



# 61 yo Man with Hyperglycemia

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Endorama

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# History of Present Illness

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- Patient is a 61 yo man with past medical history significant for cryptogenic cirrhosis s/p liver transplant in 9/2010 on tacrolimus and mycophenylate, coronary artery disease, and hypertension who presented with weeks of progressive weakness and fatigue, found to be hyperglycemic.
  - Lost 10 lbs over the past 2 weeks.
  - Increased thirst and urinary frequency.
  - Nausea, vomiting, mild diffuse abdominal pain.
  - Blurry vision.
  - No fevers or chills.
  - No shortness of breath. Dry cough.

# Past Medical History

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## Past Medical History:

- Cryptogenic cirrhosis
  - Complicated by portal hypertension, grade 3 esophageal varices, resistant ascites
  - S/p liver transplant in 9/2010
- Coronary artery disease
  - S/p 2 BMS in 2/2010
- Chronic renal insufficiency, stage 2
- Hypertension
- Medications:
  - Tacrolimus 6 mg BID
  - Mycophenolate mofetil 1000 mg BID
  - Ursodiol 300 mg BID
  - Plavix 75 mg daily
  - Metoprolol 100 mg BID
  - Fish oil QOD
  - Calcium carbonate 1200 mg QOD
  - Last dose of prednisone was in 12/2010.
- Allergies:
  - Rifaximin

# Medical History cont.

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## ○ Social History:

- Originally from Greece.
- Married with 9 children, 18 grandchildren.
- Quit tobacco 5 years ago, previously smoked 1 ppd x 41 years.
- Quit social ETOH 5 years ago.

## ○ Family History:

- Mother with DM2.
- 6 siblings without diabetes.
- No children with diabetes.

# Physical Exam

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- Ht 177.8 cm (5' 10"), Wt 90.719 kg (200 lb), BMI 28.70 kg/m<sup>2</sup>
- Temp 36.3 °C (97.3 °F), BP 134/73, Pulse 81, Resp 13, SpO<sub>2</sub> 98%
- Constitutional: Patient appears well-developed, well-nourished, in no acute distress.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm, normal rate. Systolic murmur appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended. Central obesity.
- Musculoskeletal/extremities: Tr peripheral edema.
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. No obvious acanthosis nigrans noted.
- Psychiatric: Normal mood and affect.

# Admission labs

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120 82 46  
5.8 13 1.9  
Ca 9.1

906

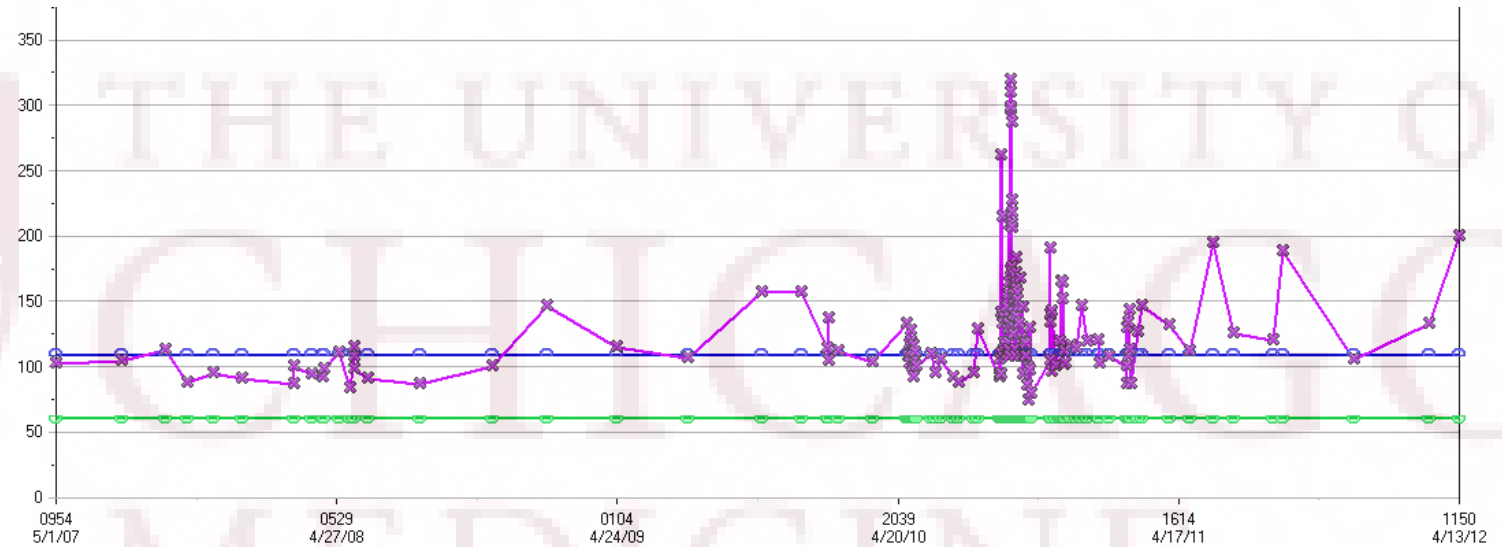
Total protein 7.0, alb 4.4  
Tbili 0.5, alk phos 224  
AST 25, ALT 33  
BOH 7.61  
Venous pH 7.2  
HgbA1c 13.9%

12  
4.3 208  
35.9

60N, 9B, 17L, 11M, 1E

- Tacrolimus:  
5.9 ng/mL (5-20)
- Mycophenolic acid:  
2.9 mcg/mL (1.0-3.5)
- U/A: Spec grav 1.028,  
pH 5.5, neg leuk est, neg  
nitrite, neg protein, neg  
blood, 3+glu, 2+ ketones
- Negative BCx, Ucx
- Unremarkable CXR, CT  
abdomen

# History of Blood Glucose



Transplant hospitalization:

SM 500 mg IV x1 to prednisone 15 mg daily

NISS 2 units for 50>120

11/29/2011 HgbA1c 5.7%

# Blood Sugars

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|           | Breakfast | Lunch | Dinner                 | Bedtime |
|-----------|-----------|-------|------------------------|---------|
| HD 1      |           |       | 906                    | 558     |
|           |           |       | Reg 10 + gtt at 9 u/hr |         |
| HD 2      | 197       | 298   | 391                    | 367     |
| Lantus 25 | 2.5 u/hr  | N 9   | N 10+15+15             | N 15+4  |
| HD 3      | 190       |       |                        |         |
| Lantus 50 | N 5       |       |                        |         |

93 units of insulin in the last 24 hours.



# Assessment & Plan

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- Diabetes mellitus, new diagnosis:
  - Check anti-GAD antibody
  - Continue Lantus 50 units daily.
  - Increase Novolog for meals to 15 units.
  - Use Novolog sliding scale before meals: 1u for BS 130-180, 3u for BS 181-230, 5u for BS 231-280, etc.

# Blood Sugars

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|           | Breakfast | Lunch   | Dinner | Bedtime |
|-----------|-----------|---------|--------|---------|
| HD 3      | 190       | 375     | 278    | 299     |
| Lantus 50 | N 5       | N 15+9  | N 15+5 | N3      |
| HD 4      | 408       | 452     | 285    | 111     |
| Lantus 60 | N 20+10   | N 20+10 | N 30+9 |         |
| HD 5      | 174       | 152     | 71     | 159     |
| Lantus 60 | N30+3     | N30+3   | N26    |         |
| HD 6      | 81, 108   | 68      |        |         |
| Lantus 60 | N 26      |         |        |         |

Discharged on Lantus 50, Novolog 20 with meals, and medium dose NISS.

# Post-transplant Diabetes Mellitus

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- High incidence:
  - >20% with high dose tacrolimus
  - 12-14% with low dose tacrolimus + azathioprine
  - 4-7% with low dose tacrolimus + mycophenolate mofetil
- Risk factors: age, non-white ethnicity (2x), and immunosuppression.
  - Conflicting evidence: family history, impaired glucose tolerance before transplantation, increasing weight, and vital status of organ donor.
- Immunosuppression regimen:
  - Tacrolimus > cyclosporine
  - Glucocorticoid pulse therapy (but not maintenance) is associated with PTDM.
- May resolve:
  - Cyclosporine-based therapy: 60 –100%
  - Low-dose tacrolimus and azathioprine: 75–90%
  - High-dose tacrolimus: 40–70%
  - Low-dose tacrolimus and mycophenolate mofetil: 30–50%

Montori et al. [Diabetes Care](#). 2002 Mar;25(3):583-92.

Yoshida et al. [Transpl Int](#). 2000;13(1):69-72.

# Calcineurin inhibitors and PTDM

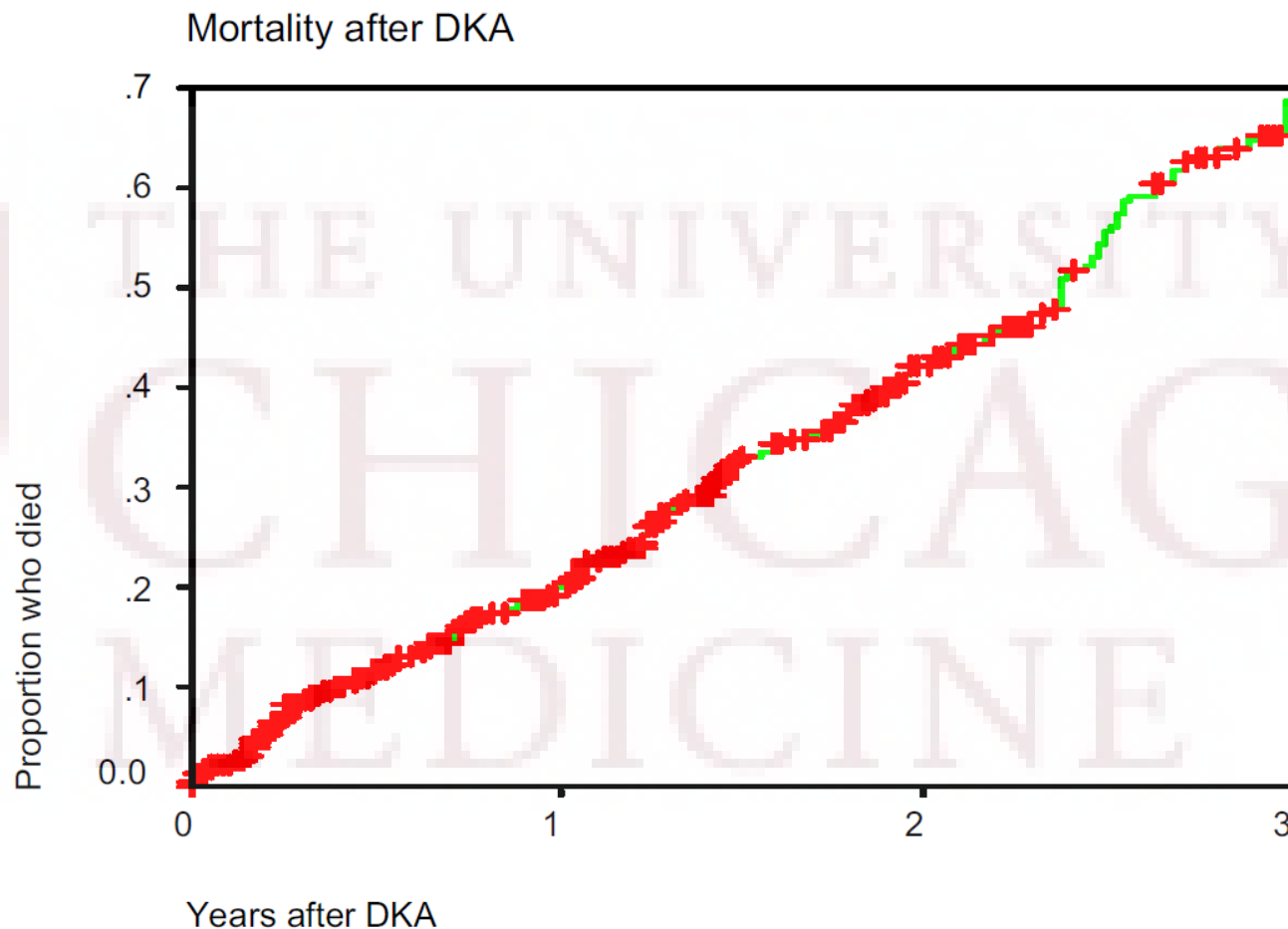
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- Calcineurin is a protein phosphatase that activates NFAT, resulting in upregulation of expression of IL-2 and subsequent activation of T cells.
  - NFAT also is involved in the stimulation of insulin gene transcription.
- Mechanism:
  - CsA and Tac impair basal and glucose-stimulated insulin secretion, dose-dependent.
    - Suppresses calcineurin phosphatase activity and calcineurin mRNA levels.
  - CsA upregulates expression of SREBP-1c.
  - CsA increased apoptosis.
  - Enhanced peripheral resistance.
    - Clinical studies: hyperglycemia with elevated C-peptide levels.

# Calcineurin inhibitors and PTDM

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- Historical cohort study of 40,000 renal transplant recipients
- Incidence of DKA was 33.2/1000 PY in pts with prior dx, 2.0/1000 PY in pts without prior dx.
  - Compared to HHS: 2.7 and 1.1
- Risk factors for DKA: younger age, graft loss, African-American, more recent year of transplant, lower BMI, and female.
- Risk factors for de novo DKA: cadaver kidneys and tacrolimus use.
  - 3-yr incidence of de novo DKA with tacrolimus was 1.56% v. 0.35% with CsA.



DKA: AHR 2.44, CI 2.10-2.85,  $p < 0.0001$   
HHS: AHR 1.87, CI, 1.22–2.88,  $p < 0.004$

# Back to the Patient

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|            |           | Breakfast | Lunch | Dinner |
|------------|-----------|-----------|-------|--------|
| Home Day 1 |           | 92        | 99    | 97     |
|            | Lantus 50 | N 20      | N 20  | N 20   |
| Home Day 2 |           | 115       | 72    | 134    |
|            | Lantus 50 | N 20      | N 20  | N 20   |
| Home Day 3 |           | 117       | 117   | 136    |
|            | Lantus 50 | N 20      | N 20  | N 20   |
| Home Day 4 |           | 117       | 77    | 162    |
|            | Lantus 50 | N 20      | N 20  | N 20   |
| Home Day 5 |           | 190       | 94    |        |
|            | Lantus 50 | N 20+3    | N 20  |        |
| Home Day 6 |           | 154       |       |        |
|            | Lantus 50 | N 20+1    |       |        |

# Back to the Patient

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- Other options:
  - Metformin:
    - Has been used in the post-kidney transplant population
    - Avoid if GFR is unstable
  - Sulfonylureas:
    - Associated with weight gain and hypoglycemia, esp. in elderly patients with limited hepatic function
  - GLP-1 agonists:
    - Decreased gut motility, nausea may interfere with oral immunosuppressive regimen
  - DPP-4 inhibitors:
    - Minimal GI side effects
  - TZDs:
    - Has been successfully used in NODAT but can cause fluid retention and weight gain



# References

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