The Latest on Insulin Pumps and Glycemia

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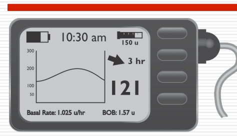
Disclosure

- Book sales – all pump companies
- Advisory Boards – Tandem Diabetes, Convatec, Halozyme, PicoLife Technologies
- Consultant – Bayer, Roche, BD, Abbott, Tandem Diabetes, Acon Laboratories
- Speakers Bureau – Tandem Diabetes, Animas
- Sub-Investigator – Glaxo Smith Kline, Animas, Lilly, Sanofi-Aventis, Bayer, Medtronic, Biodel, Dexcom, Novo Nordisk, Halozyme
- Pump Trainer – Accu-Chek, Animas, Medtronic, Omnipod, Tandem
- Web Advertising – Sanofi-Aventis, Sooil, Tandem Diabetes Medtronic, Animas, Accu-Chek, Abbott, etc.

What We'll Cover

- Pump Overview
- Actual Pump Practices Study Results
- Tuning the Bolus Calculator
- How to Find an Improved TDD
- Infusion Set Issues
- Future Developments

Insulin Pump Essentials



Line Pump - showing CGM information, current basal rate, Bolus on Board (BOB), battery life, and insulin left in reservoir

- Motor
- Reservoir/cartridge
- Basal rates & boluses
- Bolus calculator
- Infusion set
  - hub (Luer lock or proprietary)
  - tubing
  - cannula (metal or Teflon)
- Adhesive/tape

Advantages of an Insulin Pump

- Convenience
- Software calculates doses
- Easier to match varying needs
- Less insulin stacking
- Lower A1c, less severe hypoglycemia, less BG variability *
- More freedom of lifestyle
- Better data (clinicians, pumpers, parents)

* Pickup JC, Sutton AJ: Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008 Jul;25(7):765-74.

Early Insulin Pumps

Line Pumps

Patch Pumps

The Actual Pump Practices Study

In the APP Study, we looked retrospectively at over a thousand pump wearers across the U.S. Data was downloaded from Deltec Cozmo insulin pumps during a routine software upgrade in 2007.

We wanted to find out:

- How pumps are actually used and
- What influences success

APP Study Background

- 396 pumps had >95% of BGs entered from an attached meter with >73 days of data and >300 BG tests per pump
- 92.7% of pumpers used BC to cover carbs (>2 meals a day) and 96.5% used BC to correct high readings
- Pumps were divided into tertiles by avg. BG
- Basal %, CarbF and CorrF formulas were derived from the tertile with the lowest avg. BG

1. Walsh J, Roberts R, Bailey T: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010
2. Walsh J, Roberts R, Bailey T. Guidelines for Optimal Bolus Calculator Settings in Adults. J Diabetes Sci Technol 5(1): 1711-1717, 2011.

APP Study – BGs, Basal Rates, and TDDs

Glucose, Insulin and Carb Data

Group:	All 396 Pumps	Low Third	Mid Third	High Third
Avg. Meter BG	184 mg/10.2 mmol	144 mg/dl (8.0)	181 mg/dl (10.0)	227mg/dl (12.6)
BG Tests/Day	4.38	4.73	4.41	4.01
TDD	49.4	47.9	49.1	51.1
Basal %	47.6%	47.6%	47.2%	47.8%

1. J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010

APP Study – Carb Boluses and CarbFs

Glucose, Insulin and Carb Data

Group:	All 396 Pumps	Low Third	Mid Third	High Third
Avg. Meter BG	184 mg/10.2 mmol	144 mg/dl (8.0)	181 mg/dl (10.0)	227mg/dl (12.6)
BG Tests/Day	4.38	4.73	4.41	4.01
CarbBolus/Day	4.14	4.07	4.20	4.14
CarbGram/Day	189.9	185.2	196.3	187.9
CarbF	11.4	10.8	12.2	11.2

1. J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010

APP Study – Unexpected Outcomes

Between low, medium, and high avg. BG groups:

- Basal was 48% of TDD in all groups
- Groups ate same grams of carb and took same number of carb boluses and correction boluses per day
- BG testing had no meaningful impact on glucose – the high BG group tested almost as often as low group
- High BG group used MORE insulin a day – they either need more insulin OR need to stop losing it

1. J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010

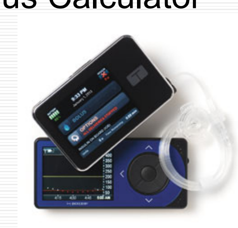
APP Study – Summary

- ❑ Get an accurate TDD
- ❑ Then derive pump settings from it

Pattern management becomes easier once TDD is accurate.

Tuning the Bolus Calculator

The BC helps user find bolus recommendations that better match carb intake and the current glucose while minimizing insulin stacking



Bolus Calculator

User Inputs: Glucose | Grams of carb

Photo courtesy www.sixuntilme.com

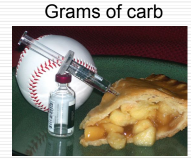


Photo courtesy emilyboller.com

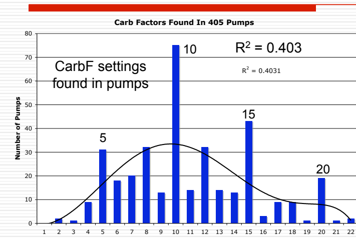
BC Output: Recommended bolus with list of units for carbs, correction (if needed), and BOB (if any)

Bolus Calculator Settings

This Setting	Helps
Basal rates	Sound sleep (~50% of TDD)
CarbF or I:C ratio	Cover carbs well
CorrF or ISF	Lower highs safely
Target glucose	Correct to specific goal
DIA	Minimize insulin stacking

The average TDD determines how often highs and lows occur

APP Study – Carb Factors Are Often Wrong[1,2]



Carb factors are not evenly distributed.

People like “magic” numbers – 5, 10, 15, and 20 g/unit.

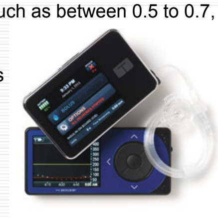
Use formulas to get accurate settings –> much better than WAG!

Don’t use “magic” numbers!

1. J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010
2. J. Walsh, D. Wroblewski, and TS Bailey: Insulin Pump Settings – A Major Source For Insulin Dose Errors, Diabetes Technology Meeting 2007

Basal Tips

- Basal rates should be similar, such as between 0.5 to 0.7, or between 1.0 to 1.4 u/hr
- Adjust basal rates in small steps (usually 0.025 to 0.1 u/hr) **<u>2 to 5 hours</u>** before need arises
- Using more than 5 basals may have little benefit.[1]

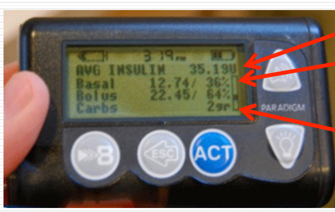


[1] Heinemann L, Nosek L, Kapitza C, et. al. Changes in basal insulin infusion: time until a change in metabolic effect is induced in patients with type 1 diabetes. Diabetes Care. 2009;32(8):1437–1439.

Basal/Bolus Balance

Ideal Basal/Bolus Balance Differs by Age		
Prior to puberty	30-45%	High carbs, low stress, honeymoon
Puberty	40-55%	High carbs, mid to high stress hormones
Adult	45-60%	Mid carbs, mid stress hormones
Thin elderly	40-50%	Mid carbs, low stress hormones

Pump Data – Avg. TDD and Basal/Bolus Balance



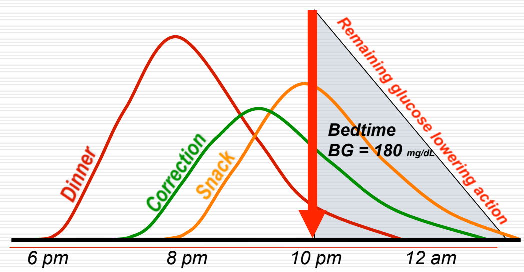
***TDD** = 35.19 u*

***Basal %** is low at 36%*

2 grams of carb/day means Bolus Wizard is not being used

Bolus on Board / Insulin Stacking

Bedtime BG = 180 mg/dl – is there an insulin or a carb deficit?



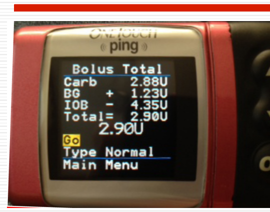
Pump BCs Can Recommend Excessive Bolus Doses

Recommended Bolus from BC			
Glucose	Units Needed	Animas	Other Pumps
#1: 119 mg/dl	0 u	0 u	5 u
#2: 121 mg/dl	0 u	5 u	5 u
#3: 200 mg/dl	2 u	5 u	5 u
#4: 300 mg/dl	4 u	5 u	5 u

A pump wearer eats 50 gram dessert 2 hrs after dinner with 5u of BOB left on 4 consecutive nights. Table shows BG on each night, the actual bolus needed and what pumps will recommend.

CarbF = 10 gr/u; CorrF = 50 mg/dl; Target = 120; DIA = 5 hrs

Verify Bolus Recommendations



If 4.35 u of BOB remain from a bolus given 3 hrs earlier, would you really give 2.9 more units for a bedtime snack?

Bolus on board (BOB) = glucose-lowering activity that remains from recent boluses

All pumps* cover carbs even when excess BOB is present.

When BOB exceeds correction bolus, consider reducing recommended bolus.

* Asante Snap has option to avoid this, and Animas Ping gives correct bolus once BG goes below target.

Clever Pump Trick – Get an Accurate Bolus

1. If BOB is SMALLER than the correction bolus, pump's recommended bolus is CORRECT
2. If BOB is LARGER than the correction bolus, subtract BOB from the combined carb plus correction bolus

Example: Carb bolus = 3.0 u (Pumps recommend 3.0 u)

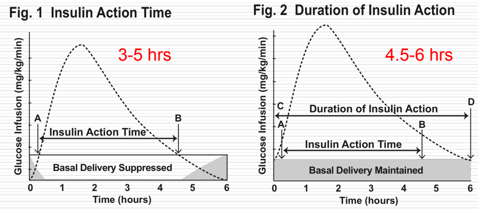
Corr bolus = 1.2 u

BOB = 4.0 u

BOB larger than Corr bolus

Accurate bolus = 3.0 + 1.2 – 4.0 = 0.2 units as needed bolus

Insulin Action is not Duration of Action



IAT is measured between points A and B, and involves suppression of basal delivery.

DIA is measured between points C and D. Once basal delivery is maintained, the PD of a bolus insulin can be directly measured.

Short DIAs Cause Unexplained Hypos

3 hours after a 10 unit bolus, table shows how much BOB a pump thinks is left with each DIA time:				
	Pump's estimate of Insulin On Board			
If DIA is set to:	3 hr	4.5 hr	5.0 hr	5.5 hr
Estimated BOB is:	0 u	2.5 u	3.4 u	4.0 u

- A short DIA hides BOB and leads to hidden insulin stacking, unexplained lows, and errors in other pump settings.
- Always set DIA from insulin's "real action time"
- Don't change DIA to "fix" control problems

Tannenberg RJ. Endocr Pract. 2010:244-248

"Dead-In-Bed" CGM data

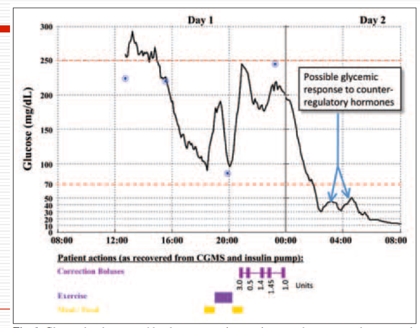
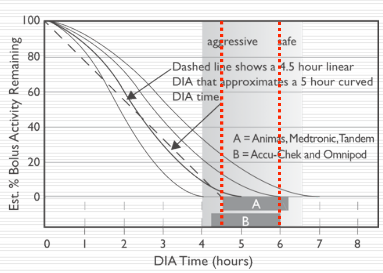


Fig. 1. Glucose levels captured by the retrospective continuous subcutaneous glucose monitoring system (CGMS) for the evening before and the morning of the patient's death. The cali-

Recommended DIA Times



Set DIA to 4.5 to 6 hrs for accurate calculation of BOB and bolus doses

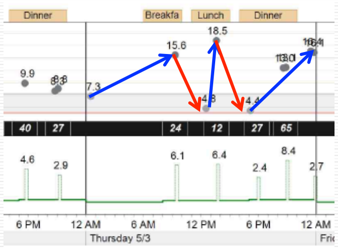
Graphic adapted from Mudaliar et al: Diabetes Care, 22: 1501, 1999

Stop Frequent Lows First

- **You cannot tell how much excess insulin there is!**
- Start with a 5% or 10% reduction in the TDD
- Compare the current TDD to an "ideal" TDD for weight.
  - Divide weight(lbs) by 4 to find an expected TDD if their sensitivity to insulin were average

Example: Someone who weighs 160 lbs would be expected to have a TDD of 40 units (160/4 = 40).

Example – Frequent Lows



41 yo female with A1c = 6.9%

TDD = 50.5 u/d

152 lb/4 = 38.0 u/d

Then Stop Frequent Highs

When the average BG is high **with few lows**:

Raise TDD by 1% for each 6 mg/dl (or for each 0.2% in A1c) you want to lower the glucose

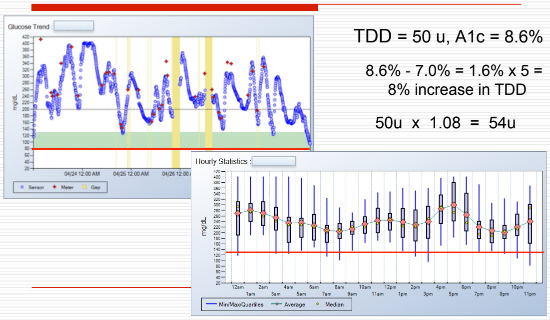
Example: Amy's avg TDD is 40 u/day. Her average meter BG is 205 mg/dl with few lows. Her BG goal (average) is 145 mg/dl:

205 mg/dl – 145 mg/dl = 60 mg/dl

60 mg/dl ÷ 6 mg/dl = 10% rise needed in TDD

40 units x 1.10 = 44 units

Example – Frequent Highs



TDD = 50 u, A1c = 8.6%

8.6% - 7.0% = 1.6% x 5 = 8% increase in TDD

50u x 1.08 = 54u

TDD Before & After Adjustment

Start TDD = 36 u

- Raised basal by 0.05 u/hr all day (+1.2 u/day)
- Lowered carb factor from 1u/13g to 1u/12g (+1.8 u/day)

End TDD = 39 u

Verify the TDD

- Compare TDD to wt(lbs)/4 [or (kgs)/1.8]
- Check frequency and severity of lows
- Contrast TDD with A1c & avg. BG on meter
- Decide if TDD should change

APP Study – Use TDD to Determine Initial Settings[1]

Basal *= ~ 48% of TDD (0.02 x TDD = avg. U/hr)*

CarbF *= 2.6 x Wt(lbs) / TDD*

Corr. Factor *= 1960/TDD (mg/dl) (1500 to 2400)*

CorrF is inversely related to TDD and to avg. BG – Poor control = need for larger correction doses

Or use Pump Settings Tool to compare current to "ideal" settings at www.diabetesnet.com/diabetes_tools/pumpsettings/

[1] *J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010*

Jerry's Starting Pump Settings

TDD = 50 u   Weight = 180 lbs   A1c = 7.0% DIA = 5 hrs

Basal = 50 u x 0.02 = 1.0 u/hr

CarbF = 2.6 x $\frac{180 \text{ lbs}}{50}$ = 9.4 grams/unit

CorrF = 1960/50 = 39 mg/dl per unit

[1]J Walsh, R Roberts, T Bailey: J Diab Science & Technology 2010, Vol 4, #5, Sept 2010

Actual/Expected TDD Measures A Person's Relative Insulin Resistance (RIR)

- Avg. insulin dose in 2 large studies off well-controlled pump patients was 0.24 U/lb (0.53 U/kg)[1] and 0.245 U/lb (0.54 U/kg)[2]

  Expected TDD = Wt(lb) x 0.24 U/lb [or Wt(lb)/4]
- Actual TDD = an average of their total daily doses (>14 days)
- An insulin-dependent individual's relative insulin resistance is:

$$\text{RIR} = \frac{\text{Actual TDD*}}{0.24 \text{ U/lb.} \times \text{Wt(lb)}}$$

1.0 = average
<1.0 = less resistant
>1.0 = more resistant

*(or better, use the person's ideal TDD)

1. Davidson PC, Hebblewhite HR, Steed RD, Bode BW. Analysis of guidelines for basal-bolus dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. Endocr Pract. 2008;14(9):1095–101.
2. Adamsson U, Lins PE. Clinical views on insulin resistance in type-1 diabetes. In: Agardh CD, Berne C, Östman J. Diabetes. Stockholm: Almqvist & Wiksell; 1992, 142–50.

Consider Meds When RIR is High

Type 1s become Type 2s and Type 2s become Type 1s – when insulin resistance is > 1, consider adding GLP-1 agonists or an oral agent:

- GLP-1 agonist
- Metformin
- Glitazone

Clever Pump Trick – How Many Carbs Are Needed for a Low?

1. 10 grams for each 80 lbs of weight
2. Plus grams = the current BOB x CarbF

Example: At 9 pm, Amy's BG is 52 mg/dl and she has 2u of BOB

- At 160 lbs, she needs 20 grams of carb
- 2 units of BOB with a CarbF of 8 gr/u = 16 grams
- For this low, Amy needs 20 g + 16 g = 36 grams

Infusion Set Issues

- Little research has been done
- Clinician and wearer reports and blogs suggest infusion set issues are widespread
- Set leaks and failures create random hyperglycemia, making their source difficult to identify.
- A major source for calls to pump companies and for pump discontinuation
- Less than 10% of pumps returned for problems have any defect

Infusion Set Failure is Common

- Most of the 16,849 adverse pump events reported to the FDA between 2006-2009[1] involved infusion sets[1]
- A 2006 review of pumps in France likewise found that most serious adverse events involved infusion sets[2]
- Auto-insertion devices have a high failure rate of 8.9%[3]
- In a survey of 1142 pumpers in 40 German diabetes clinics, 36% used auto-insertion devices and 72% reported that the device failed to work ~10% of the time, and 54% reported high BGs for unknown reasons until their infusion set was changed

1 www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralHospitalandPersonalUseDevicesPanel/UCM202779.pdf
[2] Maugendre D. Technical risks with subcutaneous insulin infusion. Diabetes Metab. 2006;32:279-284.
[3] Renard E, et al: Lower rate of initial failures and reduced occurrence of adverse events with a new catheter model for continuous SQ insulin infusion. Diabetes Technol Ther 12:769-773, 2010.
[4] Reichert D, et al. Realität der Insulinpumpentherapie in Diabetesschwerpunktpraxen: Daten von 1142 Patienten aus 40 diabetologischen Schwerpunktpraxen. Diabetes, Stoffw. und Herz 22: 367-375, 2013.

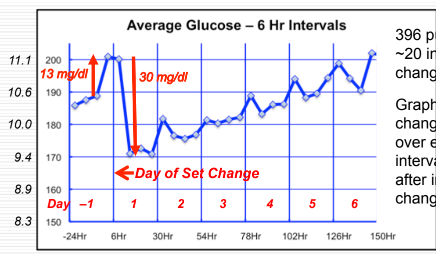
Infusion Set Auto-Inserters

Reasons that Infusion Sets Fail

- Complete pullout
- Insulin leak along Teflon to skin
- Hematoma (pool of blood)
- Occlusion
- Cannula kink
- Loose hub
- Punctured line

ALL should rarely or never happen

APP Study – Average BGs Before & After Set Change



396 pumps with ~20 infusion set changes per pump.

Graph shows change in avg. BG over each 6 hr interval before and after infusion set is changed.

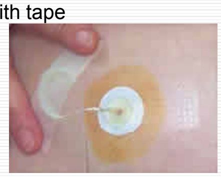
Unpublished data from Actual Pump Practices Study by J Walsh, R Roberts, and T Bailey

Does Pumper have an Infusion Set Problem?

- Do infusion sites often “go bad”?
- Is there “scarring” or “poor absorption”?
- Often have 2 or more unexplained highs in a row?
- Do correction boluses sometimes not work?
- Have high BGs (often 6-32 hrs) until set is changed?

Solutions for Infusion Set Problems

- Anchor the infusion line with tape
- Review site prep and insertion technique with clinician or trainer
- Insert set by hand
- Switch to a different brand of infusion set



Tapes: Transpore, Micropore, Durapore, Hypafix

Future Developments

Artificial Pancreas Pathway

TODAY

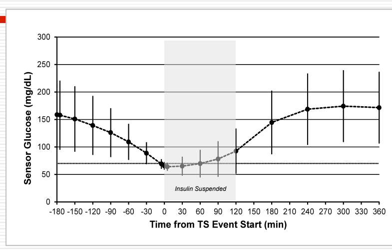
OPEN-LOOP (Patient confirmation)	SEMI-CLOSED LOOP (Semi-automated system)	CLOSED-LOOP (Fully-automated system)

• Insulin pump + glucose sensor + bolus wizard	• Iterative:
	– Threshold suspend
	– Predictive suspend
	– Overnight closed-loop
		• Free-living trials have started
		• Dual hormones?
		• Meal-handling
		  • Announce?
		  • Assist?

Early Closed Loop – Medtronic 530G

- Low Glucose Suspend (LGS) – CGM can suspend basal up to 2 hrs for a low.
- May reduce length of night lows.
- 6 day Enlite sensor
- Wearability and excess CGM alarms are an issue for some

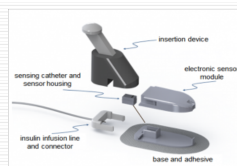
Threshold Suspend lasting at least 2 hours



Mean ± SD of sensor glucose values surrounding 2-hour TS events. The dotted line is at 70 mg/dL.

Bergenstal R. et al ADA 2013

Future CGM Advances



Pacific Diabetes Technologies

- Factory calibration
- Abbott Flash -14 day, no cal
  - Intermittent CGM at test strip pricing
- Dual sensors on one CGM set
  - 2 glucose oxidase
  - 1 glucose oxidase and 1 fluorescent
- Multi CGMs on one cannula
  - 6-8 sensors on insulin cannula (15% BG drop)

Accu-Chek and Omnipod CGMs

Accu-Chek Insight Pump

Accu-Check CGM* has 4 distinct sensor areas on the sensor wire

- Mean ARD is ~9.2%,[1] compared to ~10.7% for upcoming Dexcom Gen4 algorithm and 13.9% for Enlite[2]

Omnipod is developing its own CGM system*

One independent artificial pancreas study found a MARD of 10.8% for current Dexcom G4, 12.3% for Abbott Navigator, and 17.9% for MiniMed Enlite.[3]

* Not FDA approved

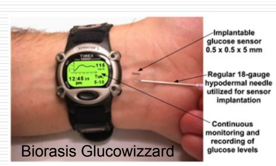
1. *E. Zschornack et al: DJST Vol 7(4), July 2013*
2. *B. Keenan et al: DTT Vol 14(3) 2012*
3. *Dr. Steven Russell of Mass. General Hosp. report at Insulindependance 2013, SD*

Implanted CGMs

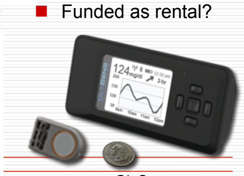
MicroCHIPS Illume

Sensionics

- Months to years of use
- No disposables
- Minor surgery
- Funded as rental?

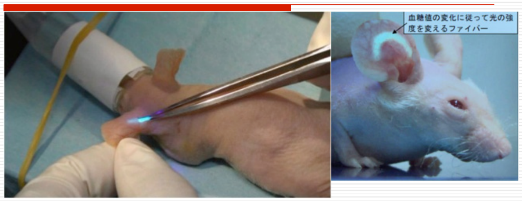


Biorasis Glucowizzard



GlySens

Implanted Fluorescent CGM



Molecules fluoresce & change color as glucose rises or falls
- Small size, low power, low cost, long life, good accuracy, minimal lag time

From Y. J. Heo et al: Institute of Industrial Science at the University of Tokyo

Faster Insulin

For better matching of carbs (< 2 hrs) with insulin (5 hrs)
- Ultra-fast insulin analogs
  - Novo Nordisk FIAsp
  - Biodel
  - MannKind Afrezza (inhaled)
- Diaport intraperitoneal delivery
- Micro-needle intradermal delivery
- Hyaluronidase
- Warming of infusion site

Goal: fewer highs and lows

Advantage of Accu-Chek Diaport or Oral Insulin

Delivery into the abdominal cavity speeds up insulin action with more insulin going directly to the liver. Oral insulin would be absorbed directly into the portal vein.

Faster in and faster out = less hypoglycemia

BD Intradermal Microneedle

- 1.5 mm intradermal needle speeds up insulin action
- Painless
- Reliable attachment of set will be critical

Future Pump Features

- How setting change impacts TDD (& BG)
- Temp basal plus bolus doses
- Super Bolus
- Meal-size boluses
- Excess BOB alert (bolus without BG but BOB is ++)
- Low BG predictor (HypoManager)
- Exercise compensator
- Infusion set monitor/leak detector
- Automated basal and bolus testing

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Slides at www.diabetesnet.com/diabetes-resources/diabetes-presentations
Books at www.diabetesnet.com/dmall/ or 800-988-4772