VIA MEDICA
EDITORIAL
ISSN 2450–7458
e-ISSN 2450–8187

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Hypercortisolism and Type 2 Diabetes: The Sinister Duo!

Whenever I see patients with type 2 diabetes (T2D) struggling to control their blood glucose levels for some time despite being adherent to the traditionally ideal and successful therapeutic and lifestyle interventions, I suspect hypercortisolism could be at play. Hypercortisolism is a condition in which the body produces excess cortisol. When a person with diabetes has chronically elevated levels of cortisol, it causes resistant hyperglycemia (Fig. 1) [1] that can overcome even the most potent T2D medications out there, including all the formidable new GLP-1/GLP1 + GIP receptor agonist agents. Cortisol is associated with inflammation in patients with T2D who have retinopathy, polyneuropathy, or kidney disease, suggesting that cortisol may play a role in the inflammatory pathway, leading to chronic microvascular complications.

Ample evidence suggests that impairments of the hypothalamic-pituitary-adrenal (HPA) axis play a crucial role in the crosstalk between psychosocial stress and metabolic disruption. Cortisol, a glucocorticoid (GC) hormone and critical component of the HPA axis, can exert counter-regulating effects on insulin via induction of hepatic gluconeogenesis and inhibition of the peripheral uptake of glucose. Physiological or psychological stressors activate the HPA axis, producing corticotropin-releasing hormone (CRH) from the hypothalamus. CRH causes the pituitary corticotropic cells to release the adrenocorticotropic hormone ACTH, which causes the adrenal cortex to secrete cortisol. Through a negative feedback loop, cortisol suppresses further release of ACTH and CRH. Activation of the HPA axis is also accompanied by stimulation of the sympathetic nervous system, resulting in the release of catecholamines and interleukin-6, which activates a cytokine cascade [2]. Chronic stress may damage the feedback mechanisms that return these hormonal systems to normal, resulting in chronic elevation in cortisol levels, catecholamines, and inflammatory markers [3].

Prolonged stress and inadequate regulation of the stress system can lead to chronic hypercortisolism or, in some cases, a blunted cortisol response to stress, contributing to subclinical inflammation, insulin resistance, increased adiposity, dyslipidemia, and T2D. Sustained psychosocial stressors may promote proinflammatory effects caused by impaired GC receptor sensitivity [4, 5]. The coexistence of dysregulated HPA-axis and increased inflammation contribute to the pathogenesis of T2D and its complications [6].

Subclinical hypercortisolism, also known as mild autonomous cortisol secretion or hidden hypercortisolism (HidHyCo), is a condition in which the body produces too much cortisol without the classic symptoms of Cushing syndrome [7]. It is more common than Cushing syndrome and is associated with an increased risk of T2D and other chronic diseases [8]. It accompanies more severe hypertension, increased aortic stiffness, and the presence of diabetic nephropathy in patients with T2D [9]. An earlier 2016 study showed that alterations in diurnal cortisol patterns [a flattened diurnal cortisol slope (the change in cortisol levels from

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Clinical Diabetology 2024, 13; 5: 243–245
DOI: 10.5603/cd.103172
Received: 8.10.2024 Accepted: 11.10.2024

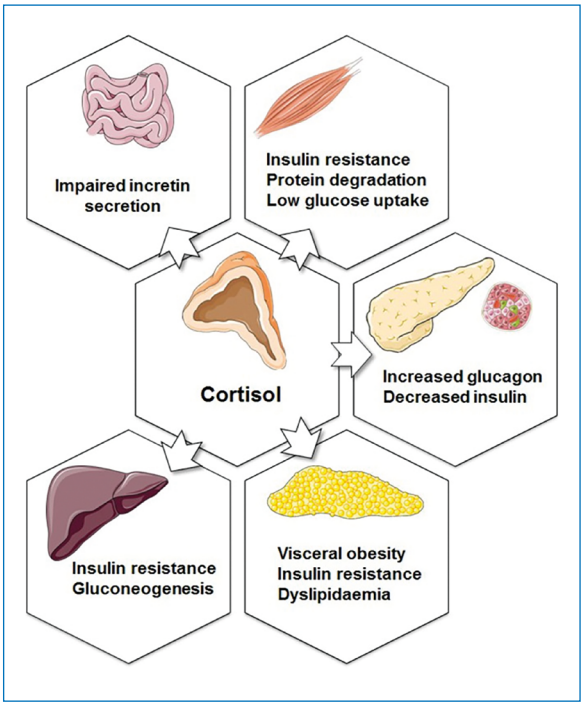

Figure 1. Metabolic Functions of Glucocorticoids. The Effects of Increased Cortisol Secretion on the Endocrine Pancreas, Adipose Tissue, Liver, Muscle, and Gastrointestinal System (From: "Glucocorticoid Metabolism in Obesity and Following Weight Loss", by E. Akalestou E., L. Genser, G Rutter, Front Endocrinol (Lausanne), 2020;11:59 [1]. Copyright© 2020 Akalestou, Genser and Rutter)

morning to evening) with high bedtime cortisol] predict future T2D [10].

Chronic stress, through its action on the neuroendocrine, metabolic, and immune systems, can contribute to specific biological and behavioral alterations punctuated by epigenetic changes in cellular biochemical pathways crucial to the body's glucose and lipid metabolism and the release of inflammatory cytokines. Additional factors, including changes in GC receptor sensitivity and enhanced 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity, may lead to the onset of obesity, diabetes, and various related complications. 11β-HSD1 is an enzyme that catalyses the conversion of inactive cortisone into active cortisol. Chronic stress can lead to enhanced activity of this enzyme. 11β-HSD1 activity in hepatocytes can increase glucose output, independent of insulin, glucagon, or free fatty acids. Overexpression of 11β-HSD1 in adipose tissue can lead to metabolic syndrome, including central obesity, hypertension, and dyslipidemia [11].

An elegant study titled "The Prevalence of Hypercortisolism in Patients with Type 2 Diabetes and Microvascular Complications: A Prospective Observational Case-Control Study" by Selma Jusufović et al., published in the current online issue of "Clinical Diabetology" journal, attempts to answer an important question: Is cortisol associated with microvascular complications in T2D? The research paper promises to make an exciting and enriching academic read because of its lucid content, evidence-based methodology, statistics, and inferences. This prospective observational case-control, single-centered study has included 107 patients with T2D and concluded that the prevalence of hypercortisolism in the recruited patients with T2D was 6.3%, in patients with complications 10.5%, and 2.0% in patients without complications. This publication creates awareness regarding the hitherto neglected endogenous hypercortisolism due to the dysfunctional HPA hormonal axis, which the researchers implicate as an essential factor responsible for persistent hyperglycemia, inflammation, and associated microvascular complications in persons with T2D.

However, despite its overall merits, this publication has some visible limitations. These include a small number of recruited patients, mandatory hospitalization for the initial 3 days, lack of imaging for the adrenal source of autonomous cortisol secretion (ACS), and non-confirmation with a high-dose dexamethasone test to rule out potential false positive DEX cortisol unsuppressed results with 1 mg DST.

The association of dysregulated cortisol secretion patterns, diabetes, and related complications is unmistakable. The recently released ongoing CATALYST trial results endorse the sinister nature of the co-morbid duo of hypercortisolism and T2D. The CATALYST trial results (released on June 24th, during the American Diabetes Association meeting, 2024) show that hypercortisolism is more common than previously thought in people with T2D. Findings of the first phase of this trial (hypercortisolism in 24% of poorly controlled diabetes patients, indicated by a post-DST morning cortisol level above 1.8 μg/dL and a dexamethasone level of 140 ng/dL or higher), although significant because they point out a major barrier to managing T2D, remain incredible. The ongoing second part of the study aims to evaluate whether medically treating hypercortisolism can enhance diabetes management and alleviate related health issues.

The Endocrine Society Guidelines recommend a 1-mg DST cutoff of > 1.8 μg/dL to screen patients who do not exhibit the clinical features or signs and symptoms but are suspected of having ACS. A 1-mg DST cutoff of > 1.8 μg/dL achieves sensitivity rates greater than 95% [12]. However, there is a 10–15% false-positive rate (failure of suppression in the ab-

sence of Cushing syndrome) due to failure to take the dexamethasone dose, increased dexamethasone metabolism, or episodic ACTH secretion.

Many questions remain unanswered, such as whether all people with mild cortisol excess require treatment, and if offered treatment, will they derive any metabolic health benefits? Future research should aim to address these lacunae and help break the ominous nexus between hypercortisolism and T2D.

REFERENCES

1. Akalestou E, Genser L, Rutter GA. Glucocorticoid Metabolism in Obesity and Following Weight Loss. Front Endocrinol (Lausanne). 2020; 11: 59, doi: 10.3389/fendo.2020.00059, indexed in Pubmed: 32153504.
2. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009; 5(7): 374–381, doi: 10.1038/nrendo.2009.106, indexed in Pubmed: 19488073.
3. Joseph JJ, Golden SH. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. Ann N Y Acad Sci. 2017; 1391(1): 20–34, doi: 10.1111/nyas.13217, indexed in Pubmed: 27750377.
4. DeSantis AS, DiezRoux AV, Hajat A, et al. Associations of salivary cortisol levels with inflammatory markers: the Multi-Ethnic Study of Atherosclerosis. Psychoneuroendocrinology. 2012; 37(7): 1009–1018, doi: 10.1016/j.psyneuen.2011.11.009, indexed in Pubmed: 22178583.
5. Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol. 2006; 20(4 Suppl): 79–84, doi: 10.1177/1359786806066063, indexed in Pubmed: 16785275.
6. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2013; 36(1): 166–175, doi: 10.2337/dc12-0702, indexed in Pubmed: 23264288.
7. Aresta C, Soranna D, Giovanelli L, et al. When to Suspect Hidden Hypercortisolism in Type 2 Diabetes: A Meta-Analysis. Endocr Pract. 2021; 27(12): 1216–1224, doi: 10.1016/j.eprac.2021.07.014, indexed in Pubmed: 34325041.
8. Prete A, Bancos I. Mild autonomous cortisol secretion: pathophysiology, comorbidities and management approaches. Nat Rev Endocrinol. 2024; 20(8): 460–473, doi: 10.1038/s41574-024-00984-y, indexed in Pubmed: 38649778.
9. Costa DS, Conceição FL, Leite NC, et al. Prevalence of subclinical hypercortisolism in type 2 diabetic patients from the Rio de Janeiro Type 2 Diabetes Cohort Study. J Diabetes Complications. 2016; 30(6): 1032–1038, doi: 10.1016/j.jdiacomp.2016.05.006, indexed in Pubmed: 27210052.
10. Hackett RA, Kivimäki M, Kumari M, et al. Diurnal Cortisol Patterns, Future Diabetes, and Impaired Glucose Metabolism in the Whitehall II Cohort Study. J Clin Endocrinol Metab. 2016; 101(2): 619–625, doi: 10.1210/jc.2015-2853, indexed in Pubmed: 26647151.
11. Gianotti L, Belcastro S, D'Agnano S, et al. The Stress Axis in Obesity and Diabetes Mellitus: An Update. Endocrines. 2021; 2(3): 334–347, doi: 10.3390/endocrines2030031.
12. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008; 93(5): 1526–1540, doi: 10.1210/jc.2008-0125, indexed in Pubmed: 18334580.