Rapid Clinical Improvements in a Patient with Difficult-to-Control Type 2 Diabetes by Addressing Underlying Hypercortisolism with Mifepristone

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Conclusions and Takeaways

- This case presents a patient with long-standing (40+ years) difficult-to-control T2D (HbA1c: 8.7%, CGM TIR: 33%, GMI [CGM-based A1c estimate]: 8.3%, mean glucose: 208 mg/dL) and multiple comorbidities (treatment-resistant hypertension, morbid obesity) that could not be effectively managed despite long-term, extensive medical interventions.
- Hypercortisolism was suspected due to the patient's multiple comorbidities and confirmed through biochemical assessment and imaging.
- The patient was treated with mifepristone, a competitive glucocorticoid receptor antagonist, for 4 months, during which he experienced substantial weight loss of 34.4 lbs (310.4 lbs to 276.0 lbs), improvement in glycemic control (at 2 months [CGM TIR: 91%, GMI: 6.6%] and 4 months [CGM TIR: 47%, GMI: 7.8%]) with reduction of insulin from U500 to U100 at 3 months, and discontinuation/reduction in 5 of 7 antihypertensive medications.
- Upon discontinuation of mifepristone, due to unrelated orthostatic hypotension, the patient's glycemic control deteriorated (at 3 months [CGM TIR: 5%, GMI: 10.2%] and 6 months [CGM TIR: 31%, GMI: 8.4%] after discontinuation), despite increased use of insulin at 2 months.
- This case emphasizes the vital importance of promptly identifying and addressing hypercortisolism in patients with challenging metabolic derangements. Failure to do so resulted in a worsening clinical picture for this patient, which was ameliorated with mifepristone by addressing the underlying hypercortisolism.

T2D, type 2 diabetes; HbA1c, hemoglobin A1c; CGM, continuous glucose monitor; TIR, time-in-range; GMI, glucose management indicator (CGM-based A1c estimate).

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Introduction

Hypercortisolism: a Serious and Under-Recognized Disease

- Endogenous hypercortisolism (Cushing syndrome), caused by prolonged exposure to excess cortisol activity, is a multisystemic, heterogeneous disease associated with significant metabolic comorbidities, leading to increased mortality.[1-3]
- Despite the detrimental clinical consequences, hypercortisolism often goes un-recognized.[4]

Identifying and Treating Hypercortisolism in Patients with T2D

- Excess cortisol may underlie abnormalities in glucose metabolism, leading to the development of T2D.[5]
- Hypercortisolism is reported in approximately 5–10% of patients with T2D, with up to 3.5 times higher prevalence in patients with difficult-to-control T2D requiring multiple therapies, insulin, or concomitant anti-hypertensive medications.[6-12]
- When diabetes remains unresponsive or only partially responsive to known effective medications, it is crucial to consider hypercortisolism as an underlying driver of T2D and, if found, initiate treatment.

1 Case History and Baseline Characterstics

- A 71-year-old man
- Weight: 310.4 lbs
- Body mass index (BMI): 44.5 kg/m^2
- **Long-standing (40+ years) difficult-to-control T2D:**
  - HbA1c: 8.7%
  - CGM TIR: 33%
  - GMI (CGM-based A1c estimate): 8.3%
  - CGM-based mean glucose: 208 mg/dL
  - Antidiabetic medications: insulin U500, glucagon-like peptide 1 (GLP-1) agonist
- **Multiple comorbidities**, including:
  - Treatment-resistant hypertension (7 antihypertensive medications)
  - Morbid obesity (with post gastric sleeve)
  - Chronic kidney disease (stage 3)
  - Carotid artery disease (with coronary artery bypass grafting)

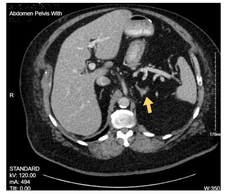
2 Biochemical Evaluation and Imaging

Biochemical Evaluation

- Serum cortisol post-1-mg dexamethasone suppression test (DST): 2.3 and 2.4 µg/dL (reference range: ≤1.8 µg/dL)
- Morning adrenocorticotropic hormone (ACTH): 19.7 pg/mL (reference range: 10–60 pg/mL)

Adrenal Imaging

- Adrenal computed tomography (CT) imaging confirmed a left adrenal sub-centimeter nodule (previously identified and stable since 2006).



3 Diagnosis and Treatment

Diagnosis:

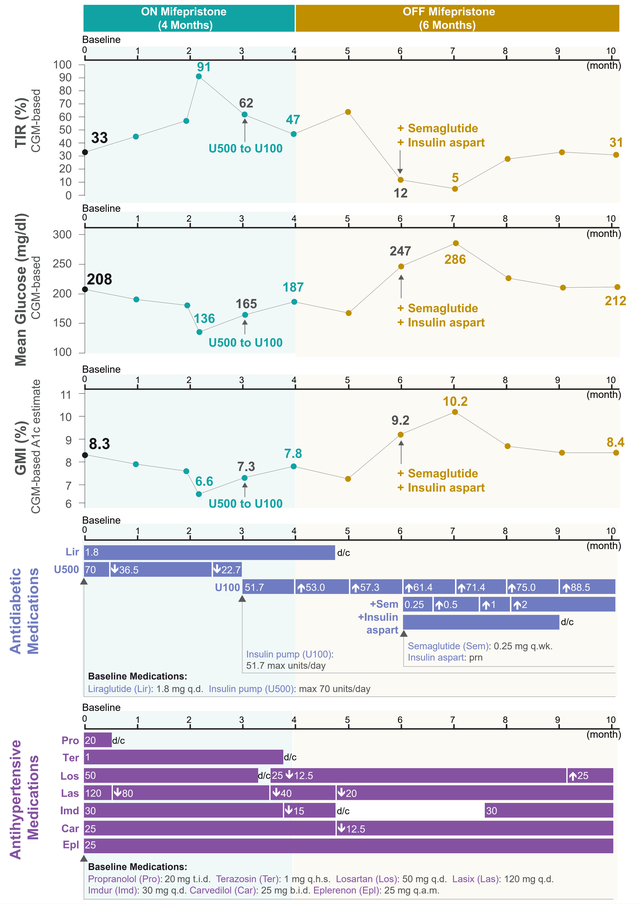
- Hypercortisolism was diagnosed based on biochemical evaluation, imaging, and multiple comorbidities (difficult-to-control T2D, treatment-resistant hypertension, morbid obesity).

Treatment:

- Mifepristone treatment: The patient was treated with mifepristone (Korlym®, Corcept Therapeutics) 300 mg q.d. for 4 months.
- Mifepristone discontinuation: After 4 months of treatment, the patient experienced orthostatic hypotension unrelated to mifepristone. Per his cardiologist's recommendation mifepristone was discontinued.

Treatment Responses:

	Improved Overall Clinical Outcomes	Deteriorated Overall Clinical Outcomes
	ON Mifepristone (4 months from baseline)	OFF Mifepristone (6 months after discontinuation)
Weight (lbs)	-34.4 (310.4 to 276.0)	-3.1 (276.0 to 272.9)
BMI (kg/m^2)	-4.8 (44.5 to 39.7)	-0.6 (39.7 to 39.1)
Glycemic Control		
Antidiabetic Medications	At 3 months: Reduced insulin (U500 to U100)	At 2 months Increased insulin (+ insulin aspart) Switched GLP-1 agonist (liraglutide to semaglutide)
HbA1c (%)	-2.5 (8.7 to 6.2)	+4.4 (6.2 to 10.6)
CGM TIR (%)	+14 (33 to 47)	-16 (47 to 31)
Mean Glucose (CGM-based, mg/dL)	-21 (208 to 187)	+25 (187 to 212)
GMI (CGM-based A1c estimate, %)	-0.5 (8.3 to 7.8)	+0.6 (7.8 to 8.4)
Blood Pressure Control		
Antihypertensive Medications	5 of 7 medications reduced/discontinued	5 of 5 medications remained
Systolic Blood Pressure (mm Hg)	-5 (120 to 115)	+11 (115 to 126)
Diastolic Blood Pressure (mm Hg)	+4 (60 to 64)	+8 (64 to 72)



4 Case Learnings

Optimal Dose:

- In the SEISMIC study, 85% of patients showed improvement in global clinical response with a dose of ≥600 mg mifepristone.[13]
- Deciding on the appropriate mifepristone dose should be based on a clinical assessment of tolerability and clinical improvement, including glycemic control and medication changes.
- It is plausible that the patient could have benefited from a higher dose of mifepristone, leading to better clinical control of hypercortisolism.

Re-initiating Mifepristone:

- The patient experienced a substantial and continued decline in clinical parameters after discontinuing mifepristone.
- This decline in the absence of mifepristone indicates treatment efficacy; re-initiation of mifepristone should have been considered.

Patient Advocacy:

- Diagnosing and managing hypercortisolism is often a lengthy and challenging process, necessitating continued patient advocacy and long-term monitoring.
- It is crucial to adopt a holistic approach, leaning on clinical judgment and tailoring treatment decisions to the individual patient's clinical needs.

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Disclosures

Jennifer Ali, MSN, APN has no disclosures. Kimberly Rizzo, RN, MSN, DNP is an employee of Corcept Therapeutics.

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