel system

- Glucose value reported every 5 minutes
- Low and High alerts to increase awareness of glucose excursions.
- User definable points for hypo- and hyperglycemia alarms
- Audio and Vibratory alert
- Integrated pump or stand alone device available



www.minimed.com

rt-CGMs Available Today

Cost:Annual / per day <small>(assuming purchase and 1/2 time use)**</small>	MDT <u>ParadigmRT</u>	Dexcom <u>Seven+</u>
	\$2773 / \$15.23	\$2010 / \$11.04
Sensor Life	3 days (+)	7 Days (+)
Sensor Ga/Length	23ga/13mm	26ga/13mm
Start up time (no readings)	2 hours	2 hours
Calibrations	Q 12 h	Q 12 hour
User Defined high-low Alarms	YES	YES
Range	6 feet	5 feet

***Based on cost calculations in my practice.

Comparing the CGMs on the Market

Glucose Range	Clark EG (A+B)A
Hypoglycemia 40-80mg/dl	Minilink - 76.1% / 60% Dexcom 7 - 84.2% / 73.5% Navigator - 67.9% / 56.1%
Euglycemia 80-180mg/dl	Minilink - 98% / 61% Dexcom 7 - 97.7% / 66.7% Navigator - 98.8% / 70.4%
Hyperglycemia 180-300mg/dl	Minilink - 86.8% / 61% Dexcom 7 - 96.4% / 71.6% Navigator - 99.4% / 93.4%

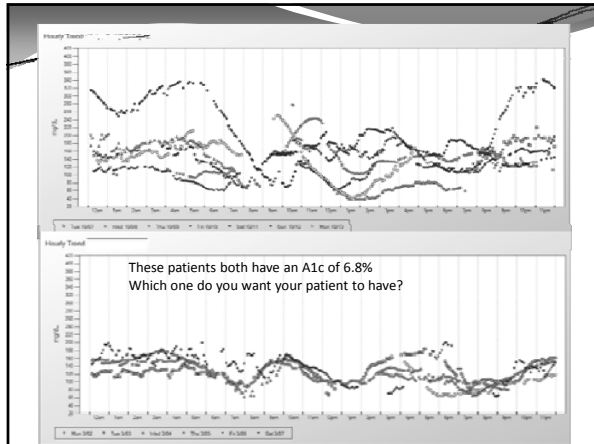
Minilink Users manual, MDT 2006, Pg 53
Diabetes Technology & Therapeutics, Garg, S, Vol 11, 2, 2009

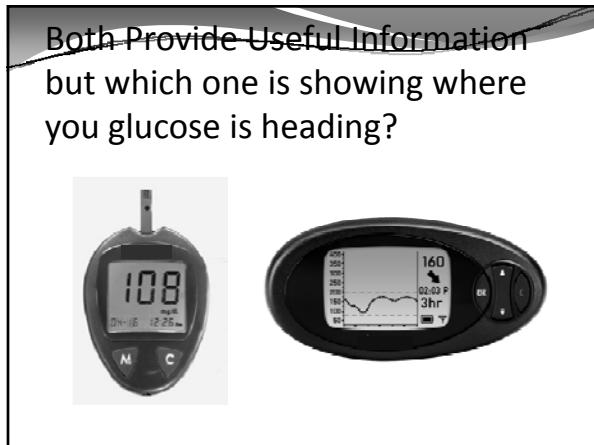
The Best
CGM System
for Every
Patient Is
the One
They Will
Wear

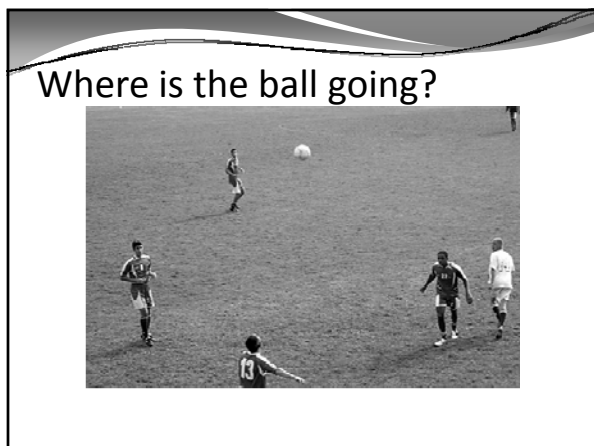
OK, so why should my patients do this....

- They are already testing
- Their HbA1c is 6.8%
- Lows are minimal
- Their control is good enough.....

A photograph showing various diabetes management supplies on a wooden surface. In the foreground, there is a glucometer with a test strip inserted. Behind it are several boxes of test strips, including one labeled 'Accu-Check'. In the background, there is an open logbook or notebook with handwritten entries.







What is important about CGM?

The WAVEFORM !!!

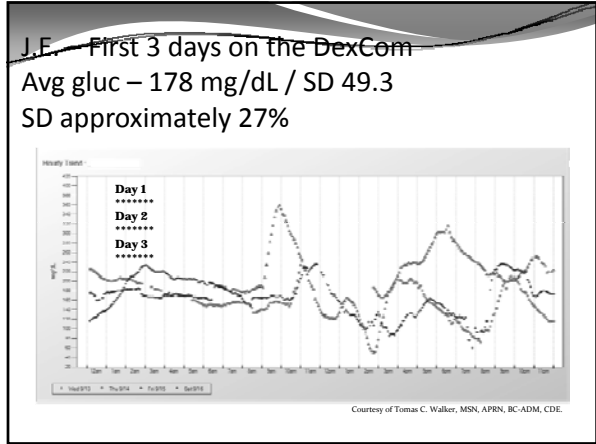
Improved Glycemic Control with Continuous Glucose Sensing

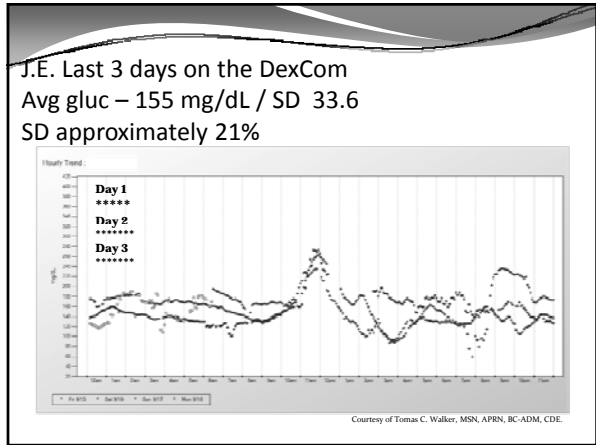
<p>Period 1: Blinded (Day 1-3) Median Glucose = 200 mg/dl Mean Glucose ± Stdev = 200 ± 69 mg/dl</p>	<p>Period 2: Unblinded (Day 4-6) Median Glucose = 176 mg/dl Mean Glucose ± Stdev = 176 ± 57 mg/dl</p>	<p>Period 3: Unblinded (Day 7-9) Median Glucose = 148 mg/dl Mean Glucose ± Stdev = 150 ± 42 mg/dl</p>
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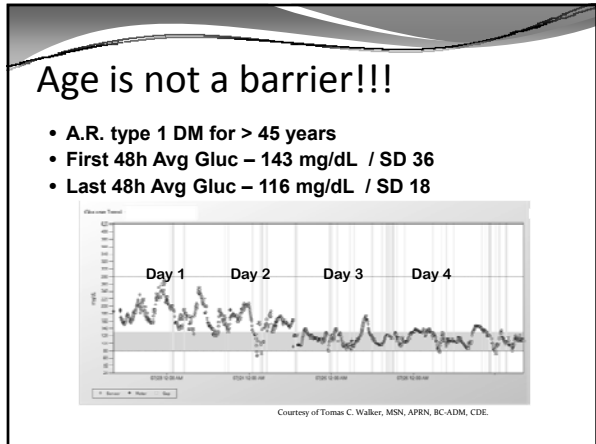
Source: Improvement in Glycemic Excursions with a Transcutaneous, Real-Time Continuous Glucose Sensor. Diabetes Care, January 2006

J.E. T1DM on MDI

"I watched my sugar, it tells me how well I did"








Research supporting rt-CGM

- Reductions in HbA1c without increases in hypoglycemia
- Increased frequency of use demonstrated greater HbA1c reductions
- Sustained HbA1c reductions of \Rightarrow 0.5-1.0% are common in the literature
- HbA1c, hypoglycemia and glucose variability reductions were seen in MDI and CSII
- Reductions in HbA1c and Hypoglycemic events were sustained out for 12 months of follow up.
- Patients who used the device consistently had the best responses

JDRF, 2009; JDRF, 2008; Garg, 2006; Deiss et al, 2006;

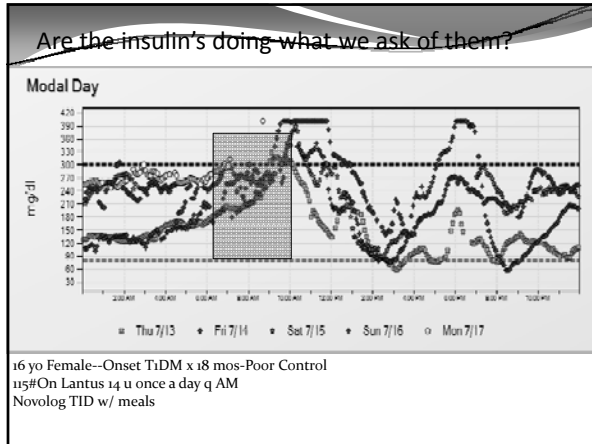
CGM is Sharing Knowledge

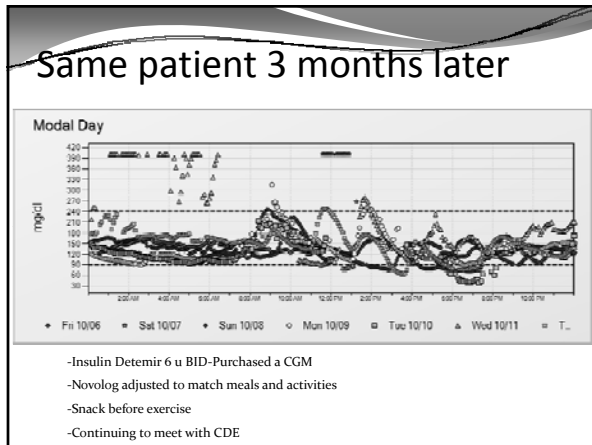


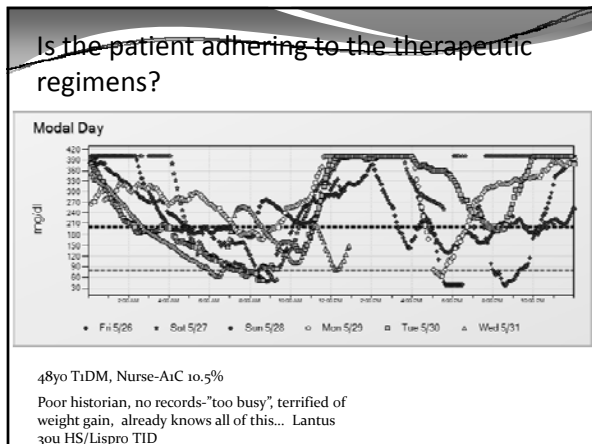
- Patient are empowered
- CGM is for patients and clinicians
- Provides trending information and insight for basal control
 - How does the pt respond to a dose of insulin?
 - Fine-tune Insulin-to-Carbohydrate and Correction Dosing
 - Analyze response to other medications and situations
- CGM lets patients see the continuum that is their glucose

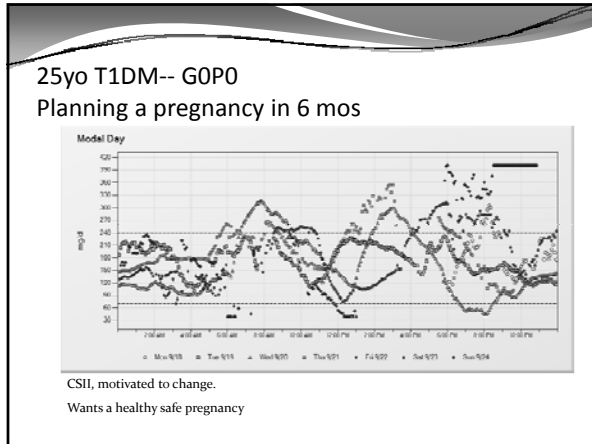
Case Studies

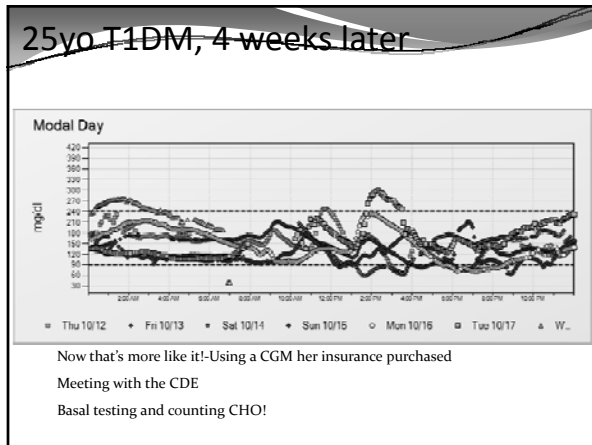
Change is not merely necessary to life, it is life.
- Alvin Toffler

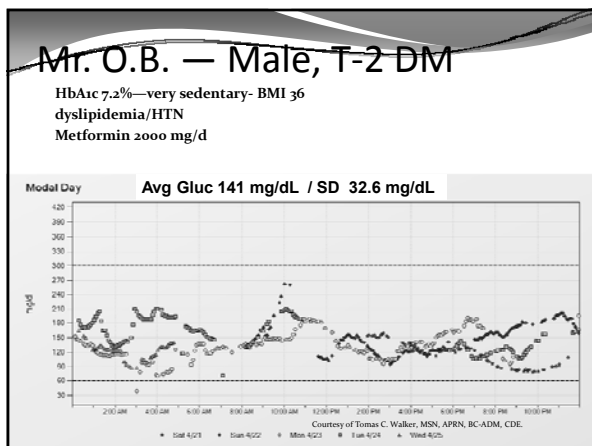










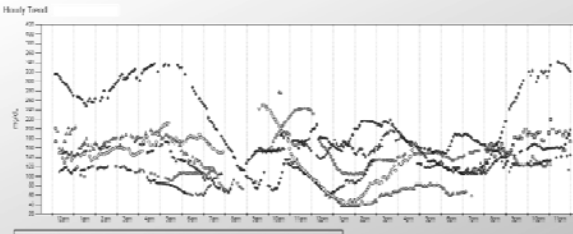


What about Pramlintide?

- G.K 49 yo Real estate agent
- Type1 DM Dx at age 20
- A1C - 7.9%
- CSII therapy for 6 years.
- Lots of stress
- High PP glucose
- Frequent rebound Hypo/Hyper events
- Occasional Nocturnal hypo events
- Has done 3 previous CGM sessions with retrospective data

G.K. at Baseline

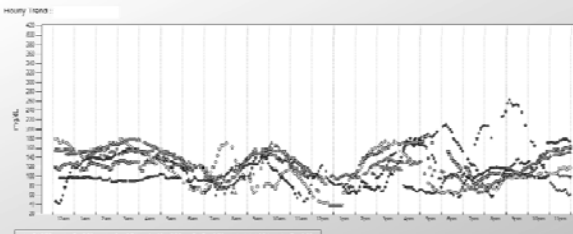
Avg Gluc, - 148.5mg/dl
S.D. 60 mg/dl



The graph displays hourly glucose levels over a period of approximately 10 weeks. The y-axis represents glucose concentration in mg/dl, ranging from 0 to 400. The x-axis shows dates from late 2010 to early 2011. The data shows significant fluctuations, with frequent peaks above 200 mg/dl and several instances of hypoglycemia (glucose levels dropping below 100 mg/dl).

Pramlintide 30 mcg TID with meals

Avg Gluc.- 120mg/dl
S.D. - 34.8 mg/dl



The graph displays hourly glucose levels over a period of approximately 10 weeks after starting Pramlintide 30 mcg TID with meals. The y-axis represents glucose concentration in mg/dl, ranging from 0 to 400. The x-axis shows dates from late 2010 to early 2011. The data shows a marked reduction in glucose variability compared to the baseline, with fewer peaks above 200 mg/dl and fewer hypoglycemic events.

Pramlintide in the middle of the night?

Before Pramlintide

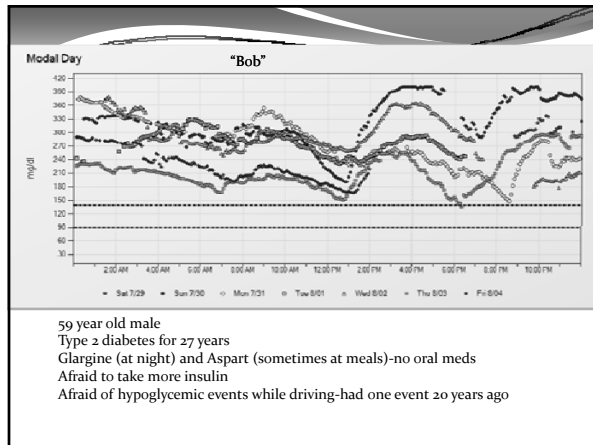
Stat	Totals	12 am	1 am	2 am	3 am	4 am	5 am	6 am
# Readings	1308	54	46	48	42	55	62	65
Average	148.5	181.5	170	175.2	192.1	180.7	158	138.3
Minimum	39	99	100	116	109	85	69	60
Quantile 25	109	137.2	124.2	146	145	113.5	95.2	106
Median	147	150.5	152.5	161	163	168	167	125
Quantile 75	174	201.8	198	178.5	274.2	193	181	178
Maximum	341	319	268	298	325	337	336	314
SD	60	68.3	55.3	54.1	76.2	77.2	72	60.8

For these 7 hours
Avg BS -170.8 mg/dl
SD - 66.2 mg/dl

After Pramlintide

Stat	Totals	12 am	1 am	2 am	3 am	4 am	5 am	6 am
# Readings	961	45	42	46	46	44	45	24
Average	127.2	149.5	148.8	150.4	156.5	154.5	147.3	127.6
Minimum	62	116	112	116	128	111	120	111
Quantile 25	103	127	133.8	132.2	135.8	142.8	137	118.5
Median	127	154	150.5	157	156	156	146	121.5
Quantile 75	151	157	156.8	164.8	173.5	164.5	155	128.2
Maximum	200	196	191	186	182	190	199	183
SD	30	20.3	19.7	19.1	18.9	17.8	17.5	17.9

For the same 7 hours
Avg BS - 147.7 mg/dl
SD - 18.7 mg/dl



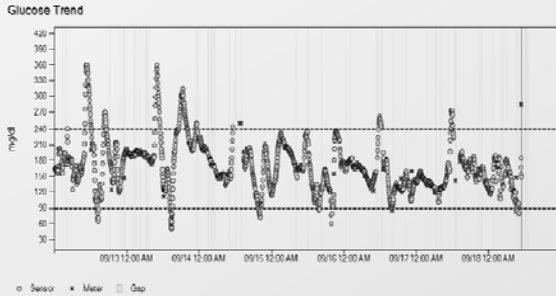
MythConceptions...

- CGMs require lots of training to use the data effectively.
 - Most patients require only 20-30 minutes of training to use the CGM device and data they are getting back.
 - Do it in small groups.
 - Charge for your time !
 - Patients are grasping this quickly-Don't underestimate them

MythConceptions:
“Retrospective data is just as good”

- This assumes the data is more useful to the clinician than the patient
- It requires the clinician to make the judgment about the patients own glucose patterns
- *Retrospective is useful when blinding is necessary, but has limits if you are using it for diagnostics*
 - Patients should keep records
 - They should test more not less during the session

MythConceptions:
“Retrospective data is just as good”

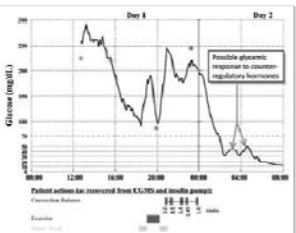


Case Report

Endocrine Practice, 2010, 16(2), 244-247

CONFIRMATION OF HYPOGLYCEMIA IN THE “DEAD-IN-BED” SYNDROME, AS CAPTURED BY A RETROSPECTIVE CONTINUOUS GLUCOSE MONITORING SYSTEM

Robert J. Taneberg, MD, FACP¹, Christopher A. Newton, MD², Almond J. Drake III, MD, FACP³



23 yo Male, T1DM x 12 years
 Had hypo seizure witnessed by his mother
 Seen by his Endo who reduced his basal rates and started a MDT retrospective study
 Found deceased at 0900
 Pump history showed he had stacked 5 bolus' in a 2.5 hour period – totaling about 1/3 of his basal TDD
 No glucose levels entered in the pump
 DIB represents 6% of the mortality in T1DM

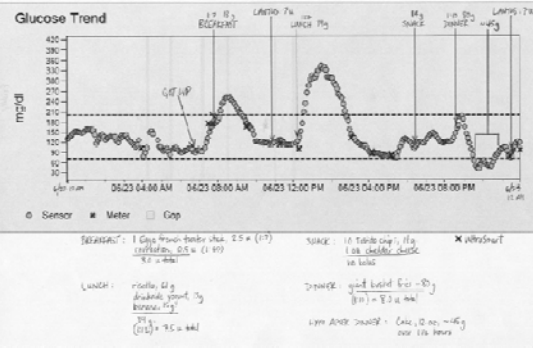
MythConception: Sensors Can not be Calibrated when Glucose is Changing Rapidly

Absolute Value of Rate-of-Change at Calibration (mg/dL/minute)	≥ 2	1 to 2	0 to 1	Overall
Mean ARD	13.8	14.6	14.3	14.3
95% Conf Intvl	9.6 – 19.6	11.8 – 17.8	12.8 – 16.7	10.6 – 18.3
Median ARD	9.2	12.9	11.5	11.6
95% Conf Intvl	6.4 – 17.0	10.3 – 15.7	10.2 – 13.6	7.2 – 15.6
N (%) paired values	291 (6.8)	986 (23.1)	2987 (70.1)	4264 (100.0)

No! There is no significant difference in accuracy after calibration during rapid glucose change

Diabetes Tech and Therapeutics, 2009, Vol 11(1),pg689-695

The patients are teaching each other... gotta love the internet...




Changes in ADA Clinical Practice Guidelines on CGM: 2008 vs 2009

2008	2009
CGM is a potential supplemental tool in lowering HbA1c	CGM can be a useful tool in lowering HbA1c in adults ≥25 yrs old
Explicitly limits CGM recommendations to type 1 diabetes	CGM beneficial for those with hypoglycemia unawareness and/or frequent hypoglycemic events
	Some younger patients may benefit from CGM



ADA. Diabetes Care. 2009;32(suppl 1):S13-S16.

The future holds...

- Longer term sensors
 - Several long-term surgically implanted are in testing currently
- Noninvasive Monitoring
 - Near IR, Ultrasonic, Microneedles
 - Significant Accuracy issues
 - Affected by temp, circulation, vasoactive meds
 - A long journey from making one proof of concept to getting it to market!
- Closing the loop? Not yet.....



Famous Words



1916 1st Edition

- *"In diabetes the careful instruction of the patient is the keystone of treatment."*

Dr. Elliot P. Joslin
(1869-1962)

Thank you for your time!

Questions?