

Vanderbilt Case Framing - Prolonged-Fasting Hyperglycemia with Delayed Ketogenesis

Patient: Chad T. Mansfield

Supervising team: VA Endocrinology & MICU (72-h fast)

Consult target: Dr. Kevin Niswender (Vanderbilt Endocrinology), Dr. Pruett

Date: {{fill-in}}

1) One-paragraph executive summary

During a supervised 72-hour fast, fasting glucose remained elevated (120–140 mg/dL) with suppressed early ketogenesis (<0.2 mmol/L β -hydroxybutyrate), only transitioning to ketosis after quetiapine administration near the end of the fast. This pattern, plus historical response to tirzepatide, supports hepatic-selective insulin resistance with sympathetic/HPA dominance and impaired mitochondrial substrate switching. Post-GLP-1 withdrawal physiology has been problematic; tirzepatide previously normalized fasting glucose and improved function.

2) Key problems & hypotheses

- **Problem A:** Fasting hyperglycemia with absent/late ketogenesis
Hypothesis: Hepatic-selective insulin resistance with cortisol/glucagon dominance blocks lipolysis and ketogenesis; central sympathetic drive contributes.
 - **Problem B:** Exercise HR plateau <100 bpm with dyspnea before glycolytic transition
Hypothesis: Mitochondrial inflexibility/redox stress limits switching; autonomic overactivity augments.
 - **Problem C:** Low DHEA-S with mid-AM cortisol; MCAS-like symptom clusters; E2 sensitivity on TRT
Hypothesis: HPA rigidity with reduced 17,20-lyase flux; histamine/autonomic inputs amplify metabolic rigidity.
-

3) Timeline & data figures

- **Fig 1.** 72-h fast timeline (with quetiapine \rightarrow ketosis): figures/timeline_fast_case.png
 - **Fig 2.** 3-lane timeline (Labs | Interventions | Symptoms): figures/three_lane_timeline.png
 - **Fig 3+.** Trends (to be added after device exports): data/plots/*_trend.png
 - **Table 1.** Final fast panel & 11/12/2025 labs (CSV: data/labs_2025-11-12.csv)
-

4) Objective data (most recent)

- **Fasting glucose:** 131 mg/dL; **Insulin:** 10.5 μ U/mL; **C-peptide:** 2.0 ng/mL
- **β -HB:** <0.2 mmol/L (absent/low)

- **Cortisol (AM):** 11 µg/dL; **DHEA-S:** 42 µg/dL
- **ALT/AST:** 46/32 U/L (mild hepatic stress)
- **Lipids:** LDL 106, HDL 48, TG 112 mg/dL
- **Platelets:** 143 K/µL (borderline low)
- Thyroid panel euthyroid; rt3 mildly elevated (stress-adaptive).

Interpretation: Hepatic insulin resistance with suppressed ketogenesis; HPA dominance; mitochondrial inflexibility. Pattern improved historically on dual incretin therapy.

5) Differential diagnosis (ranked likelihood)

1. Hepatic-selective insulin resistance with sympathetic/HPA dominance (most likely)
 2. Mitochondrial substrate-switching defect (functional/ acquired > primary)
 3. Atypical autonomic dysfunction/MCAS interplay affecting catechol-estrogen/catecholamine clearance
 4. Adrenal partial insufficiency vs rigidity (less likely; AM cortisol okay, DHEA-S low)
 5. Insulinoma/endo-hyperinsulinemia (unlikely given fasting insulin/C-pep)
-

6) Proposed confirmatory workup (prioritized)

- **Counter-regulation:** glucagon, acylcarnitines + total/free carnitine, lactate/pyruvate
 - **Metabolic switching:** fasting β-HB trajectory during 6-h mini-fast; FFA
 - **Endocrine context:** AM cortisol + DHEA-S trend; ACTH; IGF-1 (± IGFBP-3)
 - **Autonomic:** active stand test, HRV diary; morning symptom pattern 5-6 AM
 - **Optional:** OAT or mito panel if clinically available
-

7) Therapeutic implications

- **Reinitiate tirzepatide** (2.5 mg → 5 mg as tolerated): previously normalized fasting glucose and improved function; mechanistic fit (GLP-1/GIP: suppress glucagon, enhance hepatic insulin signaling, improve adipose/mitochondrial coupling).
 - **TRT hygiene:** micro-dosing schedule with stable AI; maintain hCG; reassess DHEA-S once E2 stable.
 - **Non-pharm:** circadian anchors; graded Zone-2; protein-first refeeds; MCAS-aware diet.
-

8) Why tirzepatide (mechanistic bullets)

- GLP-1/GIP dual action → **glucose-dependent insulintropic effect** + **glucagon suppression**
 - Hepatic signaling: improves **hepatic insulin sensitivity** beyond weight loss; reduces HGP
 - Adiponectin/GIP synergy → supports **mitochondrial biogenesis** and substrate switching
 - Patient-specific: historical efficacy; aligns with fast phenotype (quetiapine → ketosis suggests central/ANS gate)
-

9) Learning points (journal-style)

- Fasting hyperglycemia with suppressed ketogenesis can reflect **central/ANS-amplified hepatic IR**.
 - **Quetiapine-associated drop in sympathetic tone** coinciding with ketosis onset is a useful physiologic probe.
 - Dual incretin therapy may restore **metabolic flexibility** where metformin/lifestyle alone fail.
-

10) References (placeholders; see repo `references/references.bib`)

1. Frias JP et al. *N Engl J Med* 2021.
 2. Finan B et al. *Sci Transl Med* 2013.
 3. Niswender KD et al. *J Clin Endocrinol Metab* 2005.
 4. Cusi K. *Diabetes Care* 2022.
-

11) Patient perspective & consent

Patient authored this case framing, consents to de-identified academic discussion, and seeks collaborative guidance.