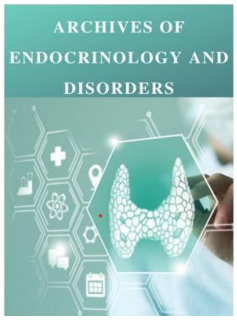

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Review Article

Functional Hypercortisolism in Type 2 Diabetes: The Endocrine Cortico-Metabolic Amplifier (ECMA) Theory

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Abstract

Background: A substantial subset of patients with difficult-to-control Type 2 Diabetes (T2D) exhibits biochemical evidence of hypercortisolism. Here we propose a unifying, testable model-the Endocrine Cortico-Metabolic Amplifier (ECMA)-that explains why functional hypercortisolism emerges, how it worsens insulin resistance and hyperglycemia and why glucocorticoid receptor antagonism improves glycemic control in this phenotype.

Hypothesis: Chronic hyperinsulinemia upregulates Hypothalamic-Pituitary-Adrenal (HPA) axis drive, creating a state of functional hypercortisolism. Intracrine regeneration of cortisol in adipose tissue via 11β-HSD1 and in subgroups, Mild Autonomous Cortisol Secretion (MACS) from adrenal incidentalomas add to systemic glucocorticoid action. Cortisol then promotes hepatic gluconeogenesis and skeletal muscle insulin resistance, amplifying visceral adiposity and hyperinsulinemia-closing a self reinforcing loop.

Evidence: The prevalence and treatment phases of the CATALYST program identified ~1 in 4 uncontrolled T2D patients with hypercortisolism under standardized screening and showed clinically meaningful A1c reductions with glucocorticoid receptor antagonism. Convergent evidence links OSA/sleep disruption and stress-related disorders to increased HPA activation, while clinical and translational data support 11β-HSD1 as an adipose amplifier of glucocorticoid action.

Implications: ECMA reframes functional hypercortisolism as both marker and amplifier-causal enough to be therapeutically tractable. We propose a pragmatic screening-to-treat algorithm and a research agenda to refine patient selection and endpoints.

Keywords: Type 2 Diabetes; Endocrine Cortico-Metabolic Amplifier; Hypothalamic-Pituitary-Adrenal; Mild Autonomous Cortisol Secretion

Key Physiological Statement

Hyperinsulinemia is also a driving force for increased activation of the Hypothalamic-Adrenal-Pituitary (HPA) axis in subjects with the metabolic syndrome, leading to a state of 'functional hypercortisolism'. This 'functional hypercortisolism' by antagonizing insulin actions may prevent hypoglycemia. It also disturbs energy balance by shifting energy fluxes away from muscles toward abdominal fat stores. Synergistic effects of hyperinsulinemia and 'functional hypercortisolism' promote abdominal visceral obesity and insulin resistance which are core pathophysiological components of the metabolic syndrome. It is hypothesized that hyperinsulinemia-induced increased activation of the HPA axis plays an important etiological role in the development of the metabolic syndrome and its consequences. Numerous studies have demonstrated reversibility of hyperinsulinemia with lifestyle, surgical and pharmaceutical-based therapies. Longitudinal studies should be performed to investigate whether strategies that reduce hyperinsulinemia at an early stage are successful in preventing increased activation of the HPA axis and the metabolic syndrome [1-5].

Introduction and Rationale

Patients with uncontrolled T2D often require polypharmacy and yet fail to meet glycemic targets. The CATALYST program has drawn attention to the high prevalence of biochemically defined hypercortisolism in this population and the glycemic benefits observed when glucocorticoid receptor signaling is antagonized. ECMA integrates classic glucocorticoid biology, intracrine adipose physiology and modern clinical observations into a single systems-endocrinology framework.

The ECMA Model: Nodes and Modulators

Node A - Hyperinsulinemic drive to the HPA axis (central set-point shift).

Chronic hyperinsulinemia increases HPA axis activation, shifting cortisol tone upward ("functional hypercortisolism"). This cortisol tone antagonizes insulin's actions, redistributes energy from skeletal muscle toward abdominal fat stores and synergizes with hyperinsulinemia to promote visceral adiposity and systemic insulin resistance.

Node B - Intracrine amplification via 11β-HSD1 in adipose tissue. Upregulation of 11β-HSD1 in adipose tissue regenerates cortisol from cortisone locally, amplifying glucocorticoid action within adipocytes, reducing adiponectin and worsening inflammation and mitochondrial function-driving insulin resistance [6].

Node C - Effector limbs: liver and skeletal muscle.

At the liver, glucocorticoids induce PEPCK and G6Pase and potentiate CREB/CRTC2 and FoxO1-PGC-1α programs to raise gluconeogenesis. In skeletal muscle, stress-kinase signaling and GR-dependent pathways impair IRS-1/AKT signaling and glucose uptake [7].

Node D - Adrenal autonomy (MACS).

A clinically important subset harbors adrenal incidentalomas with mild autonomous cortisol secretion, adding a constitutive source of cortisol to the loop [8].

Modulators - Sleep/OSA and stress-related psychopathology. OSA and sleep fragmentation increase HPA activation and cortisol; treatment with CPAP modestly lowers cortisol in meta-analyses and controlled studies. Chronic stress, anxiety and depression also dysregulate the HPA axis, potentially sustaining ECMA activity (Fig. 1).

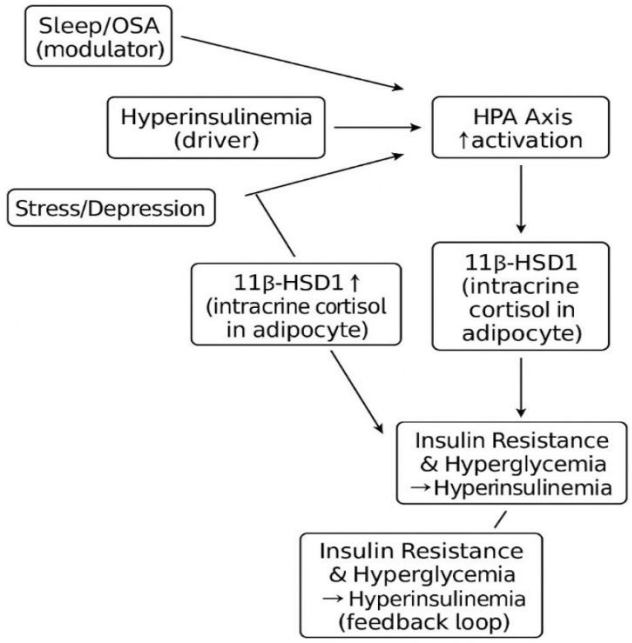

Figure 1: The ECMA loop: endocrine and intracrine drivers of glucocorticoid action in T2D. Hyperinsulinemia elevates HPA tone; systemic and intracrine cortisol act on liver/muscle; insulin resistance and hyperglycemia reinforce hyperinsulinemia. Sleep/OSA and stress are modulators; MACS adds autonomous adrenal output.

How ECMA Explains Catalyst

Prevalence phase: Standardized 1-mg dexamethasone suppression testing identified hypercortisolism in roughly one quarter of uncontrolled T2D patients, with enriched prevalence among those with resistant hypertension and frequent adrenal imaging abnormalities. Treatment phase: Glucocorticoid receptor antagonism over ~24 weeks reduced HbA1c meaningfully versus placebo, with concurrent weight and waist reductions-despite down-titration of background antidiabetic agents in many participants. Together, these findings demonstrate that excess glucocorticoid action is not a mere epiphenomenon; it is a tractable amplifier of dysglycemia in this phenotype (Fig. 2) [8-22].

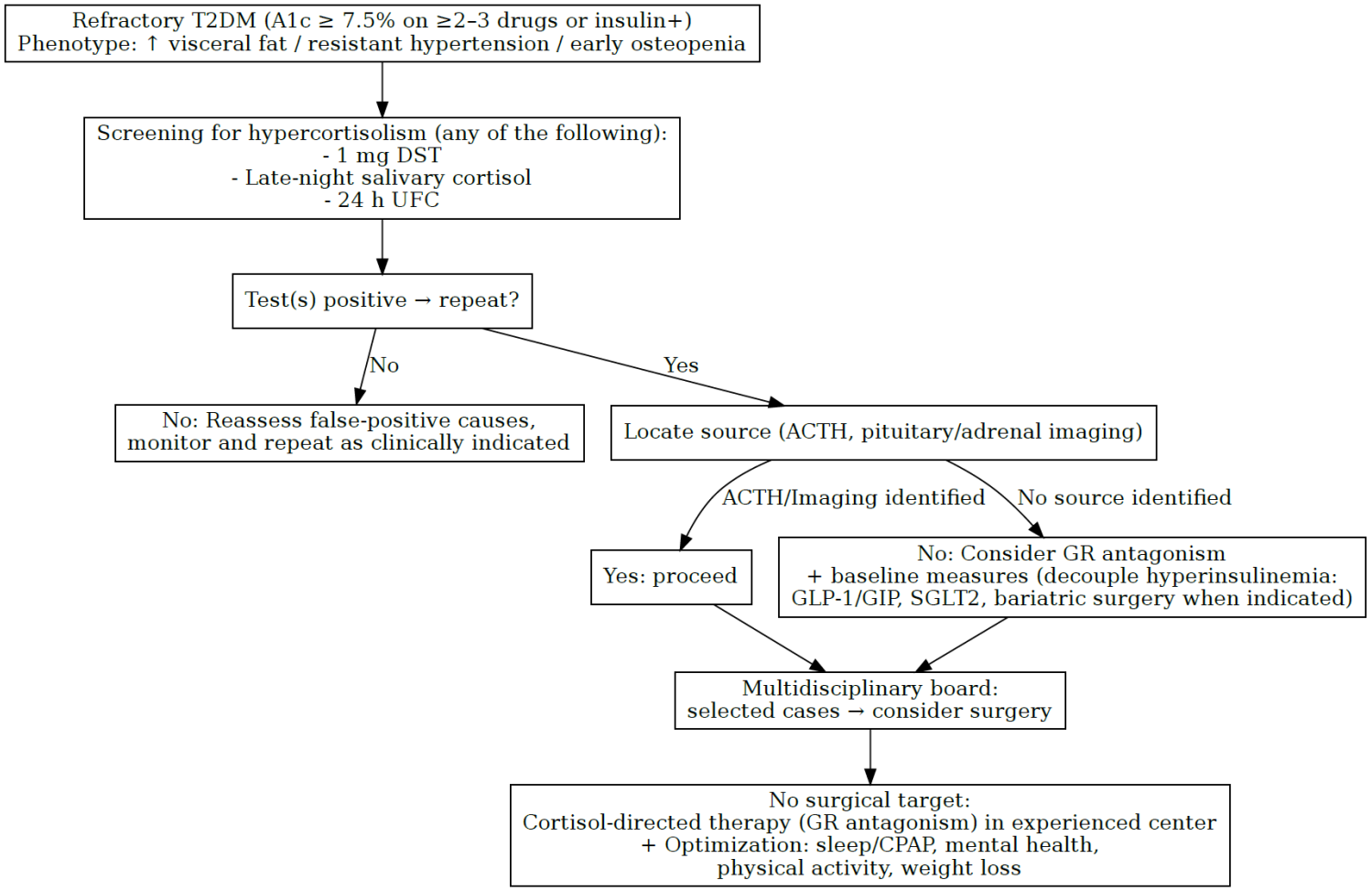

Figure 2: Screening and treatment flow for functional hypercortisolism in difficult-to-control T2D. Practical decision steps and intervention points, including base measures to reduce hyperinsulinemia and targeted GR antagonism when indicated.

Clinical Algorithm

Who to screen: Patients with HbA1c ≥7.5% despite ≥2-3 agents (or insulin plus another agent), especially with disproportionate visceral adiposity, resistant hypertension, early bone fragility, or unexplained hypokalemia. How to screen: Any of the standard first-line tests for endogenous hypercortisolism (1-mg overnight DST, late-night salivary cortisol, or 24-h UFC), with repeat confirmation of abnormal results and dexamethasone measurement to validate DST when used. If positive, localize source (ACTH and pituitary/adrenal imaging) [23-27].

Treatment: Treat surgical causes per etiology; for MACS, discuss adrenalectomy in carefully selected cases. In the absence of a surgical target, consider glucocorticoid receptor antagonism in expert centers, alongside foundational strategies to decouple the hyperinsulinemic motor (structured nutrition, GLP-1/GIP agonists, SGLT2 inhibitors and bariatric/metabolic surgery where indicated).

Predictions and Testable Implications

1) Highest-yield phenotype for screening: uncontrolled T2D with resistant hypertension and visceral adiposity will show the highest prevalence of functional hypercortisolism and adrenal imaging abnormalities. 2) Chronobiology: flatter diurnal cortisol rhythms will correlate with worse time-in-range; OSA treatment will modestly improve cortisol metrics and glycemic endpoints. 3) Surgical subset: in MACS with cardiometabolic disease, adrenalectomy will outperform conservative management for metabolic outcomes. 4) Therapeutic hierarchy: systemic GR antagonism will produce larger short-term A1c effects than isolated 11β-HSD1 inhibition. 5) Prevention: early reduction of hyperinsulinemia should lessen HPA overactivation and prevent establishment of the ECMA module [28-33].

Research Agenda

- Strategy RCT: "screen-and-treat" functional hypercortisolism in uncontrolled T2D vs usual care, with hierarchical endpoints (A1c, time-in-range, BP, waist, CV risk markers)
- Biomarker signature: composite of DST/late-night salivary cortisol/UFC, ACTH, imaging features and adipose 11β-HSD1 surrogates to predict responsiveness to GR blockade
- Motor disruption trials: longitudinal studies testing early hyperinsulinemia-lowering strategies (nutrition/GLP-1-based therapies/SGLT2/bariatric surgery) on HPA activity and incident functional hypercortisolism

Conclusion

Functional hypercortisolism is best conceptualized as a causal amplifier within ECMA. It is both a biomarker of metabolic stress and a lever for intervention. CATALYST provides functional proof-of-concept that targeting glucocorticoid action can unlock glycemic control in a hard-to-treat T2D phenotype-while early strategies that reverse hyperinsulinemia may prevent the module's emergence.

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial Disclosure

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References

1. Janssen JAMJL. Hyperinsulinemia and increased activation of the hypothalamic-pituitary-adrenal axis: A framework for functional hypercortisolism in metabolic disease. Int J Mol Sci. 2022;23(24):15418.
2. Buse JB, Fonseca V; CATALYST Investigators. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes: Results from the CATALYST program. Diabetes Care. 2025;48(6):e123-30.
3. American Diabetes Association. ADA press release: Mifepristone improves HbA1c in uncontrolled T2D with hypercortisolism (CATALYST). 2025.
4. ADA Meeting News. Treatment phase of the CATALYST trial demonstrates glycemic benefit of glucocorticoid receptor antagonism. 2025.
5. Drug Topics. Mifepristone reduces HbA1c in T2D with hypercortisolism: ADA 2025 late-breaking data. 2025.
6. UNC Health News. CATALYST prevalence study highlights underrecognized hypercortisolism in T2D. 2025.
7. Fassnacht M, Arlt W, Bancos I. Management of adrenal incidentalomas and mild autonomous cortisol secretion: 2023 European Society of Endocrinology guideline. Eur J Endocrinol. 2023;189(1):G1-47.
8. Nieman LK, Biller BMK, Findling JW. The diagnosis of Cushing's syndrome: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526-40.
9. Fleseriu M, Biller BMK, Findling JW, Molitch ME. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in Cushing's syndrome. J Clin Endocrinol Metab. 2012;97(6):2039-49.
10. Rosenstock J, Banarer S, Fonseca V. The 11β-HSD1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin. Diabetes Care. 2010;33(7):1516-21.
11. Feig PU, Shah S, Hermanowski-Vosatka A. Effects of an 11β-HSD1 inhibitor (MK-0916) in overweight and obese patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes Obes Metab. 2011;13(6):498-504.
12. Morgan SA, McCabe EL, Gathercole LL. 11β-HSD1 is a major determinant of tissue-specific glucocorticoid amplification in obesity. Endocr Rev. 2014;35(4):578-609.
13. Seckl JR, Walker BR. 11β-Hydroxysteroid dehydrogenase type 1 and the metabolic syndrome. Mol Cell Endocrinol. 2012;350(2):215-23.

14. Engeli S, Böhnke J, Feldpausch M. Regulation of 11β-HSD genes in human adipose tissue: Influence of obesity and weight loss. Obes Res. 2004;12(1):9-17.
15. Beaupère C, Garcia M, Moulis M. Molecular mechanisms of glucocorticoid-induced insulin resistance. Cells. 2021;10(11):3019.
16. Barres R, Osler ME, Yan J. Non-Cushing glucocorticoid exposure and insulin resistance in human skeletal muscle. J Clin Invest. 2009;119(2):451-63.
17. Kuo T, Harris CA, Wang JC. Metabolic functions of glucocorticoid receptor in skeletal muscle. Mol Cell Endocrinol. 2013;380(1-2):79-88.
18. Rizza RA, Mandarino LJ, Gerich JE. Mechanism and significance of insulin resistance in noninsulin-dependent diabetes mellitus. Diabetes. 1981;30(12):990-5.
19. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: Is hyperinsulinemia the cart or the horse? Diabetes Care. 2008;31(Suppl 2):S262-8.
20. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14(3):173-94.
21. Liang Y, Zheng D, Zhou X. Morning cortisol and continuous glucose monitoring metrics in type 2 diabetes. Diabetes Technol Ther. 2021;23(7):480-8.
22. Kritikou I, Basta M, Vgontzas AN. Sleep apnea, sleepiness, inflammation and the HPA axis in middle-aged men and women. J Clin Endocrinol Metab. 2015;100(4):1359-68.
23. Wang Y, Zhang H, Chen Y. Effect of CPAP on cortisol levels in obstructive sleep apnea: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021;95(5):702-11.
24. Terzolo M, Pia A, Reimondo G. Adrenal incidentaloma: A new cause of the metabolic syndrome? J Clin Endocrinol Metab. 2002;87(3):998-1003.
25. Ren X, Li J, Wang T. Adrenalectomy versus conservative treatment in patients with mild autonomous cortisol secretion: A meta-analysis. Front Endocrinol (Lausanne). 2024;15:1405678.
26. Ueland GÅ, Husebye ES. Randomized trial of adrenalectomy in mild autonomous cortisol secretion: Metabolic and quality-of-life outcomes. Endocr Connect. 2025;14(2):e230456.
27. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
28. Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes. JAMA. 2014;311(23):2373-83.
29. Lean MEJ, Leslie WS, Barnes AC. Durability of a primary care-led weight-management intervention (DiRECT): 5-year outcomes. Lancet Diabetes Endocrinol. 2024;12(1):35-45.
30. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and obesity. Nat Rev Endocrinol. 2014;10(10):585-96.
31. Perry RJ, Camporez JPG, Kursawe R. Hepatic acetyl-CoA links adipose tissue inflammation to hepatic insulin resistance and gluconeogenesis. Cell. 2015;160(4):745-58.
32. Kroon J, Koorneef LL, van den Heuvel JK. Selective GR antagonism prevents and reverses obesity and glucose intolerance in mice. Endocrinology. 2016;157(5):1839-50.
33. Fenton C, Birmingham BK. Pharmacology of mifepristone as a glucocorticoid receptor antagonist. Clin Pharmacokinet. 2011;50(6):403-17.