48 M admitted for preoperative optimization prior to weight-loss surgery

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Endorama
September 8, 2016

HPI:

- 48 M with obesity (BMI 50)
  - Obesity since childhood with resultant complications:
  - DM2, HTN, dyslipidemia, HF, arthritis, gout, GERD, OSA, hepatic steatosis
  - >20 admissions in past few years for HF and other obesity-related comorbidities.
- Diabetes history:
  - Diagnosed in 2000, on insulin since 2006 and on a pump since 2007
  - Failed multiple oral medications (metformin – fluctuating renal function, glipizides, thiazolidinediones, DPP4s. Recently started on GLP1RA and SGLT2 by PCP in addition to pump therapy)
- Prior attempts at weight loss:
  - Exercise + Sibutramine – centrally-acting serotonin-norepinephrine reuptake inhibitor (SNRI), now off the market due to association with increased CV events.
  - Nadir 88kg (195#) but regained weight following knee injury

More history:

- ROS: notable for DOE, LE edema, back pain, dizziness/weakness.
- PMH: hypothyroidism, ankylosing spondylitis (HLA B27+, iritis), hypogonadism
- PSH: None
- Soc: EtOH – none, never smoker, Computer science degree, previously working at Lowe's
- FH: Brother and Sister with T2DM
- Current meds: ?**abiglutide**, **dapagliflozin, insulin pump**, levothyroxine, calcium carbonate, cholecalciferol, allopurinol, hydroxychloroquine, ASA, atorvastatin, eplerenone, lisinopril, metoprolol, torsemide, pantoprazole, dicyclomine, pregabalin, sildenafil.

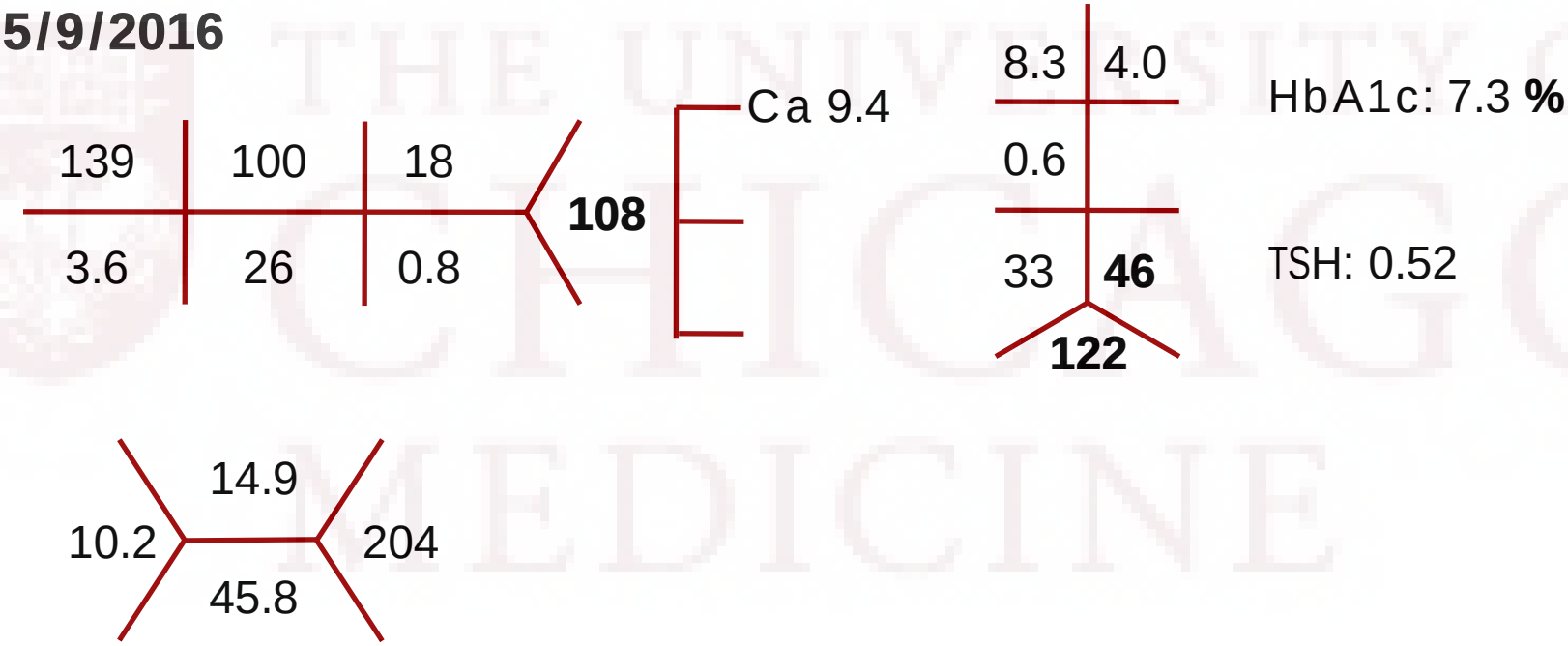
Physical Exam

- VS: T 36.1C, BP 120/63, P 73, RR 16, SpO2 98% RA, Ht 162.6 cm, Wt 132.9 kg, **BMI 50.3 kg/m^2**

- Constitutional: Morbidly obese Asian M in no distress, pleasant, mobile about room.
- Head: Normocephalic and atraumatic.
- Eyes: Conjunctivae are normal. Pupils are equal, round, and reactive to light.
- Neck: Normal range of motion. Neck supple. No thyromegaly present (limited).
- Cardiovascular: Normal rate and regular rhythm, no murmurs **+Bilateral 1-2+ LE edema**
- Pulmonary/Chest: Effort normal and breath sounds normal.
- Abdominal: Soft. Bowel sounds are normal.
  Musculoskeletal: No deformities or joint swelling.
- Neurological: AOx4, no focal deficits.
- Skin: Skin is warm and dry. No rashes. **+acanthosis nigricans, skin tags**
- Psychiatric: Normal mood and affect. Behavior is normal. Judgment and thought content normal.

Labs:

5/9/2016


139
100
18
3.6
26
0.8
108
Ca 9.4
8.3
4.0
0.6
33
46
122
HbA1c: 7.3 %
TSH: 0.52
14.9
10.2
204
45.8

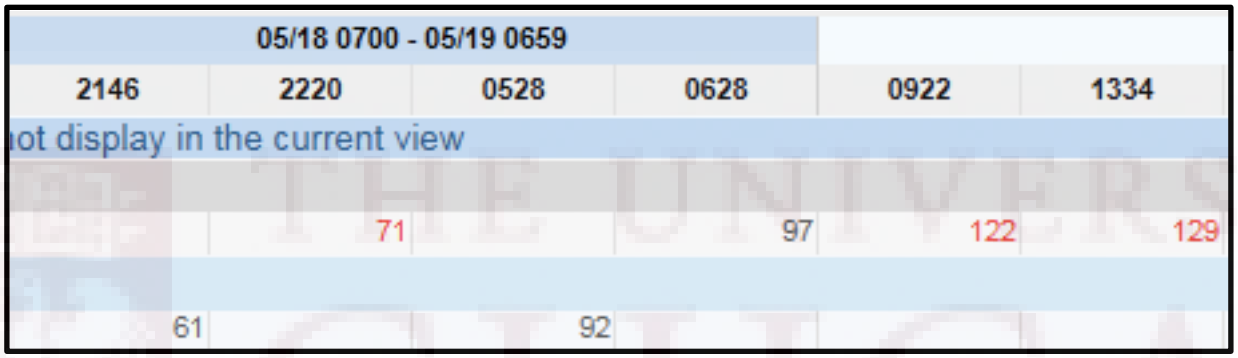
Insulin pump settings on admission:

- U500 Insulin
- Basal Rates
  - **12AM: 2.0** (10 U/hr U100)
  - **06AM: 4.0** (20 U/hr)
  - **09AM: 3.0** (15 U/hr)
  - **12:30PM: 2.5** (12.5 U/hr)
- **Total daily basal: 62** (310 Units /day)
- **I:C 2.5** (1U for 0.5g carbs)
- **ISF 37** (7.4)

6PM Page:

"Patient is running low on insulin, does not have supplies or home insulin at bedside, please advise"

What would you like to do?



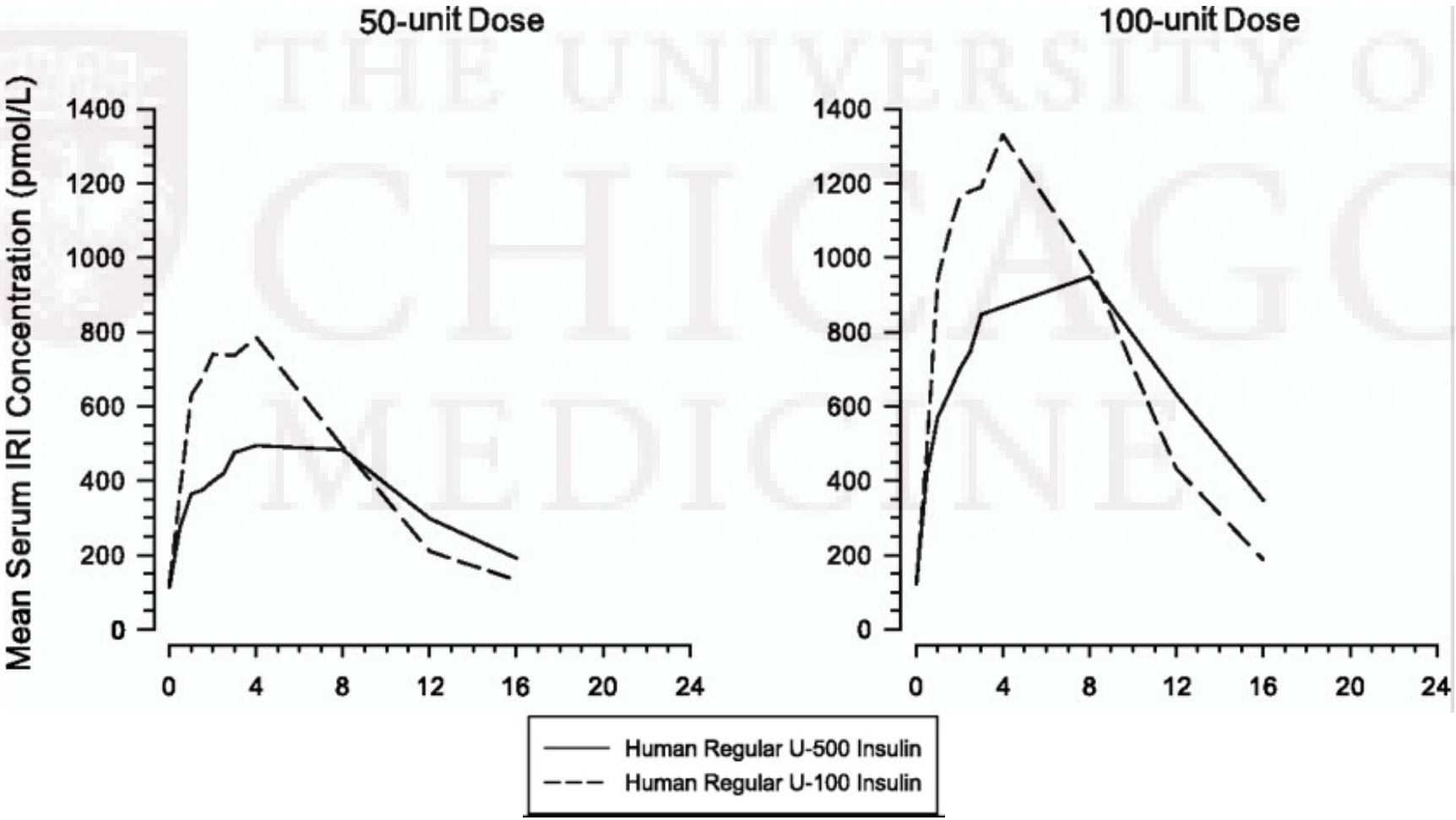
05/18 0700 - 05/19 0659					
2146	2220	0528	0628	0922	1334
ot display in the current view					
	71		97	122	129
61		92			

- Basal Rates
  - **12AM: 2.0** (10 U/hr U100)
  - **06AM: 4.0** (20 U/hr)
  - **09AM: 3.0** (15 U/hr)
  - **12:30PM: 2.5** (12.5 U/hr)
- **Total daily basal: 62** (310 Units)
- **I:C 2.5** (1U for 0.5g carbs)
- **ISF 37** (7.4)

U500

- In the process of making U500 available by special request in the pharmacy
- Requirements
  - Endocrine consult
  - Pharmacy must draw up each dose
- Regular U-100 insulin: peaks at 2–4 h, duration of action is 5–7 h.
- Regular U-500 more closely resembles NPH with a flatter peak 4-10 h and a more prolonged duration of action of 10-18 h and up to 24 h

U500 vs U100



Diabetes Care 2011 Dec; 34(12): 2496-2501

A little more history…

- 3/2015 Endocrine visit – U500 pump settings adjusted:

Time	Old Rate (U/hr)	New Rate (U/hr)
0:00	2.5	3.5
7:00	6.0	7.0
9:00	7.5	8.5
18:00	6.5	7.5
21:00	6.35	7.5
	TDD: 677.75 Units	**TDD: 800 Units**

- Prior hospitalization several years ago, pt was on ~ 800 Units of insulin/day. Recs:
  - Lantus 200 Units BID (given in 100 U injections)
  - 75 Units of Novolog TIDAC + 4:50>130

6PM Page: Our plan

- Reduce basal settings by ~20% due to lows
- Stop bolusing from pump for meals, start Novolog 2 Units for every 1 g carbs + 5:50>150 high blood sugar correction

- **If no pump supplies by 10PM,** start Lantus 90 Units (given in two 45 Unit injections) Q12 hours and discontinue pump
  - Total basal dose reduction of 25% from lowest basal rate

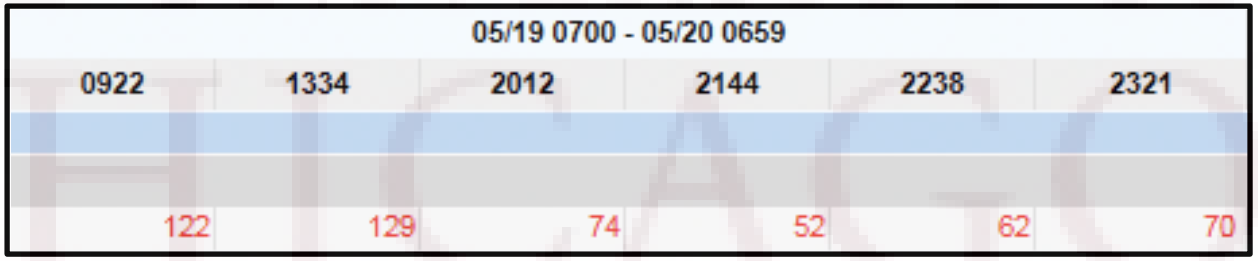
Transition from U-500 to U-100 in the inpatient setting is safe

- Retrospective review of inpatients on U-500
  - N=27 patients
  - 62 separate admissions.
  - Patients:
    - 64.4 years
    - BMI 38.9 kg/m2
    - HgbA1c of 8.7% (eAG 234 mg/dL)
  - All patients converted from U-500 to U-100 on admission
  - Average TDD of insulin was 91 units inpatient vs. 337 units as outpatients ($p < 0.001$)
  - Overall, 89% of patients received ≤ 50% of their outpatient TDD.
  - The average inpatient glucose was slightly higher than the outpatient eAG, 234 mg/dl vs. 203 mg/dl ($p = 0.003$).
- Tripathy et al. compared patients maintained on U-500 continued on 85% TDD vs. 35% TDD in those switched to U-100
- How did these patient do on return to the outpatient setting?

Paulus et al. Endocr Pract. 2016 Jun 30, ePub
Tripathy PR, Lansang MC. Endocr Pract. 2015;21:54-8

Day	Basal
5/18	313
5/19	255

Diet: diabetic



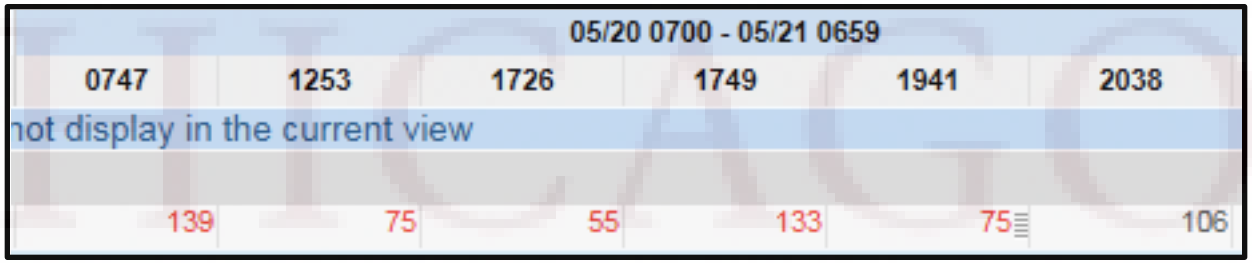
20% reduction in basal dose

More accurate carb counting?

Pump suspended temporarily for persistent lows overnight

Day	Basal
5/18	313
5/19	255
5/20	135

Diet: diabetic

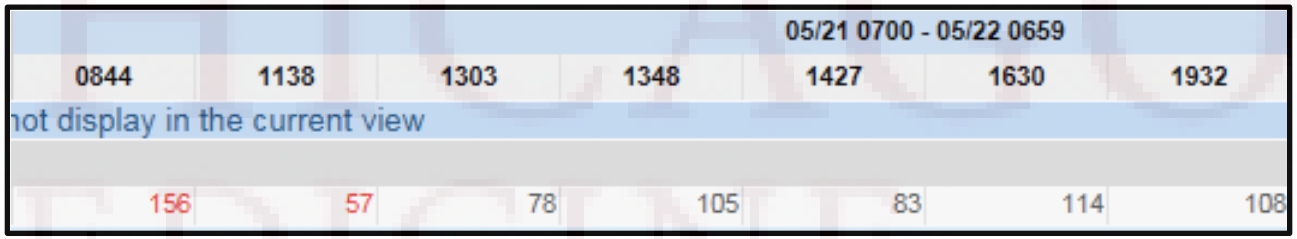


40% reduction in basal dose

Go back to the way you were counting carbs at home

Day	Basal
5/18	313
5/19	255
5/20	135
5/21	135

Diet: diabetic

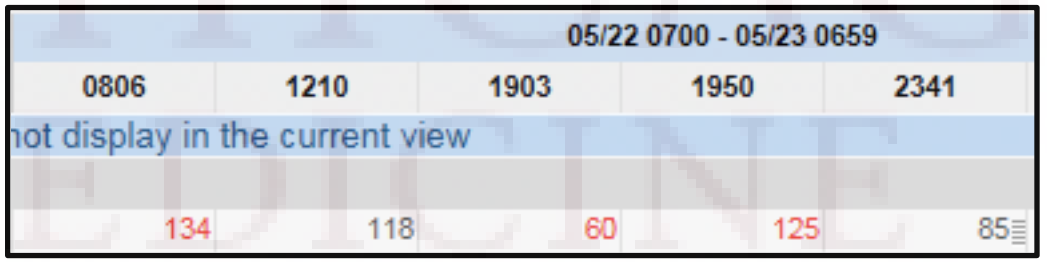


Carb ratio: 2.5→5 (1U/1g)

Pump suspended temporarily overnight due to lower BGs

Day	Basal
5/18	313
5/19	255
5/20	135
5/21	135
5/22	120

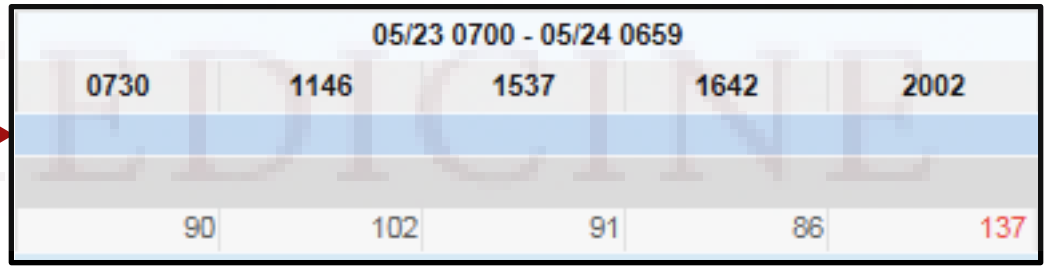
Diet: clears→NPO for procedure overnight



10% reduction in basal dose

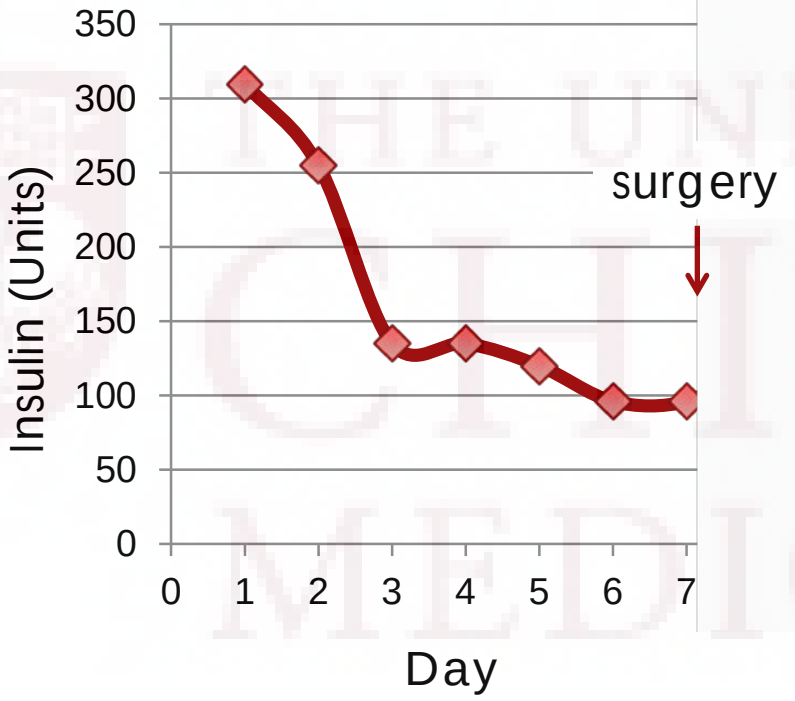
Day	Basal
5/18	313
5/19	255
5/20	135
5/21	135
5/22	120
5/23	96

Diet: NPO most of the day for procedure



Suspend pump for procedure

Overall decline in total daily basal insulin



- Why were we able to reduce the dose so much prior to surgery?

Any thoughts on potential contributors / mechanisms?

What is insulin-mediated insulin resistance?

- Chronic exposure to insulin promotes insulin resistance
- First proposed by James Gavin III in 1974
  - Exposed human lymphocytes to 10 M insulin
  - Decreased insulin receptor concentration in chronically exposed (5-16 hours) but not acutely exposed (0-2h) cells
- Subsequent mouse and human data demonstrates chronic hyperinsulinemia leads to insulin resistance

Gavin JR 3rd et al. Proc Natl Acad Sci U S A. 1974 Jan;71(1):84-8.
James R. Gavin III, MD, PhD—A Humble and Remarkable Trailblazer, Scientist, Advocate, Mentor, and Educator for Diabetes. Diabetes Care 2015 Jun; 38(6): 963-967

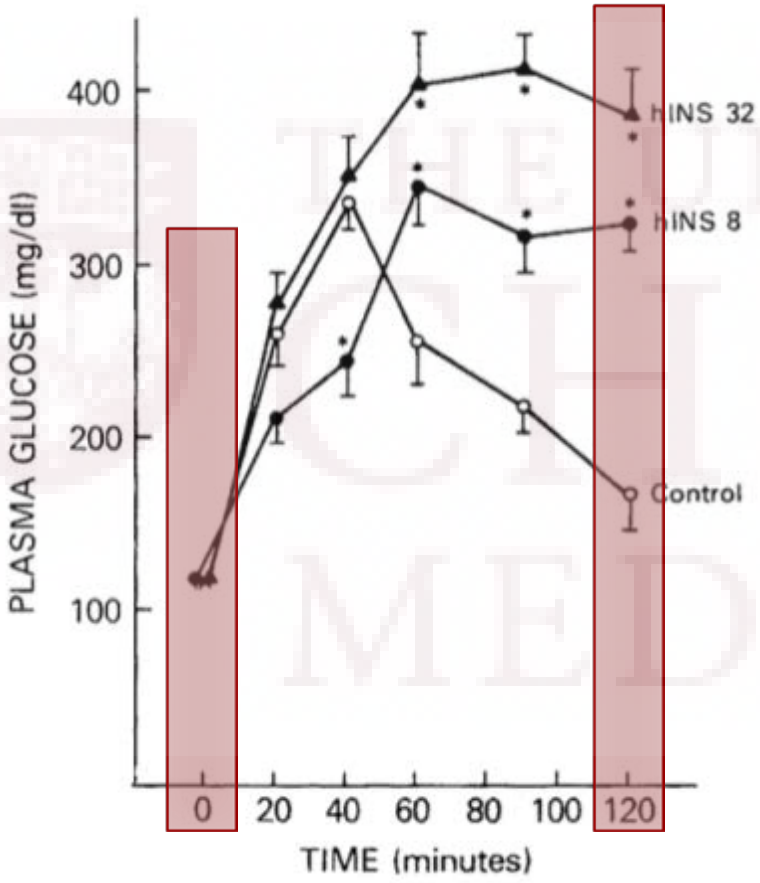
Animal models of chronic hyperinsulinemia show impaired glucose regulation

1) Transgenic mice with **0, 8, or 32** extra copies of the human insulin gene

- Achieved **two and four times** higher than normal basal plasma insulin levels
- **Normal body weight, normal fasting glucose**

2) Mice treated with exogenous insulin (NPH)

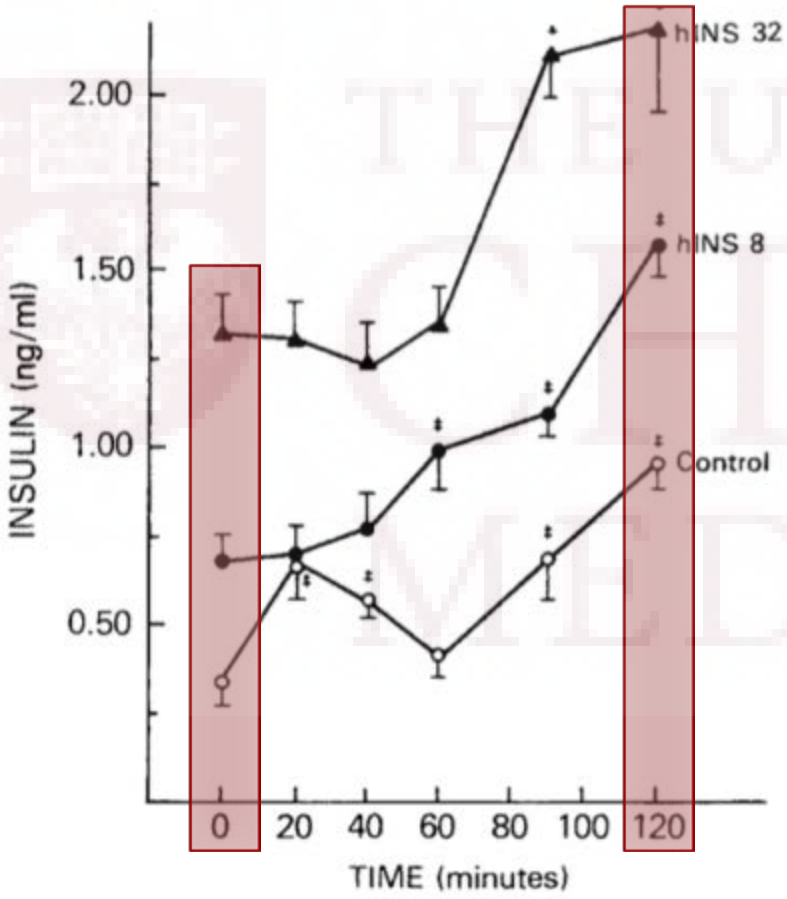
Insulin over-expressing mice have normal fasting plasma glucose but impaired response to glycemic challenge



- IP injection of glucose
- BG and insulin measured every 20 minutes

Marban SL, Roth J. *Lessons from Animal Diabetes VI.* 6th ed. Shafrir E, Boston, Birkhauser, 1996, p. 201–224 as adapted in DIABETES CARE, VOLUME 31, SUPPLEMENT 2, FEBRUARY 2008

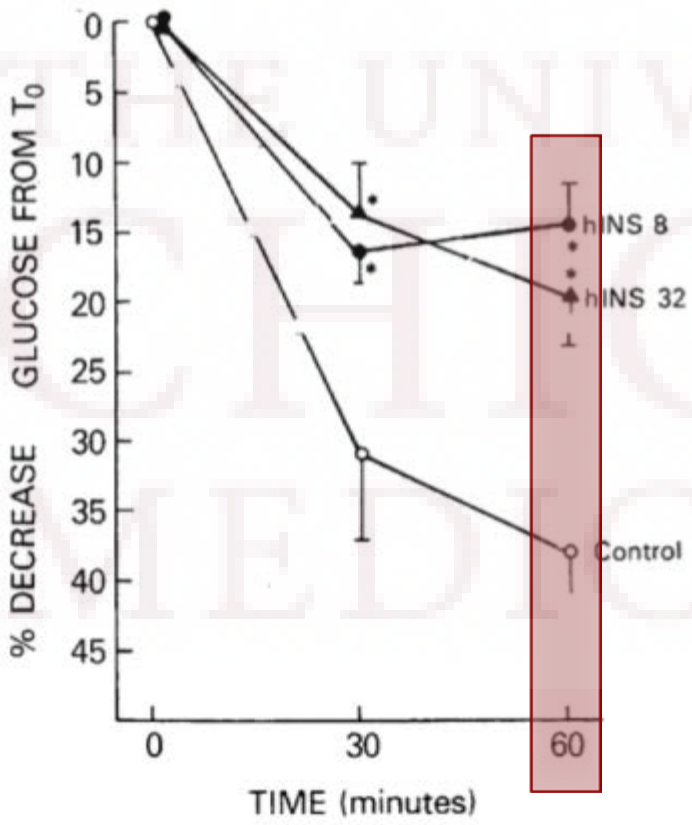
…and this is in spite of an exaggerated insulin response



- Fasting hyperinsulinemia
- Delayed secretion
- Ineffective glucose disposal in spite of higher levels of insulin

Marban SL, Roth J. *Lessons from Animal Diabetes VI.* 6th ed. Shafrir E, Boston, Birkhauser, 1996, p. 201–224 as adapted in DIABETES CARE, VOLUME 31, SUPPLEMENT 2, FEBRUARY 2008

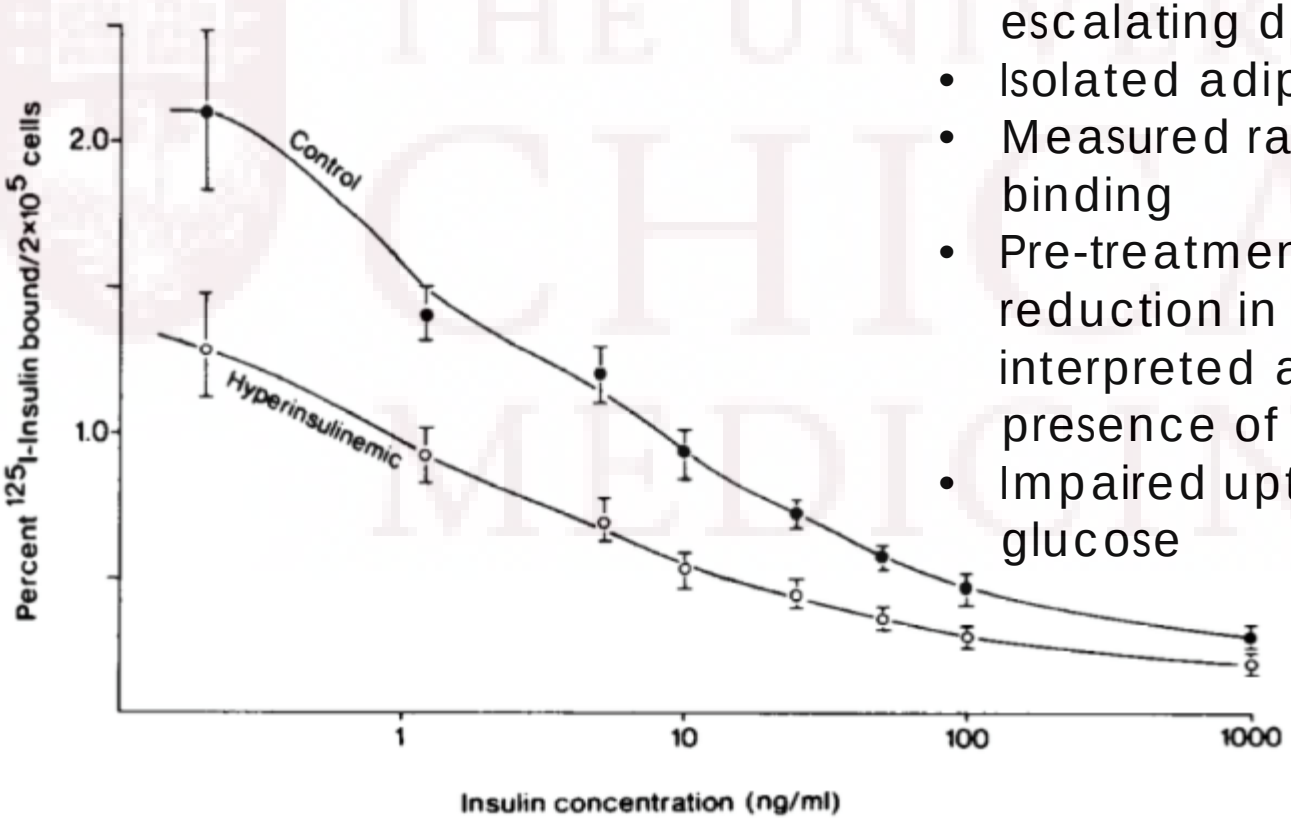
Hyperinsulinemic mice also have impaired glucose disposal during insulin tolerance test



- IP injection of insulin
- Reduction in BG from baseline measured at 30 and 60 minutes

Marban SL, Roth J. *Lessons from Animal Diabetes VI.* 6th ed. Shafrir E, Boston, Birkhauser, 1996, p. 201–224 as adapted in DIABETES CARE, VOLUME 31, SUPPLEMENT 2, FEBRUARY 2008

Hyperinsulinemia from exogenous insulin causes reversible downregluation of insulin receptors on adipoctyes

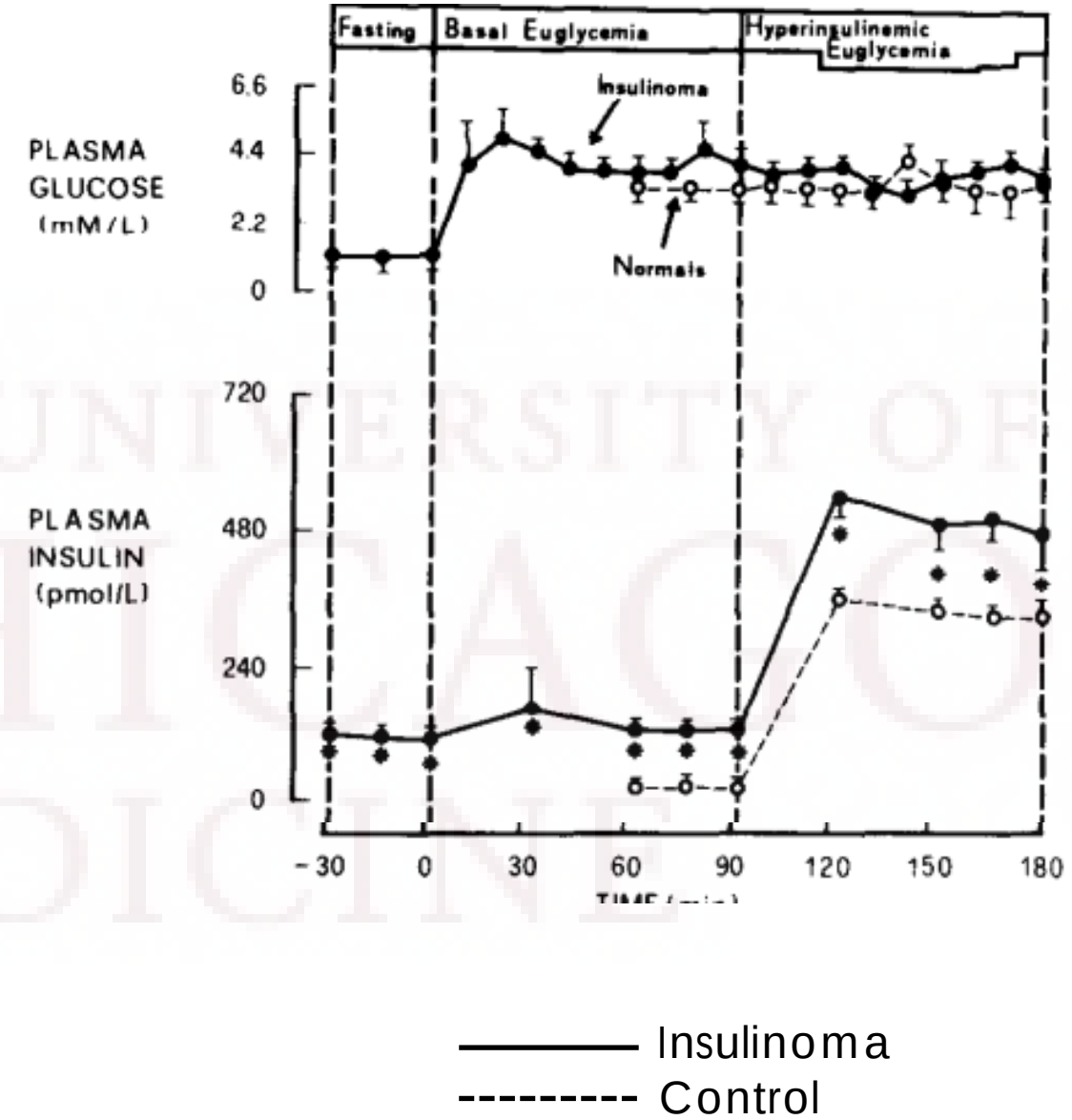


- NPH injected into rats at gradually escalating doses for 14 days
- Isolated adipocytes at day 15
- Measured radiolabeled insulin binding
- Pre-treatment with insulin led to 40% reduction in insulin binding, interpreted as a reduction in presence of insulin receptors
- Impaired uptake of radiolabeled glucose

Kobayashi et al. Am J Physiol. 1978 Jul;235(1):E53-62.

Patients with chronic hyperinsulinemia due to insulinomas are insulin resistant

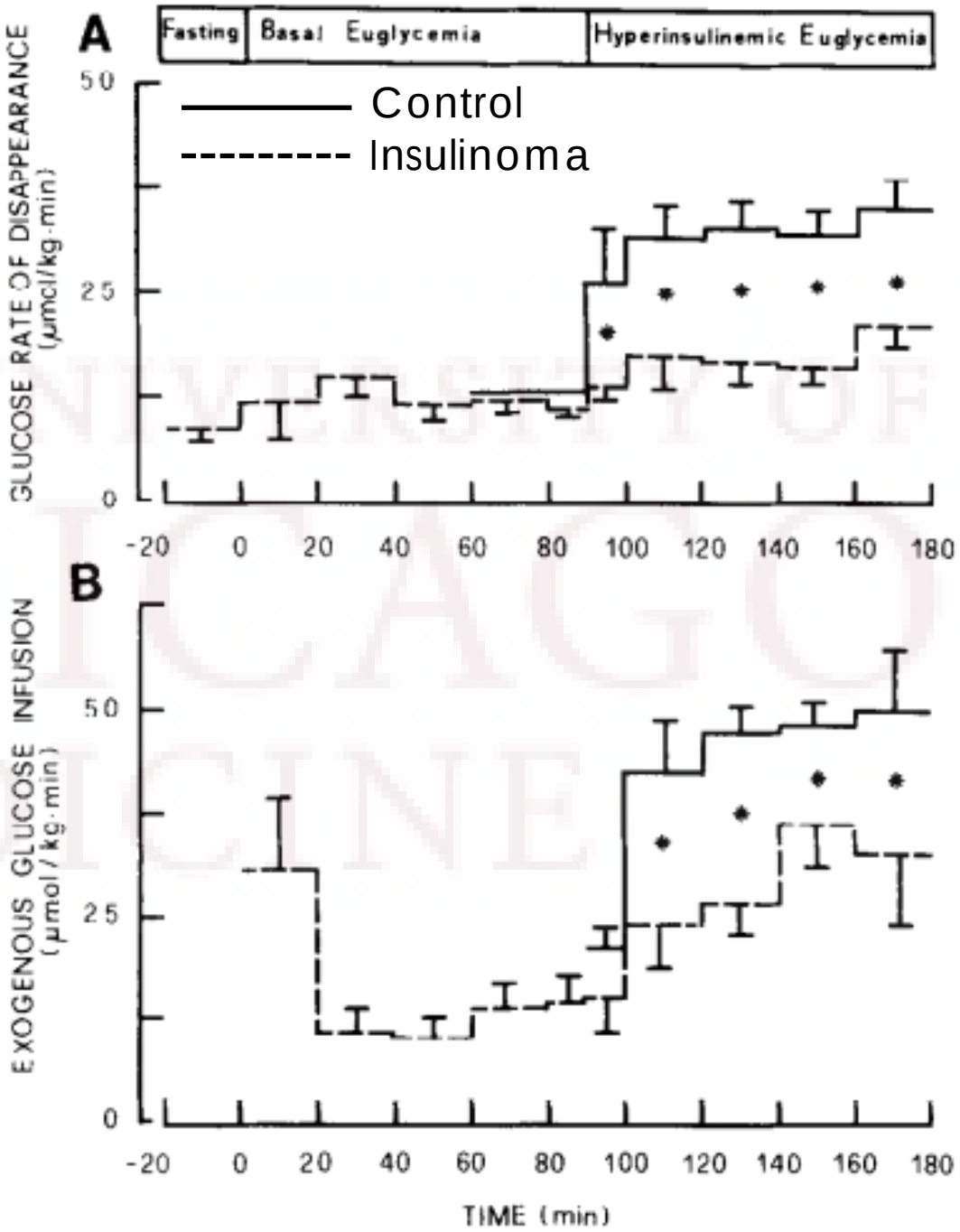
- Hyperinsulinemic, euglycemic clamp
- Insulinoma patients have higher levels of insulin



Del Prato et al. Metabolism 42: 24–29

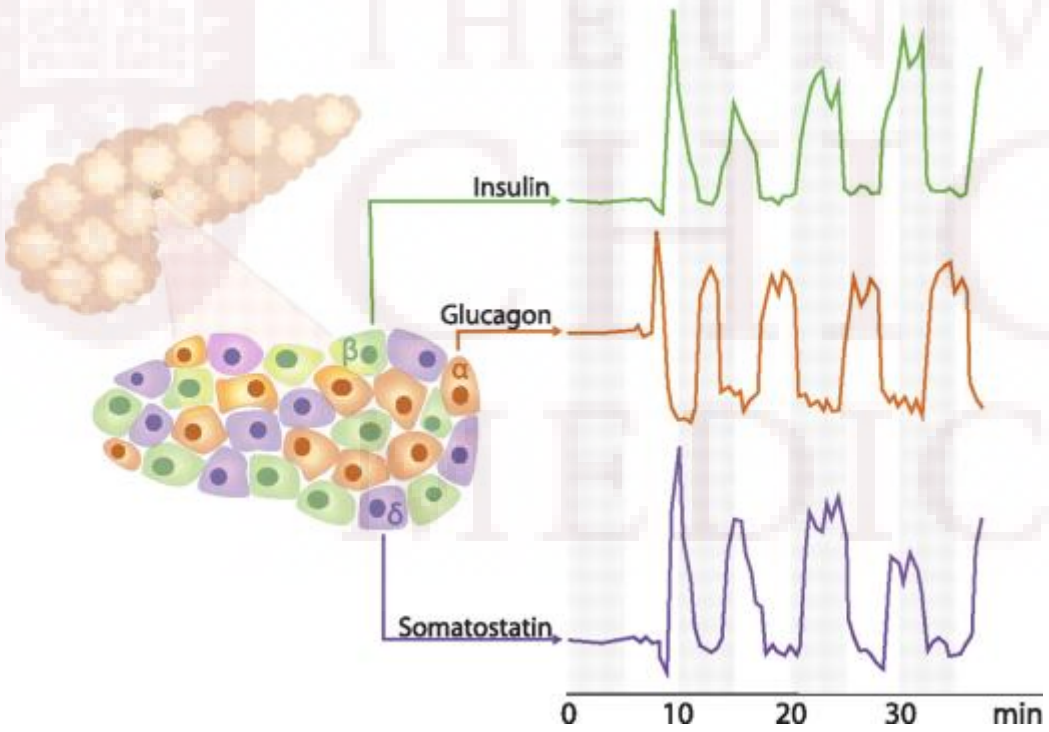
Patients with chronic hyperinsulinemia due to insulinomas are insulin resistant

- Insulinoma patients have reduced glucose disposal and require a lower glucose infusion rate (in spite of higher levels of insulin)



Del Prato et al. Metabolism 42: 24–29

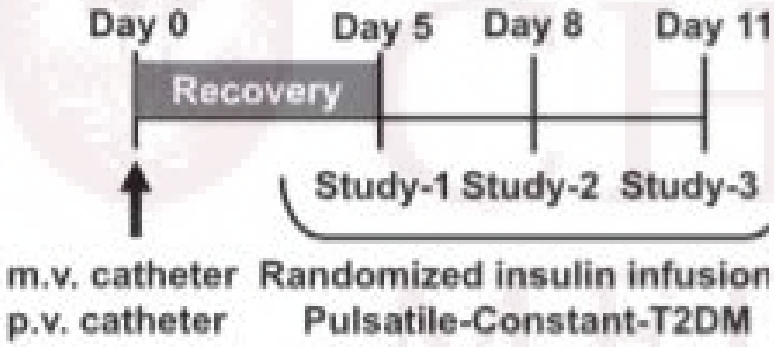
Endogenous Insulin is released in a pulsatile fashion

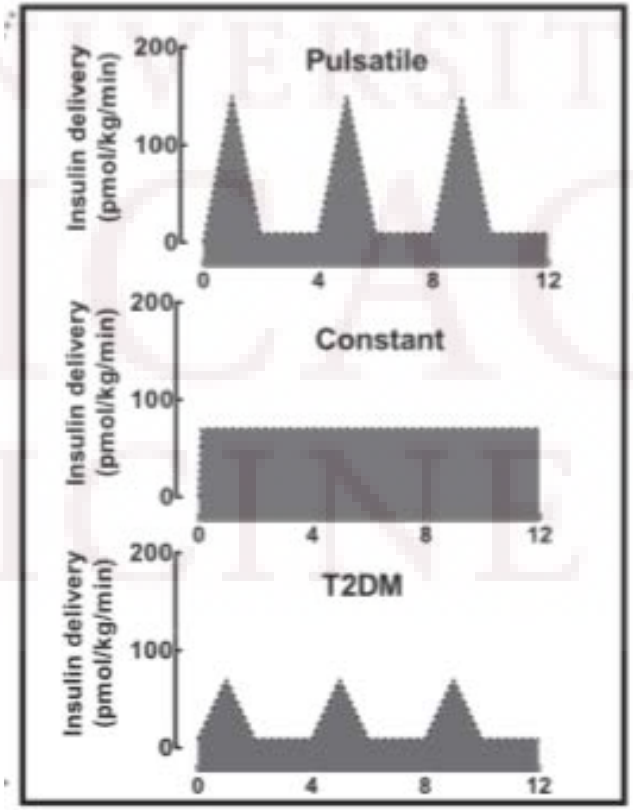


- Insulin secreted into hepatic portal vein every 5 minutes
- Increased amplitude with meals (0.5-1 nmol/L fasting→5 nmol/L with meals)
- Pulsatile insulin delivery is disrupted in diabetes
- Similar to other hormones (GH, GnRH, PTH)

Wahren et al. Diabetes Sep 2012, 61 (9) 2228-222

In vivo model of pulsatile vs. continuous insulin secretion





Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

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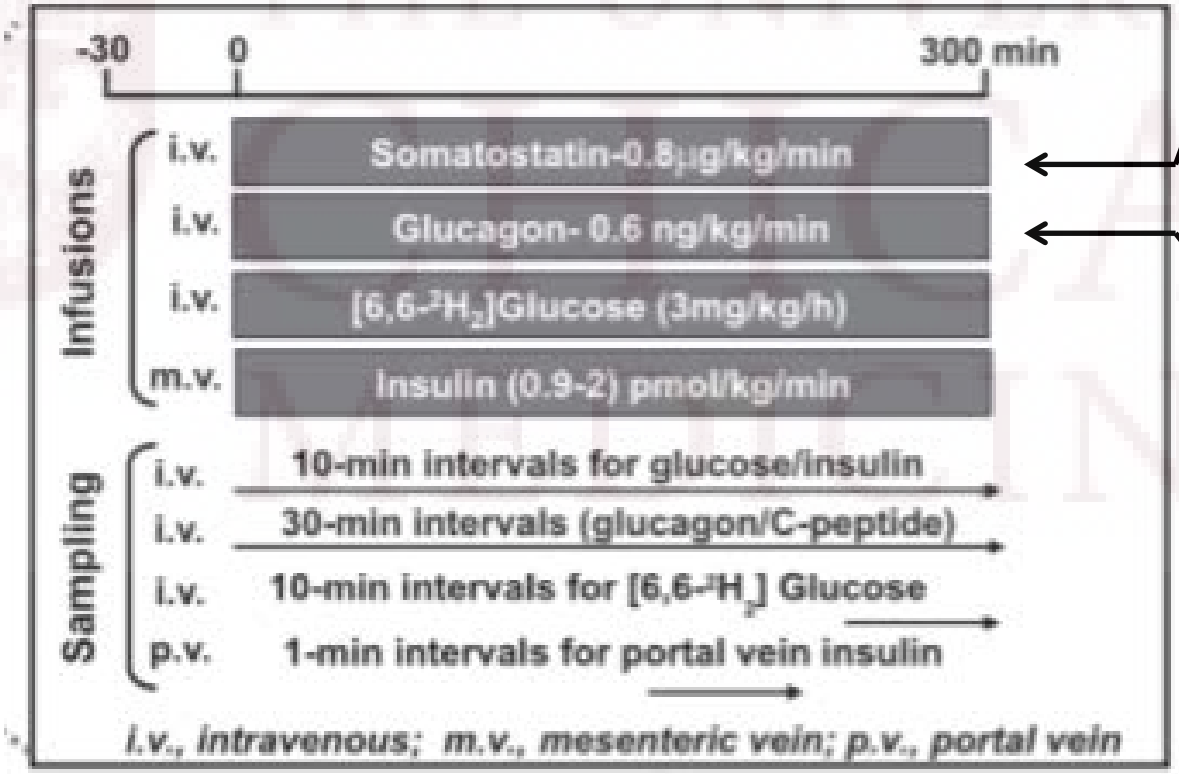
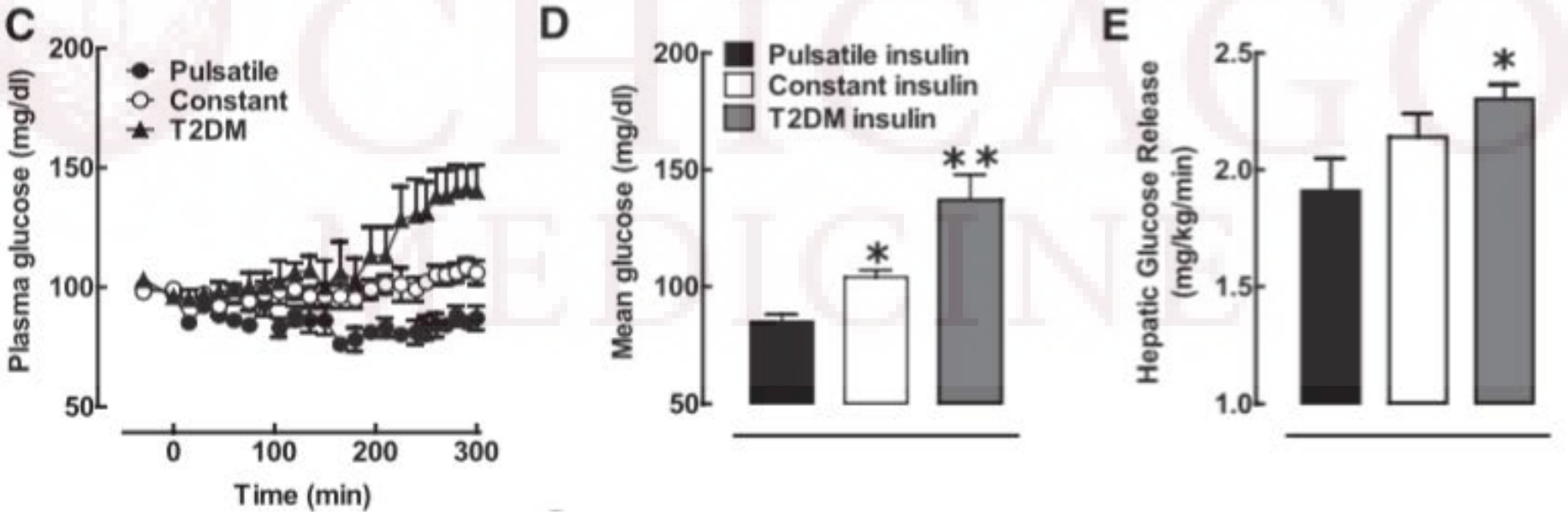


Suppression of endogenous insulin (and glucagon) production

Glucagon Replacement

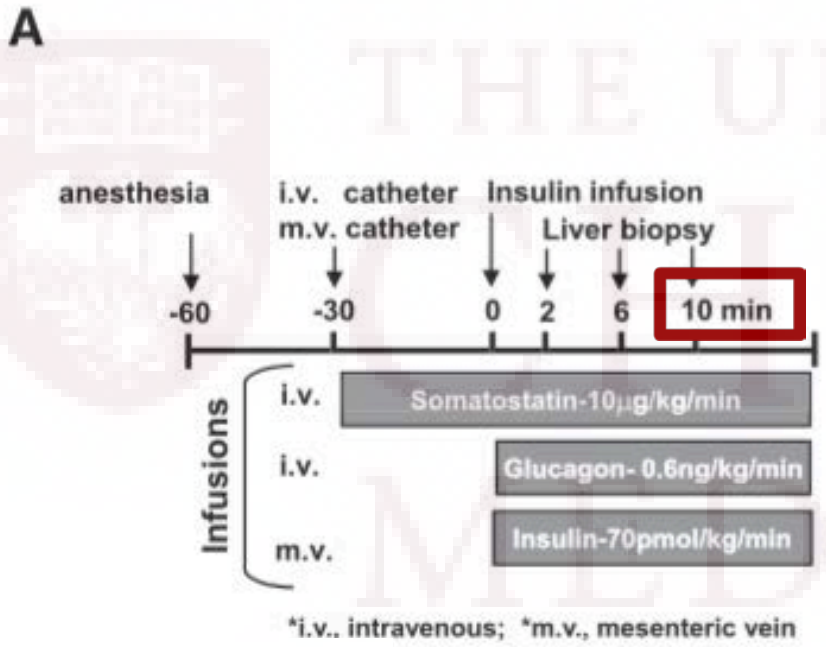
Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

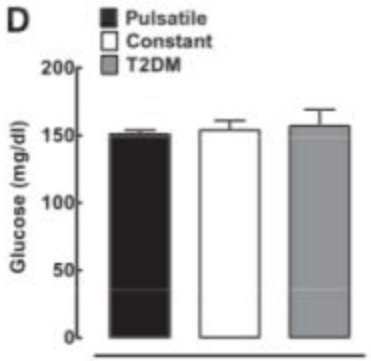
Continuous insulin delivery leads to relative hyperglycemia

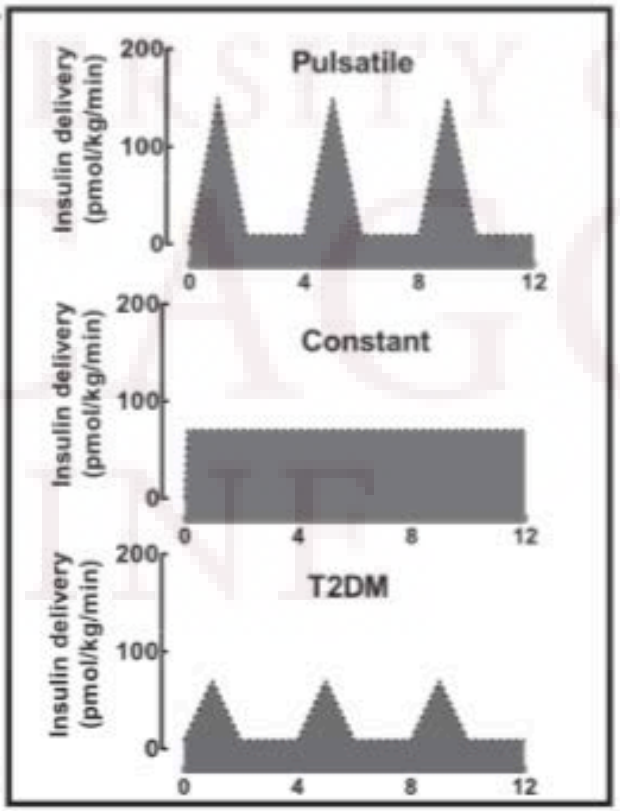


Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

Continuous insulin delivery leads to impaired insulin action in liver







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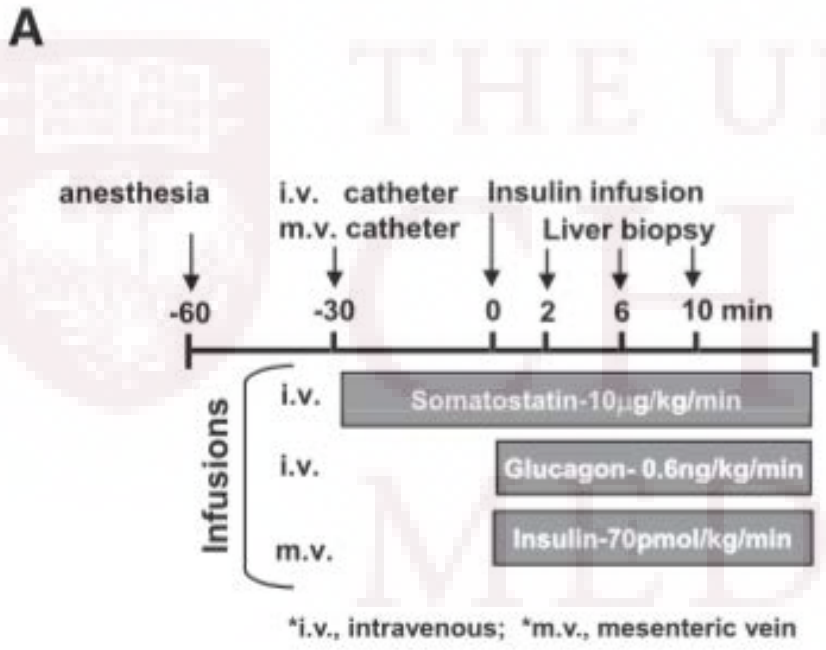
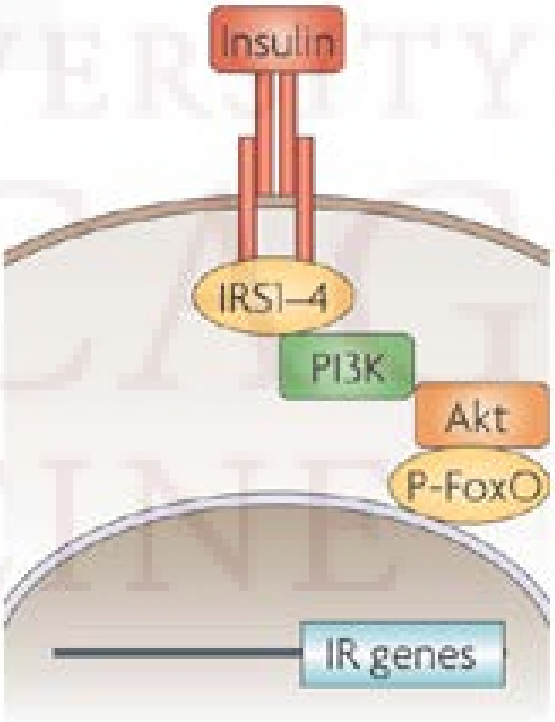
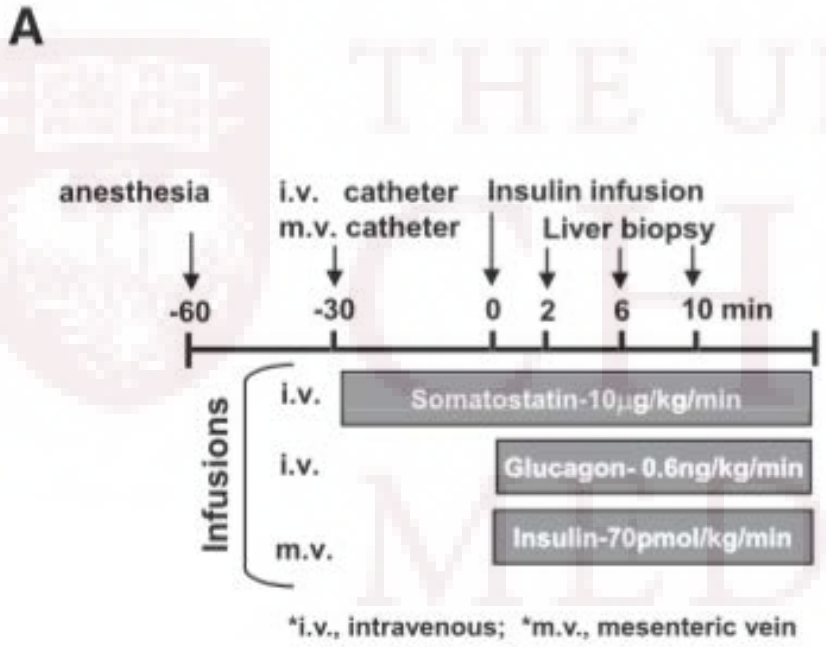


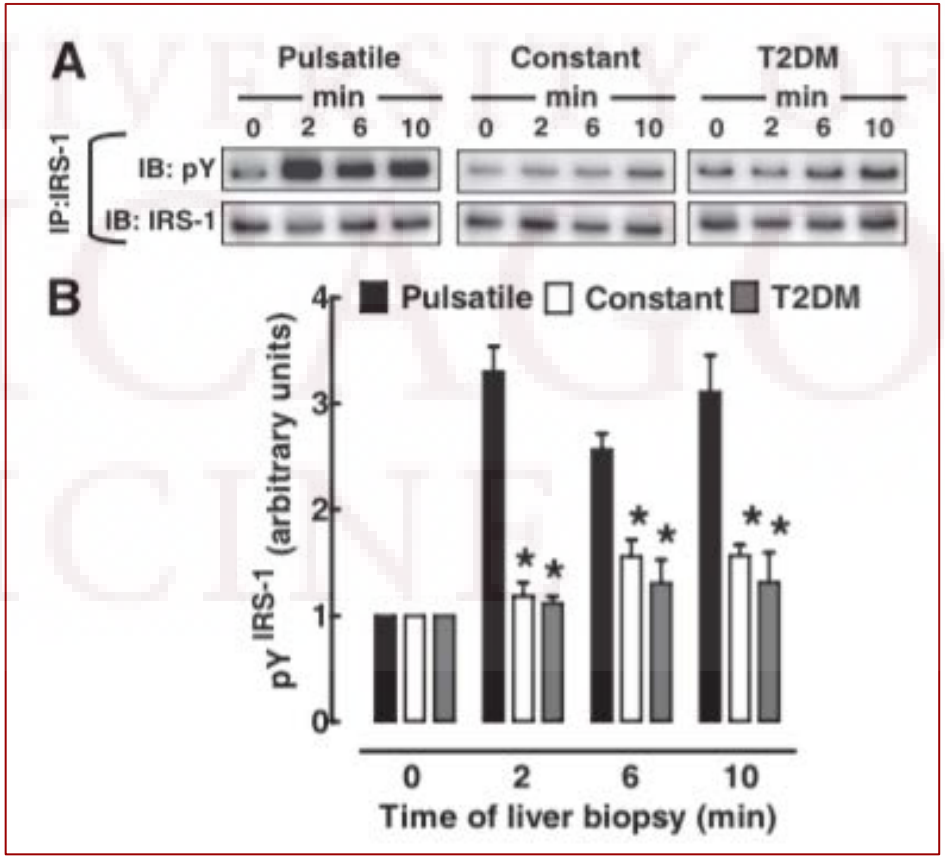


Sridhar Hannenhalli & Klaus H. Kaestner.
Nature Reviews Genetics 10, 233-240. 2009

Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

Continuous insulin delivery leads to impaired insulin action in liver



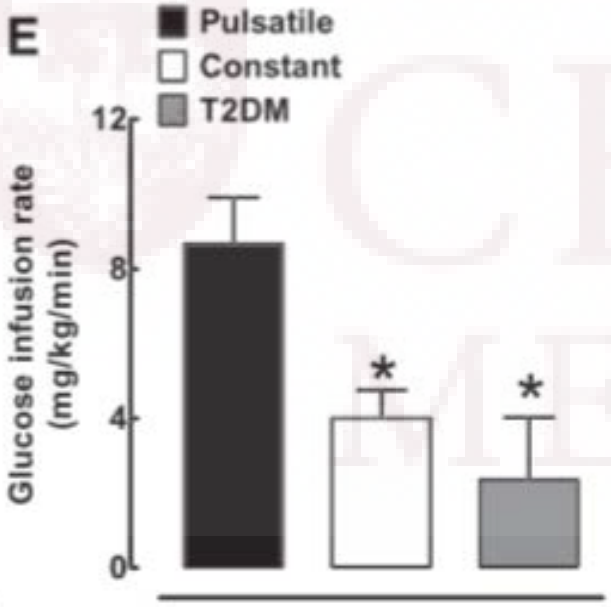


- Impaired activation of insulin signaling intermediates:
  - IRS-1 and IRS-2 associated PI3K pY and p85
  - AKT pSer 473
  - FOXO pSer 256

Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

Continuous insulin delivery leads to impaired insulin action in liver

Insulin tolerance test



At 30 min, with euglycemic clamp:

- 50-70% reduction in glucose infusion rate with constant or T2DM-like insulin delivery
- Reduction in signaling activation of signaling intermediates:
  - AKT p Ser 473
  - FOXO p Ser 256

- 120 min basal + bolus (to simulate a meal) showed similar results.

Matveyenko, A. V. *et al*. *Diabetes* **61,** 2269–2279 (2012).

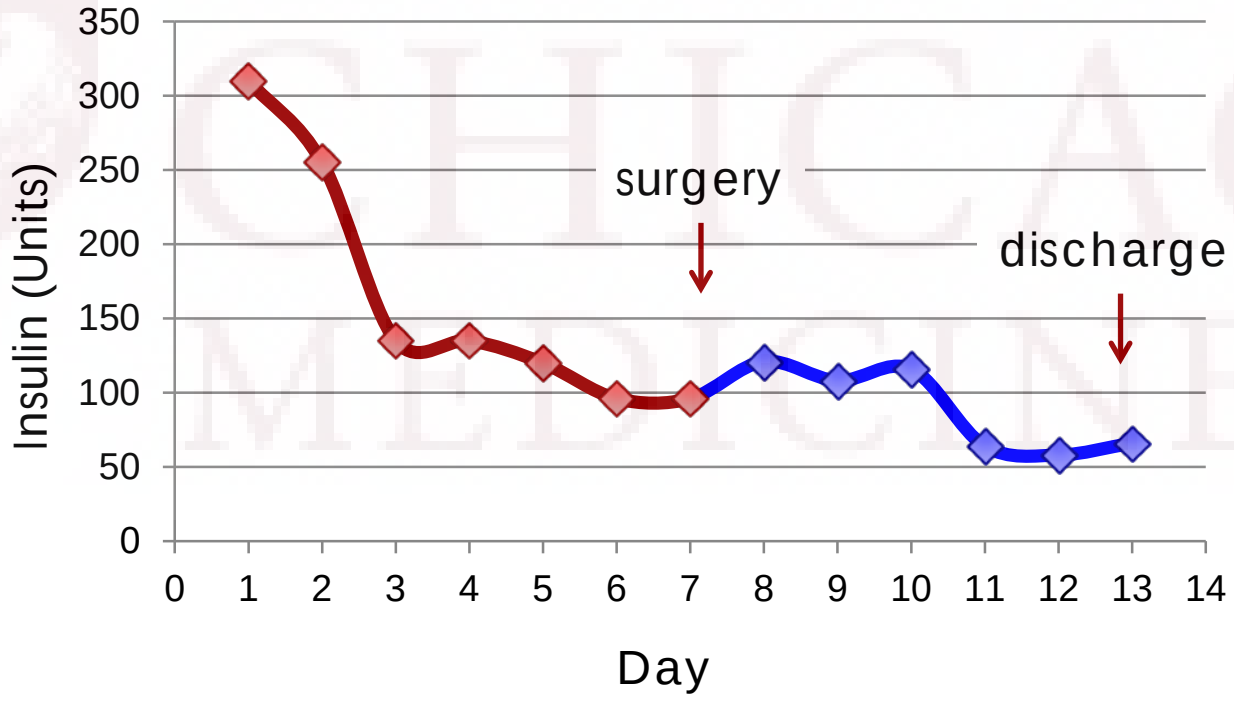
Is hyperinsulinemia the trigger or the response (or both)?

- Chronic hyperinsulinemia leads to increased insulin resistance (impaired insulin action) in mice and humans.
- Continuous insulin delivery leads to hyperglycemia and impaired insulin action, and downregulation of insulin receptor expression in experimental models
- Endogenous insulin secretion is pulsatile. Restoring pulsatile insulin delivery may be more physiologic and lead to improved insulin action

Long and ultra-long acting insulins – are they really better (or just more expensive)?

- Deglutec U100 or U200 (Tresiba)
  - Onset 1 hour
  - Duration up to 42 hours, dose every 8-40 hours
- Glargine U300 (Toujeo)
  - Onset 6 hours
  - Duration up to 36 hours, dose once daily
- Glargine (Lantus)
  - Onset 3-4 hours
  - Duration 11-30 hours
- Detemir (Levemir)
  - Onset 3-4 hours
  - Duration 6-23 hours (dose-dependent)

Back to our patient: continued insulin reduction post-operatively



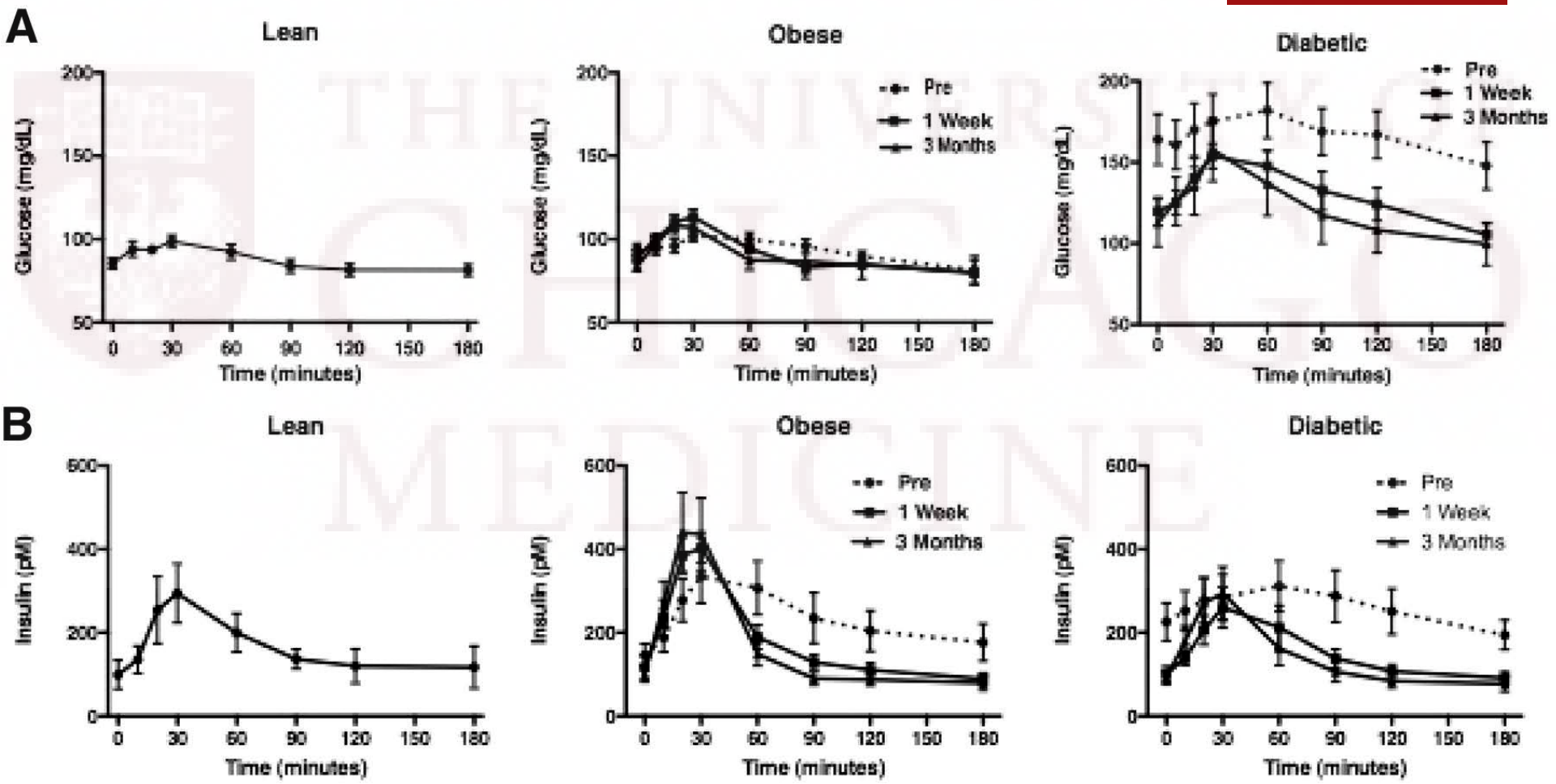
Total daily Basal
TDD

How does RYGB affect dysglycemia?

- Subjects (N=9 for each group)
  - Lean (BMI 25) – no surgery
  - Severely obese (BMI 35)
  - Severely obese with T2DM (BMI 35, A1c 8.7%)
- Assessed glucose, insulin, GLP-1
  - Preoperatively
  - 1 week post-op
  - 3 months post-op

Reed, M. A. *et al. J. Clin. Endocrinol. Metab.* **96,** 2525–2531 (2011).

RYGB improves fasting hyperglycemia and hyperinsulinemia



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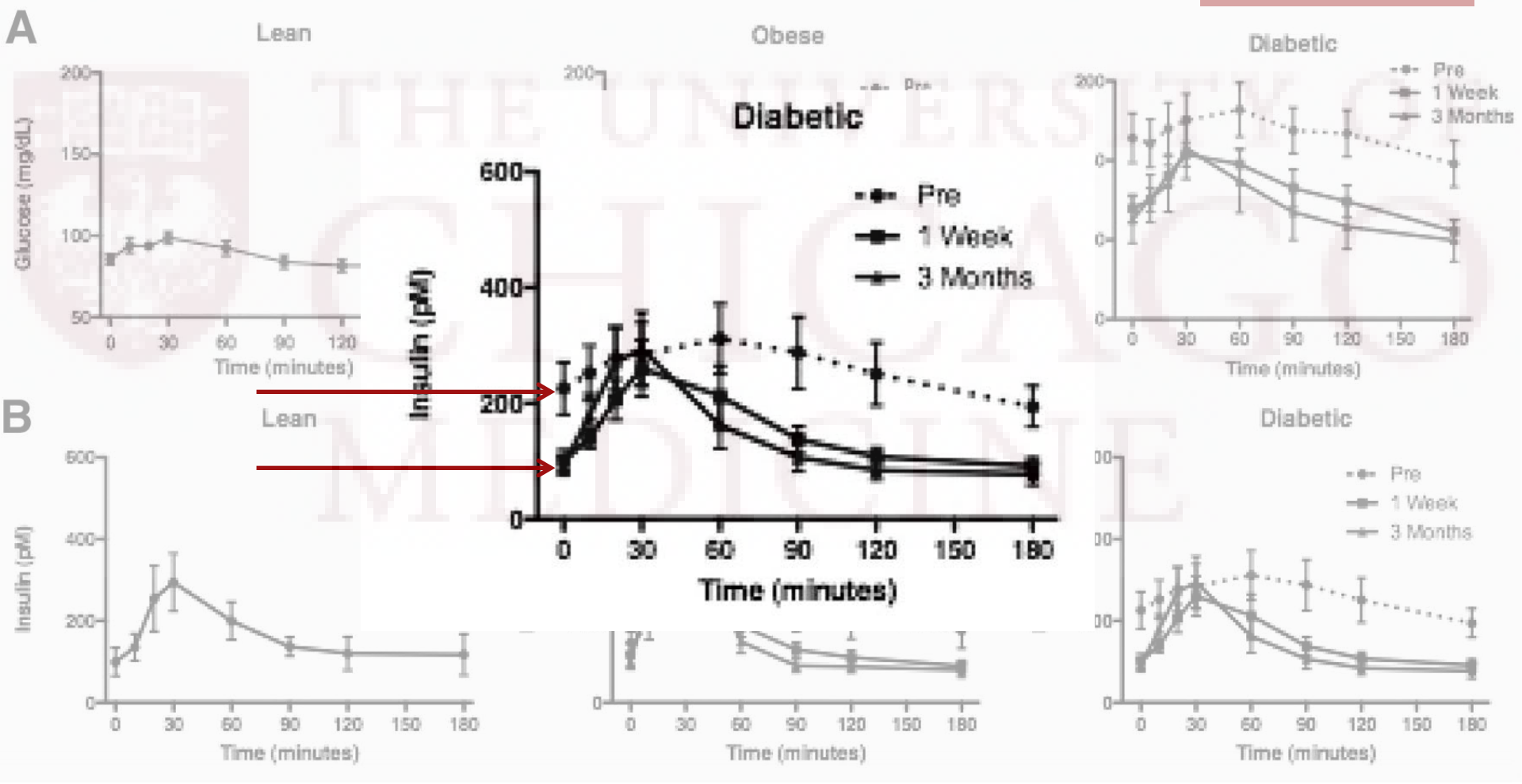
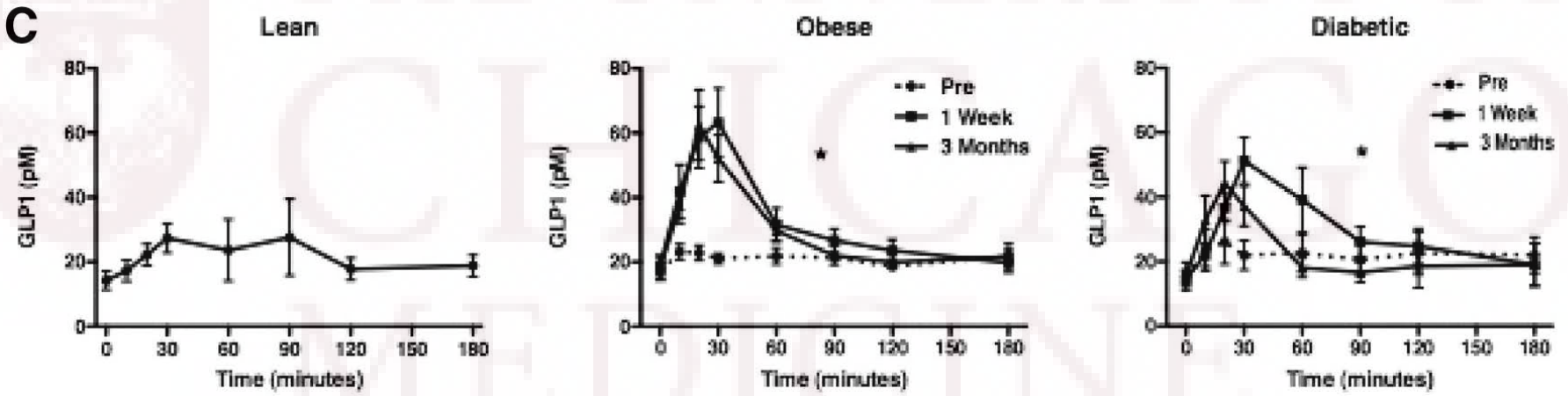
RYGB improves fasting hyperglycemia and hyperinsulinemia



Reed, M. A. *et al. J. Clin. Endocrinol. Metab.* **96,** 2525–2531 (2011).

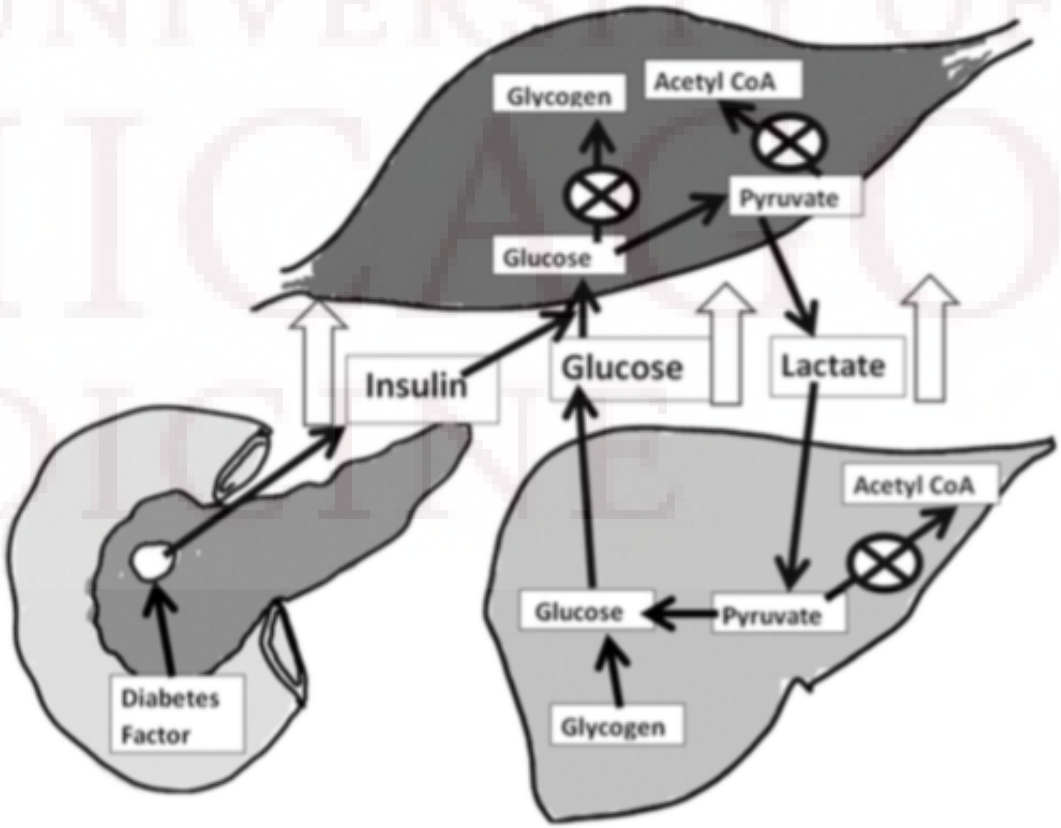
GLP1 response is also restored following RYGB



Reed, M. A. *et al. J. Clin. Endocrinol. Metab.* **96,** 2525–2531 (2011).

Does the foregut provide a stimulus for hyperinsulinemia?

- **Pories et al. proposed a GI-centric hypothesis:**
- Diabetogenic signal from the foregut→islet→chronic basal hyperinsulinemia
- + Muscle insulin resistance
- →Impaired glucose disposal
- Overnight fasting→ increased gluconeogenesis in the face of high basal insulin



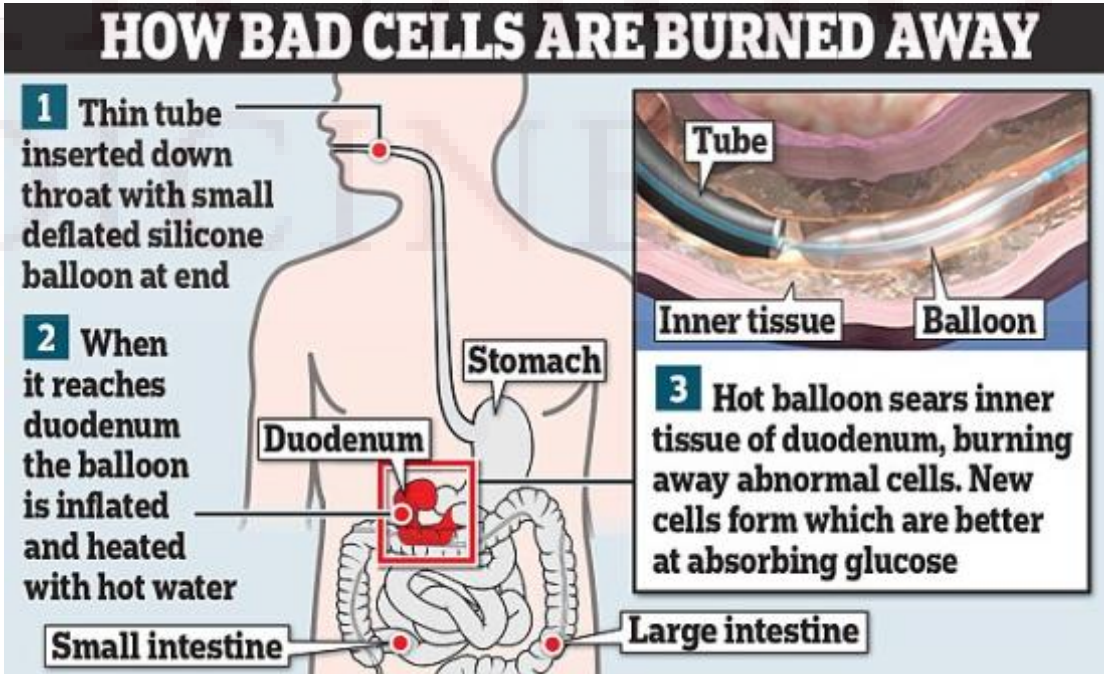
Pories, W. J. & Dohm, G. L. *Dia Care* **35,** 2438–2442 (2012).

Daily Mail .com

Diabetes could be halted by tiny balloon that burns the gut - helping the body absorb sugar again

- Patients with type 2 diabetes are being recruited to a revolutionary new trial
- Test will see whether the treatment could help them come off medication
- Doctors insert tube down throat with deflated silicone balloon on the end

By PAT HAGAN FOR THE DAILY MAIL
PUBLISHED: 17:31 EST, 12 June 2016 | **UPDATED:** 06:17 EST, 13 June 2016

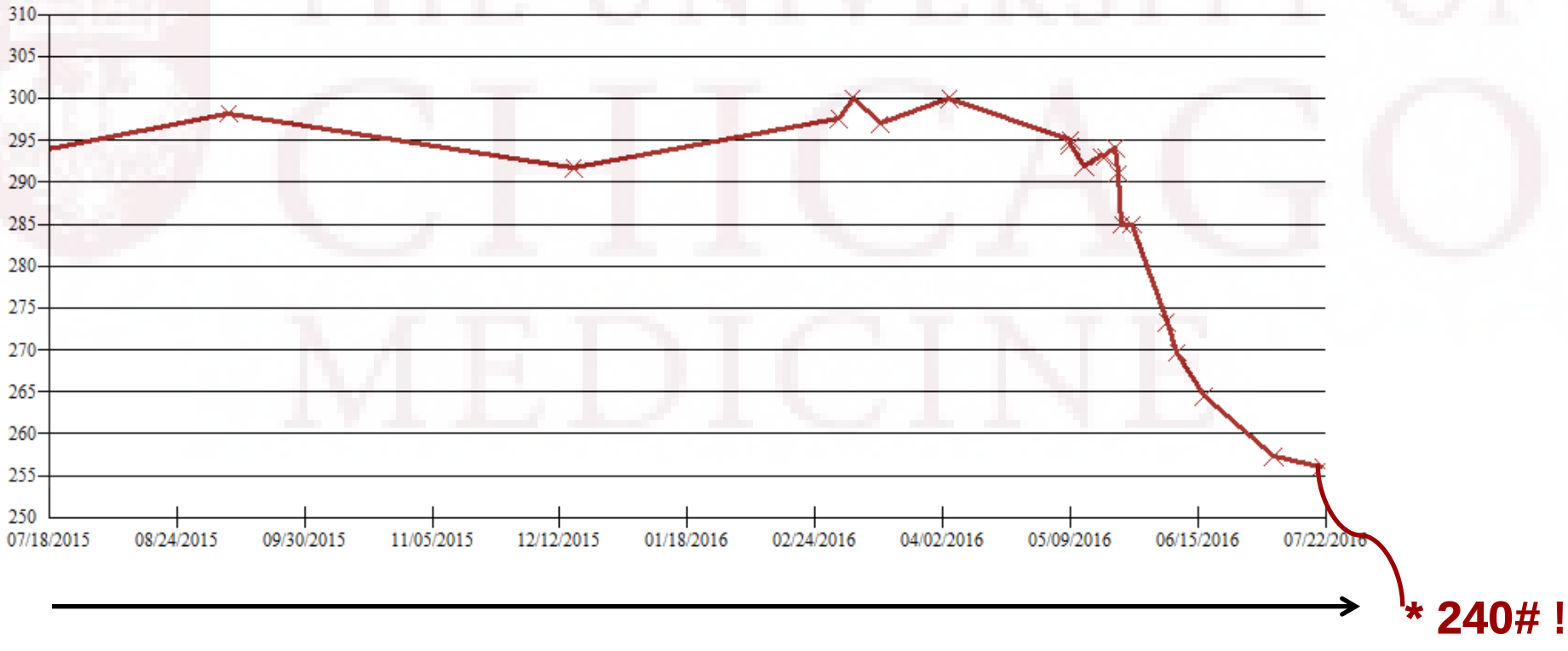


Endoscopic duodenal mucosal resurfacing

- N=39 patients
  - T2 DM (A1c 9.5%) on oral meds
  - BMI 31 kg/m^2
  - N=28 → long duodenal segment ablated (9.3 cm)
  - N=11 → short duodenal segment ablated (3.4 cm)
  - Complications: duodenal stenosis (3)
- HbA1c reduction at 6 mo by 1.2% overall
  - LS 2.5% at 3 mo, 1.4% at 6 mo
  - SS 1.2% at 3mo, 0.7% at 6 mo

Fractyl laboratories
Rajagopalan, H. *et al.*. *Dia Care* dc160383 (2016). doi:10.2337/dc16-0383

Pt's course:
Post-op weight trend



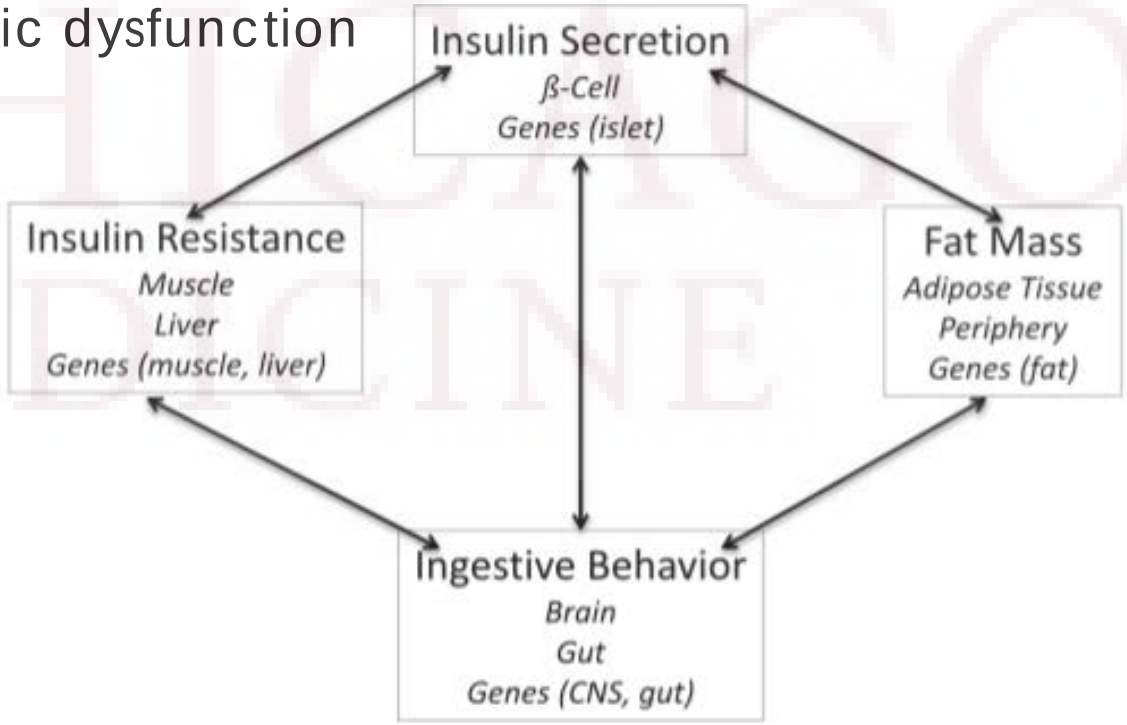
Pt's course continued: Post-op insulin requirement

- Diet: 90g carbs per day
- Exercise: 1:30-6PM every day (pool and gym); pump suspended
- **Basal rates: U-100**
  - 12A 3.1
  - 7A 3.75
  - 7P 3.0
- TDD 80 units (65 units), 86% basal, 14% bolus.
- **Carb ratio: 7**
- **Sensitivity: 20**

What would you like to do now?

Prevailing model of metabolic dysregulation:

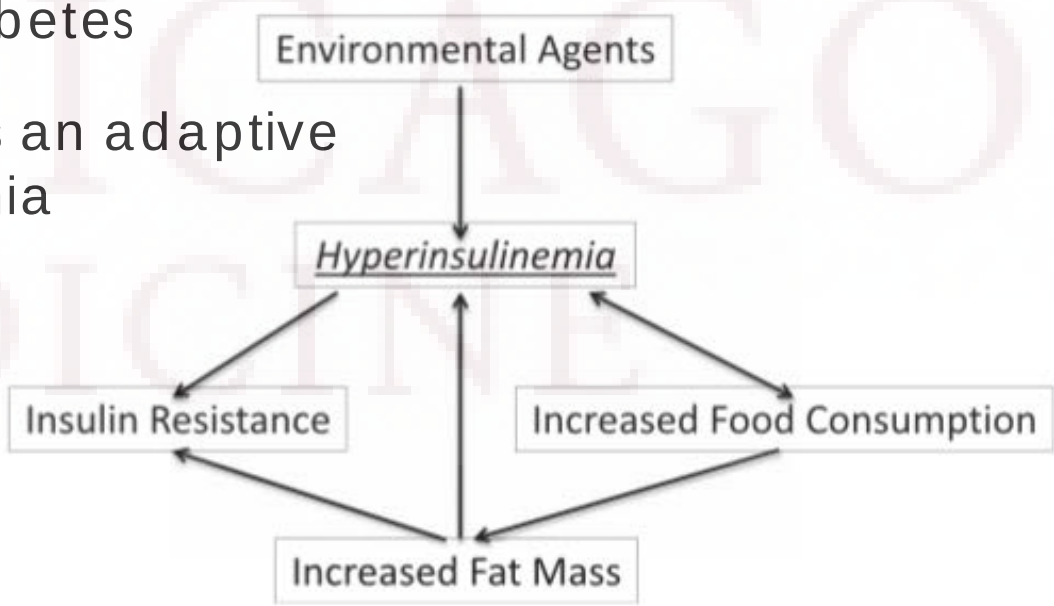
- Calorically dense diet and inactivity lead to obesity→insulin resistance→pancreatic dysfunction and diabetes



Corkey, B. E. *Dia Care* **35,** 2432–2437 (2012)

Consider:

- Changes in food consumption (increase or decrease) does not lead to sustained gain/loss of weight in controlled settings
- Not all overweight/obese individuals have insulin resistance/diabetes
- Perhaps insulin resistance is an adaptive response to hyperinsulinemia



Corkey, B. E. *Dia Care* **35,** 2432–2437 (2012)

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