CLINICAL LEARNINGS BASED ON A CASE SERIES: CONSIDERATIONS FOR IDENTIFYING AND TREATING HYPERCORTISOLISM IN PATIENTS WITH DIABETES

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Summary & Conclusions

- When diabetes remains unresponsive or only partially responsive to known effective medications, endogenous hypercortisolism may be a potential underlying driver of the disease
- Patient characteristics associated with a high risk of hypercortisolism include hard-to-control diabetes despite standard-of-care therapy and additional morbidities such as obesity and hypertension
  - In these patients, screening for hypercortisolism is warranted
- This case series highlights the importance of recognizing hypercortisolism as a differential diagnosis in patients with hard-to-control diabetes
- The patients were diagnosed with hypercortisolism based on their clinical presentation, biochemical evaluation (1-mg overnight dexamethasone suppression test), and radiologic imaging results
- Treatment of hypercortisolism with mifepristone was initiated, which resulted in meaningful clinical benefits, including cardiometabolic improvements and reductions in antihyperglycemic and antihypertensive medication burden
  - To ensure the best possible outcomes for each patient, diagnosis and treatment should be tailored to the individual with the patient's medical history considered

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Introduction

- In patients with endogenous hypercortisolism (Cushing syndrome), prolonged exposure to excess cortisol activity can lead to cardiometabolic morbidity and mortality[1]
- Excess cortisol can be an underlying driver of diabetes, with direct and indirect effects on glucose metabolism resulting in insulin resistance and beta cell dysfunction[2]
- Preliminary results from the prospective, multicenter, US-based study CATALYST (NCT05772169) indicated that 24% (252/1057) of patients with hard-to-control type 2 diabetes (T2D) had hypercortisolism[3]
- Hypercortisolism should be considered as a potential underlying driver of diabetes that remains uncontrolled after treatment with standard-of-care antihyperglycemic therapies
- Guidance for identifying and screening of hypercortisolism in patients with hard-to-control diabetes, however, remains limited

Aim

- This case series presents clinical insights on screening, diagnosing, and treating hypercortisolism in 10 patients seen at our practice with hard-to-control diabetes with the goal of optimizing patient outcomes

Overview

PATIENT POPULATION
10 patients with hard-to-control diabetes despite being treated with multiple antihyperglycemic medications were screened for hypercortisolism.

COMORBIDITIES
Additional morbidities included obesity, hypertension, and renal impairment.

SCREENING
Patients were screened using the 1-mg dexamethasone suppression test (cortisol cutoff 1.8 µg/dL), with dexamethasone levels (cutoff 140 ng/dL) to confirm adequate suppression.

DIAGNOSIS
Hypercortisolism diagnosis was based on clinical findings (comorbidites and medical history), biochemical evaluations, and imaging.

TREATMENT
All patients were treated for hypercortisolism with mifepristone (Korlym®, Corcept Therapeutics).

OUTCOMES
Mifepristone treatment resulted in significant clinical improvements, including better glycemic control, weight loss, and reduced medication needs.

Baseline Clinical Characteristics

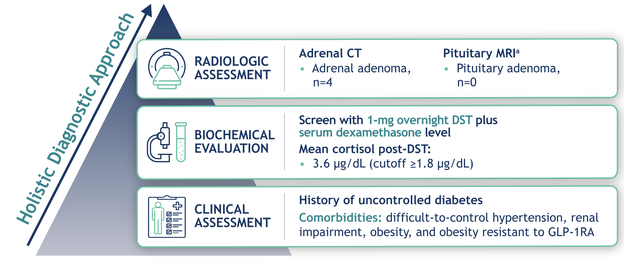
- At baseline, 6 of 10 patients were receiving insulin plus other antihyperglycemic medications and mean HbA1c was 7.7%

Characteristic	Patients (N=10)
Female, n (%)	5 (50)
Age, years	67.6 (46, 76)
Weight, lbs	225.8 (152, 352)
BMI, kg/m²	36.1 (28, 50)
Glucose control	
HbA1c, %	7.7 (5.3, 10.1)
CGM-TIR, %[a]	62.1 (36, 79)
FBG, mg/dL	155.5 (93, 229)
Antihyperglycemic medications, n	
Insulin plus other medications[b]	6
Insulin alone	2
Other medications[b]/no insulin	2
Blood pressure control	
Systolic BP, mmHg	138.3 (115, 172)
Antihypertensive medications, n	
1 medication	1
2 medications	2
3 medications	3
4 or more medications	4
Renal function	
Serum creatinine[c], mg/dL	1.12 (0.50, 2.01)
eGFR, mL/min	65.9 (36, 104)

Data are shown as mean (min, max) unless otherwise noted.
[a]Data available for 7 patients. [b]Other medications included canagliflozin, empagliflozin plus metformin, dapagliflozin plus metformin, dapagliflozin, glipizide, metformin, pioglitazone, semaglutide, and tirzepatide. [c]Normal range is 0.74 to 1.35 mg/dL for adult men and 0.59 to 1.04 mg/dL for adult women.
BMI, body mass index; BP, blood pressure; CGM-TIR, continuous glucose monitoring time-in-range; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

Hypercortisolism Diagnosis

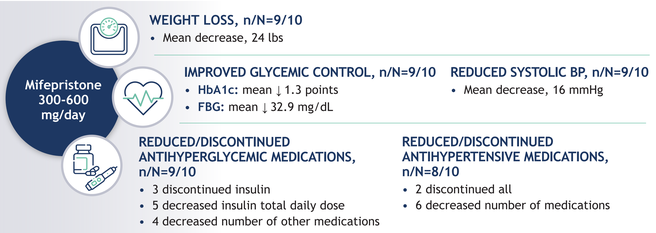
- Patients were diagnosed with hypercortisolism based on their clinical findings, biochemical evaluation, and imaging results



[a]Pituitary MRI was performed in patients who had an ACTH level >5 pg/mL and was negative for all 5 patients who had the imaging performed.
ACTH, adrenocorticotropic hormone; CT, computed tomography; DST, dexamethasone suppression test; MRI, magnetic resonance imaging.

Improved Clinical Outcomes With Mifepristone

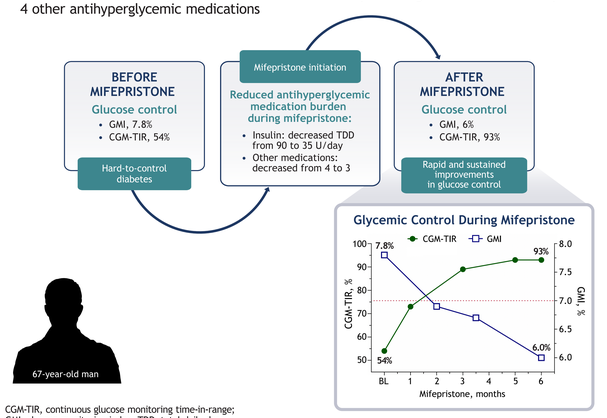
- Patients were treated with mifepristone and experienced significant clinical improvements and were able to reduce their antihyperglycemic and antihypertensive medication burden



BP, blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c.

Improvements in CGM-TIR: Patient Case Highlight

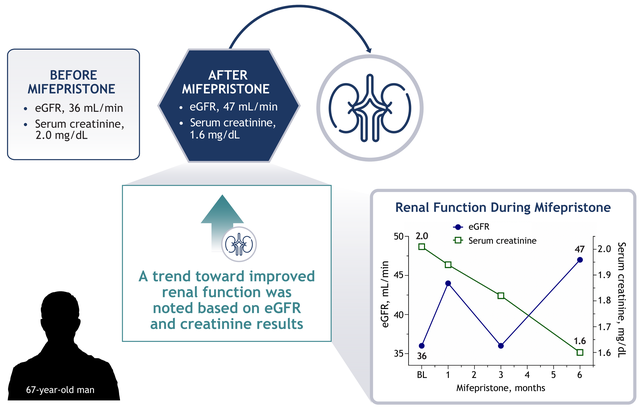
- This is the case of a 67-year-old man with diabetes despite being treated with insulin plus 4 other antihyperglycemic medications



CGM-TIR, continuous glucose monitoring time-in-range; GMI, glucose monitoring index; TDD, total daily dose.

Improvements in Renal Function: Patient Case Highlight

- This patient also had chronic kidney disease at baseline



eGFR, estimated glomerular filtration rate.

Safety

- Temporary glucocorticoid withdrawal symptoms (eg, nausea, fatigue, headache) are expected during mifepristone treatment
- In this case series, 8 patients reported glucocorticoid withdrawal symptoms
  - All patients' symptoms resolved or were resolving at last follow-up
- Other cortisol-related adverse events included edema and hypokalemia, which were reported in 8 patients
  - These adverse events were managed with diuretics, mineralocorticoid receptor antagonists, and potassium supplementation

References

1. Chaudhry HS, Singh G. *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2023.
2. Mazziotti G, et al. *Trends Endocrinol Metab*. 2011;22(12):499-506.
3. Buse JB, et al. *Diabetes Care*. 2025 [Epub ahead of print].