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

Mizuho Mimoto
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
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/m²
- 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.
- 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
Labs:

5/9/2016

139 100 18
3.6 26 0.8

108

Ca 9.4
8.3 4.0
0.6 33
33 46
122

14.9 10.2
45.8 204

HbA1c: 7.3%
TSH: 0.52
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)
“Patient is running low on insulin, does not have supplies or home insulin at bedside, please advise”
What would you like to do?

- **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)

- **I:C 2.5** (1U for 0.5g carbs)

- **ISF 37** (7.4)

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<th>Date</th>
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- **Total daily basal:** 62 (310 Units)
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

**50-unit Dose**

**100-unit Dose**

Mean Serum IRI Concentration (pmol/L)

- Human Regular U-500 Insulin
- Human Regular U-100 Insulin

Diabetes Care 2011 Dec; 34(12): 2496-2501
A little more history…

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

<table>
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<tr>
<th>Time</th>
<th>Old Rate (U/hr)</th>
<th>New Rate (U/hr)</th>
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<tr>
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<td>18:00</td>
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<td>21:00</td>
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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 patients do on return to the outpatient setting?
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Diet: diabetic

20% reduction in basal dose

More accurate carb counting?

Pump suspended temporarily for persistent lows overnight
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40% reduction in basal dose

Go back to the way you were counting carbs at home

Diet: diabetic
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Diet: diabetic

Carb ratio: 2.5→5 (1U/1g)

Pump suspended temporarily overnight due to lower BGs
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Diet: clears → NPO for procedure overnight

10% reduction in basal dose
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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

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.

...and this is in spite of an exaggerated insulin response.

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

Hyperinsulinemia from exogenous insulin causes reversible downregulation of insulin receptors on adipocytes

- 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

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

In vivo model of pulsatile vs. continuous insulin secretion

Continuous insulin delivery leads to relative hyperglycemia.

Continuous insulin delivery leads to impaired insulin action in liver

Continuous insulin delivery leads to impaired insulin action in liver


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
  - AKTpSer 473
  - FOXO pSer 256

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\text{pSer} 473
  - FOXO\text{pSer} 256
- 120 min basal + bolus (to simulate a meal) showed similar results.

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
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

RYGB improves fasting hyperglycemia and hyperinsulinemia

RYGB improves fasting hyperglycemia and hyperinsulinemia

GLP1 response is also restored following RYGB

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

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
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HOW BAD CELLS ARE BURNED AWAY

1. Thin tube inserted down throat with small deflated silicone balloon at end
2. When it reaches duodenum the balloon is inflated and heated with hot water
3. Hot balloon sears inner tissue of duodenum, burning away abnormal cells. New cells form which are better at absorbing glucose
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 3 mo, 0.7% at 6 mo

Fractyl laboratories
Pt’s course: Post-op weight trend

* 240#!
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)
References

- Diabetes Care 2011 Dec; 34(12): 2496-2501
- Del Prato et al. Metabolism 42: 24–29
- Tripathy PR, Lansang MC. Endocr Pract. 2015;21:54-8
- Corkey, B. E. Dia Care 35, 2432–2437 (2012)