



A Case of Hyperglycemia Secondary to Hypercortisolism

Millie, a 55-year-old woman with difficult-to-control T2D and high medication burden

This is a real patient case. All diagnoses and management decisions detailed within were made by the patient's healthcare provider based on their clinical judgment.

T2D, type 2 diabetes.



MILLIE'S CLINICAL PRESENTATION

Millie is an active schoolteacher who was diagnosed with T2D 10 years ago. She is frustrated with her health issues, as she finds that they now impact her ability to function at work and at home.



Difficult-to-Control T2D

HbA1c: 9.2%

4 antidiabetic medications, including insulin



Obesity

214 lb

BMI: 32.5 kg/m²

30-lb weight gain over 6 months



Hypertension

120/85 mmHg, controlled with medication



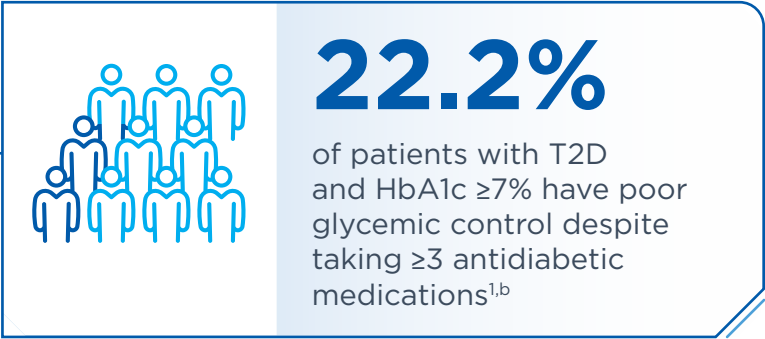
Hyperlipidemia



Depression

Baseline Medications^a

Condition	Medication(s)
T2D	Insulin glargine 36 units QHS Insulin lispro 25 PRN Metformin 1,000 mg BID Semaglutide 2 mg QW
Hypertension	Lisinopril 10 mg QD
Hyperlipidemia	Simvastatin 40 mg QD
Depression	Citalopram HBr 20 mg QD



Consider the Clinical Picture

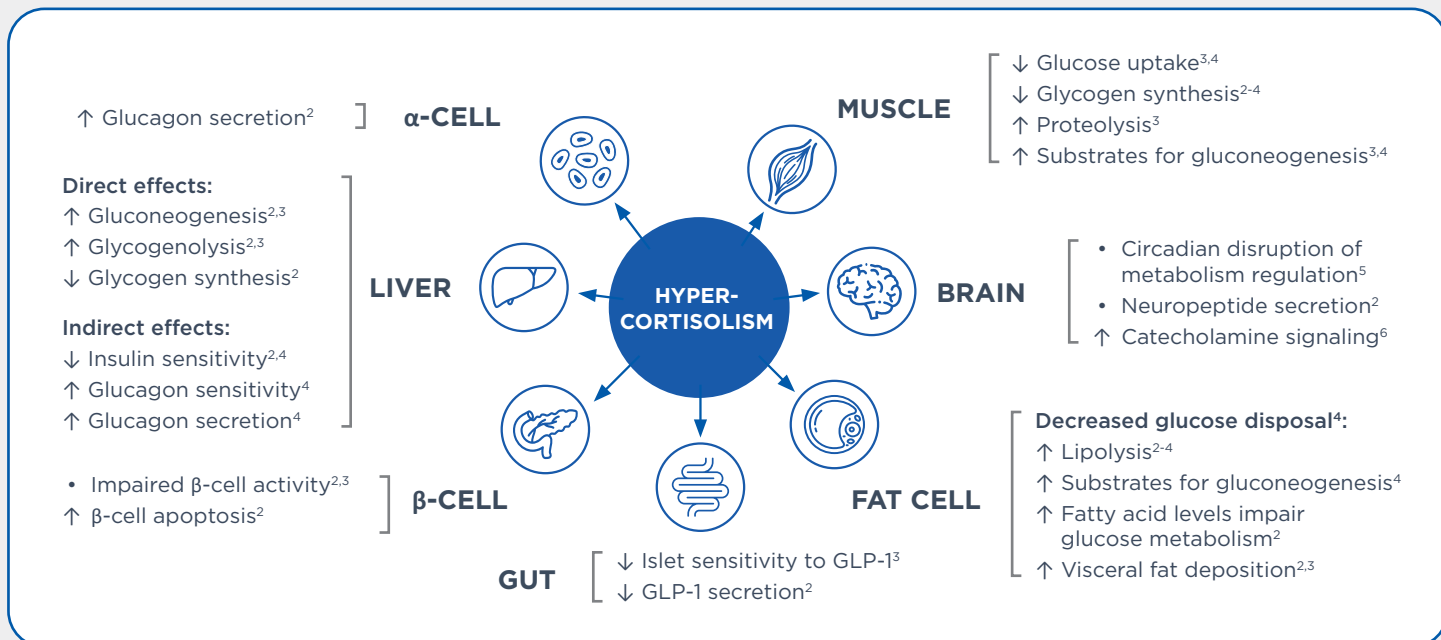
Millie has multiple difficult-to-control metabolic derangements and a high medication burden.

BID, twice daily; BMI, body mass index; HBr, hydrobromide; PRN, as needed; QD, once daily; QHS, once daily at bedtime; QW, once weekly.

^aThese medications were present at initial visit; other medications may have been added or discontinued during treatment course. ^bFrom a cross-sectional analysis of data from US adults with diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2018. The objective was to assess national trends in risk-factor control and treatment in US adults with diabetes, and to identify subgroups most likely to have untreated risk factors.¹

HYPERCORTISOLISM IMPACT AND PREVALENCE IN PATIENTS WITH T2D

Elevated Cortisol Levels Cause Metabolic Dysfunctions, Leading to Hyperglycemia



Patients With Difficult-to-Control T2D May Represent an Enriched Population for Hypercortisolism Screening^{7,a,b}



~3.5x more likely in patients with **advanced T2D**



~2x more likely in patients with **T2D and hypertension**



>2x more likely in patients with **T2D requiring insulin treatment**

DST, dexamethasone suppression test; GLP-1, glucagon-like peptide-1; LDDST, low-dose DST; LNSC, late night salivary cortisol; UFC, urinary free cortisol.

^aAdvanced T2D was defined as the prevalence of microvascular and/or macrovascular complications, the prevalence of insulin treatment plus hypertension, or the prevalence of hypertension treated with ≥2 drugs.⁷ ^bFrom a review of 6 studies that classified patients as having hidden hypercortisolism using a 1-mg DST, LDDST, LNSC, and/or UFC.⁷

MILLIE'S EVALUATION

Millie's healthcare provider is concerned because her blood glucose remains uncontrolled despite the growing number of antidiabetic medications she takes. Due to her clinical presentation, her provider's suspicion is that Millie's T2D and other comorbidities may be secondary to hypercortisolism.



85%

of patients with hypercortisolism who present with both T2D and hypertension have an adrenal source (n=11/13)^{8,a}

Biochemical Evaluation

Test	Result(s)	Normal Range ⁹⁻¹¹
Fasting blood glucose (mg/dL)	150; 200	70–99
HbA1c (%)	9.2	4.0–5.6
1-mg DST (µg/dL)	3.1; 2.8	<1.8
AM dexamethasone (ng/dL)	284; 483	>140 (is sufficient to suppress serum cortisol)
LNSC (µg/dL)	0.22; 0.40; 0.10	<0.145
UFC (µg/24 h)	14.5	4–50
ACTH (pg/mL)	8; 6	10–60
DHEA-S (µg/dL)	27	44–332
Total cholesterol (mg/dL)	104	<200
eGFR (mL/min/1.73 m ²)	90	>60
Serum potassium (mmol/L)	4.3	3.5–5.0
Triglycerides (mg/dL)	354	<150

Confirm Evidence of Hypercortisolism

Millie has multiple lines of biochemical evidence suggesting possible autonomous ACTH-independent hypercortisolism.^b

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; eGFR, estimated glomerular filtration rate.

^aFrom a review of 49 published patient cases of “unusual presentations of hypercortisolism” in which the patient presented with bone fragility, hypertension, and/or T2D.⁸ ^bGuidelines specify that at least 2 diagnostic tests (DST, LNSC, or UFC) should be performed to determine hypercortisolism status. Due to discordant results, Millie's healthcare provider performed more than 2 diagnostic tests to gauge the full clinical picture.¹¹

GUIDELINE RECOMMENDATIONS

1-mg Overnight DST Is Recommended for Initial Screening for Adrenal Autonomous Cortisol Secretion¹¹⁻¹³



The 1-mg overnight DST with a cutoff of $<1.8 \mu\text{g/dL}$ is recommended for initial screening for hypercortisolism, due to its high sensitivity. It is also considered the most valuable test for screening patients for adrenal autonomous cortisol secretion.

UFC and LNSC Diagnostic Tests May Not Be Appropriate in All Patients With Adrenal Adenomas

- UFC tests are frequently normal in patients with adrenal autonomous cortisol secretion¹⁴
- LNSC tests may have low sensitivity for predicting the presence of adrenal autonomous cortisol secretion¹³

Supportive Assessments Can Help Further Clarify the Clinical Picture

	Use	Interpretation
 AM Dexamethasone^{10,11}	Confirms the validity of 1-mg DST results by ruling out false positives	$>140 \text{ ng/dL}$ is sufficient to suppress serum cortisol
	Use	Interpretation
 Plasma ACTH¹⁵	Differentiates ACTH-dependent from ACTH-independent causes of hypercortisolism via an early morning draw	$<10 \text{ pg/mL}$ suggests an ACTH-independent source $>20 \text{ pg/mL}$ suggests an ACTH-dependent source
	Use	Interpretation
 DHEA-S¹⁶	Identifies ACTH-independent causes of hypercortisolism	$<40 \mu\text{g/dL}$ suggests an ACTH-independent source

MILLIE'S IMAGING AND ASSESSMENT

Imaging

Due to her biochemical results, Millie was sent for imaging to identify any possible adrenal mass. Her CT scan revealed a 22-mm left adrenal adenoma.



Determine the Source of Hypercortisolism

Millie's imaging confirmed an ACTH-independent source, and she was diagnosed with hypercortisolism due to an adrenal adenoma.

TREATMENT OPTIONS FOR HYPERCORTISOLISM FROM AN ADRENAL SOURCE

	Adrenalectomy ^{17,18}	Medical Therapy ^{19,20}	Active Surveillance ^{21,22}
 RECOMMENDED USE	First-line treatment for adrenal hypercortisolism for eligible patients	- Adjunctive treatment to reduce cortisol levels and/or activity - Patients who have failed or are ineligible for surgery - Bridge to adrenalectomy	- Patients with a nonfunctional adenoma - Patients with few comorbidities attributable to hypercortisolism
 BENEFITS	- Immediate resolution of hypercortisolism - Improvement in many manifestations of disease - Metabolic (blood pressure, weight, control of T2D) - Physical features	- Noninvasive - Can be stopped if not tolerated or no improvement seen - May help stabilize acutely ill patients prior to adrenalectomy	- Noninvasive - May avoid potential complications of an adrenalectomy
 CONCERNS	- Postoperative adrenal insufficiency may last for several years - Lifelong dependency on glucocorticoids and mineralocorticoids after bilateral adrenalectomy	- Adverse reactions - Frequent monitoring may be required	- Potential for disease worsening - Frequent monitoring may be required

Implement a Treatment Plan

Millie's healthcare provider understands the need for early intervention, since patients with adrenal autonomous cortisol secretion who do not receive treatment for their hypercortisolism are at an increased risk for CV events and CV mortality.²³

CV, cardiovascular.

1. Fang M, et al. *N Engl J Med*. 2021;384(23):2219-2228. 2. Scaroni C, et al. *Endocr Rev*. 2017;38(3):189-219. 3. Mazziotti G, et al. *Trends Endocrinol Metab*. 2011;22(12):499-506. 4. Pivonello R, et al. *Neuroendocrinology*. 2010;92(Suppl 1):77-81. 5. Mason IC, et al. *Diabetologia*. 2020;63(3):462-472. 6. Thau L, et al. *StatPearls* [Internet]. Updated August 29, 2022. Accessed February 3, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK538239/> 7. Aresta C, et al. *Endocr Pract*. 2021;27(12):1216-1224. 8. Giovanelli L, et al. *J Endocrinol Invest*. 2021;44(8):1581-1596. 9. American Board of Internal Medicine. Updated January 2023. Accessed April 18, 2023. <https://www.abim.org/Media/bfijryql/laboratory-reference-ranges.pdf> 10. ARUP Laboratories. Accessed June 21, 2023. <https://ltd.aruplab.com/Tests/Pub/2003248> 11. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 12. Zeiger MA, et al. *Endocr Pract*. 2009;15(Suppl 1):1-20. 13. Chiodini I, et al. *J Endocr Soc*. 2019;3(5):1097-1109. 14. Vaidya A, et al. *Endocr Pract*. 2019;25(2):178-192. 15. Lacroix A, et al. *Lancet*. 2015;386(9996):913-927. 16. Yener S, et al. *Endocrine*. 2015;48(2):669-676. 17. Di Dalmazi G, Reincke M. *Endocrinol Metab Clin North Am*. 2018;47(2):385-394. 18. Chiodini I, et al. *J Clin Endocrinol Metab*. 2010;95(6):2736-2745. 19. Tritos NA, Biller BMK. *Endocrinol Metab Clin North Am*. 2018;47(2):427-440. 20. Nieman LK, et al. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831. 21. Fassnacht M, et al. *Eur J Endocrinol*. 2023. doi:10.1093/ejendo/lvad066 22. Zografos GN, et al. *Hormones (Athens)*. 2014;13(3):323-337. 23. Petramala L, et al. *Endocrine*. 2020;70(1):150-163.

MILLIE'S JOURNEY TO TREATMENT

1

Consider the Clinical Picture

- Multiple comorbidities associated with cortisol excess
- Difficult-to-control T2D with a high medication burden
- Increased weight gain despite modified diet, exercise, and the initiation of a GLP-1 agonist medication

2

Confirm Evidence of Hypercortisolism

- 2 abnormal 1-mg DSTs
- Low ACTH and DHEA-S, suggesting an ACTH-independent source

3

Determine the Source of Hypercortisolism

- CT scan revealed a 22-mm adrenal adenoma on the left adrenal gland

4

Implement a Treatment Plan

- Early intervention is necessary to target the root of the cause—hypercortisolism

