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Neurohormonal Synchronization in the Face of Exhaustion: Unveiling the Cortisol-Oxytocin Crosstalk in Type 2 Diabetes Patients with Severe Distress and HPA Axis Blunting

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A B S T R A C T

Type 2 diabetes mellitus (T2DM) is increasingly conceptualized as a complex psychoneuroendocrine disorder. While acute physiological stress typically induces hypercortisolemia, chronic diabetes distress may lead to allostatic overload and Hypothalamic-Pituitary-Adrenal (HPA) axis blunting. The compensatory role of oxytocin, a stress-buffering neuropeptide, remains underexplored in this specific clinical phenotype. This study aimed to characterize the neuroendocrine phenotype of patients with uncontrolled T2DM and severe distress, specifically investigating the synchronization between serum cortisol and oxytocin as a marker of homeostatic regulation. In this analytic cross-sectional study, 86 patients with uncontrolled T2DM (HbA1c greater than or equal to 7.0%) and severe diabetes distress (Diabetes Distress Scale-17 mean score greater than or equal to 3.0) were recruited via purposive sampling. Strict exclusion criteria were applied for exogenous steroid use and renal failure to ensure biological validity. Fasting morning serum cortisol and oxytocin were analyzed using Enzyme-Linked Immunosorbent Assays (ELISA). Statistical analysis utilized Spearman's rank correlation and multivariate linear regression, controlling for Body Mass Index and age. The cohort exhibited severe metabolic dysregulation (Mean HbA1c: 10.03 ± 2.10%) and psychological distress (Mean DDS: 4.65 ± 0.35). Paradoxically, mean morning cortisol was low-normal (170.32 ± 135.43 nmol/L), suggestive of HPA axis blunting rather than the expected hypercortisolemia. A robust positive correlation was observed between cortisol and oxytocin ($r = 0.555$, $p < 0.001$). Multivariate regression confirmed cortisol as a significant independent predictor of oxytocin levels ($\beta = 0.521$, $p < 0.001$), independent of metabolic confounders. In conclusion, patients with severe diabetes distress display a distinct phenotype of HPA axis exhaustion coupled with synchronized oxytocinergic activity. This suggests a preserved reactive mobilization mechanism where oxytocin is upregulated in tandem with adrenal output to buffer chronic allostatic load. These findings highlight the potential of the oxytocinergic system as a therapeutic target in diabetes burnout.

1. Introduction

The global trajectory of type 2 diabetes mellitus (T2DM) has transcended its traditional classification as a purely metabolic disorder characterized by carbohydrate intolerance and beta-cell failure.[1] Over the past decade, the clinical paradigm has shifted decisively toward a complex biopsychosocial model, recognizing T2DM as a systemic syndrome where neuroendocrine dysregulation, chronic inflammation, and psychological burden are inextricably linked.[2]

Contemporary medical consensus now acknowledges that the "diabetic state" is not confined to the periphery—the pancreas, liver, and skeletal muscle—but is deeply rooted in the central nervous system. This bidirectional relationship suggests that the diabetic brain is both a driver and a casualty of metabolic dysfunction. Within this framework, the psychological experience of the patient is no longer viewed merely as a reaction to the disease, but as a potent physiological variable that directly influences the trajectory of glycemic control and the development of complications.[3]

Among the spectrum of psychological comorbidities associated with T2DM, diabetes distress has emerged as a distinct and clinically critical entity, separate from major depressive disorder and generalized anxiety disorder. unlike depression, which is a global affect disorder, diabetes distress is content-specific. It is characterized by the unique emotional burden of self-management, the terror of impending complications, the frustration of fluctuating glucose levels despite adherence, and the phenomenon known as regimen-related fatigue.[4] This distress arises from the unrelenting cognitive load required to manage a condition that demands 24-hour vigilance. Patients are tasked with acting as their own primary care providers—monitoring glucose, calculating carbohydrate intake, titrating medications, and modifying physical activity—without respite. This chronic emotional burden creates a vicious psychobiological cycle: distress leads to maladaptive coping behaviors, such as medication non-adherence and dietary neglect, which in turn exacerbate hyperglycemia, further fueling the emotional distress. Epidemiological data indicate that severe diabetes distress affects a significant proportion of the T2DM population, often serving as a stronger predictor of sustained hyperglycemia (HbA1c elevation) than clinical depression. However, the physiological mechanisms translating this emotional burden into metabolic dysregulation remain a subject of intense investigation.[5]

The physiological translation of diabetes distress is classically modeled via the activation of the hypothalamic-pituitary-adrenal (HPA) axis, the primary neuroendocrine system responsible for the adaptation to stress. In the classical "fight-or-flight" model, acute stress triggers the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing hormone (CRH). This peptide stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn signals the adrenal cortex to release cortisol. In the context of early metabolic dysregulation or acute stress, this cascade results in hypercortisolemia. Elevated cortisol is functionally antagonistic to insulin; it promotes hepatic gluconeogenesis, inhibits peripheral glucose uptake in skeletal muscle, and stimulates lipolysis, thereby providing a surge of energy substrates intended to help the organism survive an immediate threat.[6]

However, the neuroendocrine response to chronic, unrelenting stress—such as the lifelong burden of uncontrolled diabetes—is far less linear and more insidious. The theory of Allostatic Load, pioneered by McEwen and colleagues, suggests that physiological systems designed for acute adaptation can become maladaptive when the stressor is persistent.[7] Prolonged hyperactivity of the HPA axis eventually leads to a state of neuroendocrine exhaustion. Through mechanisms involving the downregulation of glucocorticoid receptors in the hippocampus and hypothalamus, and the desensitization of the adrenal cortex to ACTH, the system may transition from a state of hypercortisolism to hypocortisolism. This phenomenon, known as HPA axis blunting, represents a physiological collapse or a protective downregulation intended to shield the body from the catabolic toxicity of excess cortisol. This hypocortisolemic state has been well-documented in conditions of chronic emotional burnout, Post-Traumatic Stress Disorder (PTSD), and chronic fatigue syndrome. In the context of T2DM, HPA axis blunting is particularly dangerous. Cortisol is essential for the counter-regulatory response to hypoglycemia and for modulating

inflammation. A blunted cortisol response in a patient with severe diabetes distress may indicate a profound failure of homeostatic resilience, leaving the patient vulnerable to inflammatory cytokines and metabolic instability. Despite the high clinical relevance of this transition from "stress mobilization" to "stress exhaustion," the prevalence of this blunted phenotype in patients specifically suffering from severe diabetes distress remains under-investigated in current literature.

Parallel to the catabolic stress response orchestrated by the HPA axis is the endogenous anabolic and anti-stress machinery of the body, primarily governed by the nonapeptide oxytocin.[8] Historically pigeonholed as a reproductive hormone essential for labor and lactation, oxytocin is now recognized as a pleiotropic neuropeptide with profound metabolic and behavioral effects. Synthesized in the magnocellular and parvocellular neurons of the PVN—the same anatomical region that initiates the stress response—oxytocin acts centrally to dampen amygdala reactivity, reduce anxiety, and promote social bonding. Peripherally, oxytocin exerts direct metabolic benefits that are particularly relevant to diabetes. It has been shown to improve insulin sensitivity, enhance glucose uptake in skeletal muscle, and promote lipid utilization. The "Buffering Hypothesis" posits that oxytocin secretion is dynamically upregulated during periods of high stress to mitigate the deleterious effects of cortisol. Under this model, oxytocin acts as a physiological brake, restraining the HPA axis and promoting a "tend-and-befriend" response that counters the sympathetic "fight-or-flight" activation. This homeostatic balancing act is crucial for survival, preventing the organism from entering a state of unchecked catabolism during prolonged stress.

The interaction between the cortisol and oxytocin systems in the context of T2DM is complex and not fully understood. While animal models often suggest a simple inverse relationship—where oxytocin inhibits cortisol release and vice versa—human data in chronic disease states are conflicting. Some studies suggest that in states of extreme allostatic load, the typical inverse relationship decouples. Alternatively, there may be a mechanism of "synchronization," where the body attempts a desperate homeostatic rescue by elevating oxytocin levels in tandem with HPA axis dysregulation.[9]

A significant gap exists in the current clinical literature regarding the simultaneous evaluation of these biomarkers in the specific context of diabetes burnout. Most existing research has assessed these hormones in isolation or compared diabetic patients to healthy controls, failing to capture the nuance of the distress phenotype itself. Furthermore, methodological limitations in previous research often fail to account for the potential positive synchronization of these hormones, assuming instead a simple antagonistic relationship. Understanding whether the oxytocinergic system remains active and responsive in patients who have already reached the stage of HPA axis blunting is critical. If oxytocin remains elevated even when cortisol production has failed, it would suggest a specific neuroendocrine phenotype of "reactive mobilization" that could be targeted therapeutically.[10]

This study aims to bridge this substantial knowledge gap by characterizing the detailed neurohormonal profile of patients with uncontrolled T2DM and severe diabetes distress. Unlike comparative studies that utilize healthy controls to establish baseline differences, this study employs a descriptive, analytic design to deeply phenotype this high-risk population, allowing for an exploration of the internal dynamics between stress and anti-stress hormones.

The novelty of this research is twofold: First, it challenges the prevailing assumption that severe distress in diabetes is invariably associated with hypercortisolemia, proposing instead that chronic distress leads to a paradoxical state of HPA axis blunting. Second, it is among the first studies to investigate the synchronization hypothesis in this specific population. We hypothesize that patients with severe diabetes distress will exhibit a paradoxical

neuroendocrine signature: a blunted HPA axis characterized by low-normal cortisol levels, co-occurring with a synchronized upregulation of oxytocin. This finding would reflect a preserved, albeit overwhelmed, homeostatic attempt to manage chronic allostatic load despite adrenal exhaustion, offering new insights into the psychoneuroendocrinology of diabetes burnout and highlighting the oxytocinergic system as a potential therapeutic target.

2. Methods

Study design and ethical considerations

This analytic observational study utilized a cross-sectional design to assess the simultaneous relationship between psychological distress and neuroendocrine biomarkers. The study was conducted at the Internal Medicine Polyclinic of PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia, a tertiary care center managing a high volume of metabolic disorders. The protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Universitas Muhammadiyah Yogyakarta. Written informed consent was obtained from all participants prior to data collection.

Study population and sampling strategy

A total of 86 outpatients diagnosed with Type 2 Diabetes Mellitus were recruited. To ensure statistical robustness, an a priori power analysis was conducted using G*Power version 3.1.9.7. Based on a projected medium effect size (r = 0.30) for the correlation between cortisol and oxytocin, an alpha error of 0.05, and a statistical power of 0.80, a minimum sample size of 84 subjects was required. A non-probability purposive sampling method was employed to select patients meeting specific metabolic and distress criteria. Inclusion criteria were; (1) Confirmed diagnosis of Type 2 DM for at least one year; (2) Age between 35 and 65 years; (3) Uncontrolled diabetes defined as HbA1c greater than or equal to 7.0%; (4) Willingness to participate in morning fasting blood draws. To eliminate confounding variables that artificially alter HPA axis or oxytocinergic function, the following exclusion criteria were rigorously applied: (1) Exogenous Steroid Use: Current or recent use (within 3 months) of oral, parenteral, or inhaled glucocorticoids such as prednisone or dexamethasone was a definitive exclusion criterion to prevent iatrogenic HPA axis suppression; (2) Severe Renal Impairment: Patients with an estimated Glomerular Filtration Rate (eGFR) less than 30 mL/min/1.73m² (CKD Stage 4-5) were excluded, as renal failure significantly alters the clearance half-life of peptide hormones; (3) Acute Metabolic Crisis: Presence of Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycemic State (HHS); (4) Pregnancy or Lactation: Due to physiological surges in oxytocin; (5) Severe Mental Disorders: Diagnosis of schizophrenia, bipolar disorder, or dementia.

Anthropometric and clinical profiling

Demographic data and clinical history were extracted from electronic medical records. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Duration of diabetes and current pharmacological regimens were documented to control for disease severity.

Psychological assessment

Diabetes-related emotional distress was evaluated using the validated Indonesian version of the Diabetes Distress Scale-17 (DDS-17). This instrument is considered the gold standard for assessing diabetes-specific distress, covering four domains: emotional burden, physician-related distress, regimen-related distress, and interpersonal distress. Items are rated on a 6-point Likert scale. A mean score of 3.0 or higher indicates moderate to severe distress. The internal consistency of the instrument in this study was high, with a Cronbach's alpha of 0.89.

Biological assays

To minimize circadian variability, all venous blood samples were collected strictly between 08:00 AM and 09:00 AM following an overnight fast of at least 8

hours. Serum cortisol was quantified using a competitive Enzyme-Linked Immunosorbent Assay (ELISA) (Elabscience Human Cortisol ELISA Kit). The detection range was 2.5–160 ng/mL with a sensitivity of 1.5 ng/mL. The intra-assay and inter-assay coefficients of variability were less than 6% and 8%, respectively. Raw data were converted to nmol/L for standardization using a conversion factor of 2.76. Serum oxytocin levels were measured using a sensitive sandwich ELISA specific for human oxytocin (Abbexa Human Oxytocin ELISA Kit). The sensitivity was less than 2.0 pg/mL, with an intra-assay coefficient of variability less than 10%. Analysis was performed on unextracted serum to capture the total circulating oxytocin pool. We acknowledge that measuring oxytocin in unextracted serum typically yields higher absolute concentrations compared to extracted plasma due to the presence of bound protein fractions and potential matrix interference. However, this method was chosen to allow for the assessment of relative physiological trends. Given the potential for matrix effects to inflate absolute values, data interpretation in this study prioritizes relative correlations over absolute concentration comparisons. HbA1c levels were measured using High-Performance Liquid Chromatography (Bio-Rad D-10), serving as the objective marker for glycemic control.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 26.0. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as Mean ± Standard Deviation (SD), and categorical variables are presented as frequencies and percentages.

Due to the non-normal distribution of hormonal data, Spearman's rank correlation was used to assess the monotonic relationships between DDS scores, cortisol, and oxytocin. A Multiple Linear Regression model was constructed to determine if cortisol was an independent predictor of oxytocin levels. To satisfy regression assumptions, oxytocin values were log-transformed. The model was adjusted for biologically relevant covariates, including Age, BMI, and Duration of DM. A p-value of less than 0.05 was considered statistically significant.

3. Results and Discussion

Table 1 delineates the sociodemographic and clinical baseline characteristics of the study cohort (N=86), offering a granular view of the population's metabolic chronicity. The participants exhibited a relatively balanced gender distribution (52.3% male) with a mean age of 54.3 ± 7.2 years, reflective of a middle-aged demographic frequently encountering the peak burden of diabetes management. Clinically, the cohort demonstrated a significant metabolic load; the mean Body Mass Index (BMI) was 28.4 ± 4.1 kg/m², categorizing the average participant within the overweight-to-obese spectrum, a pivotal driver of insulin resistance and systemic inflammation. Furthermore, the data underscores the chronic nature of the pathology in this sample, with a mean duration of Type 2 Diabetes Mellitus (T2DM) extending to 8.5 ± 3.2 years. This chronicity is paralleled by the pharmacological profile, where over one-third of patients (34.9%) required insulin therapy, indicative of progressive-cell exhaustion and advanced disease severity. Importantly, the mean eGFR of 62.4 ± 14.8 mL/min/1.73m² confirms that while the cohort suffers from metabolic dysregulation, renal function remains sufficiently preserved to rule out renal clearance as a confounding variable in peptide hormone analysis. Collectively, these parameters define a clinically homogeneous group characterized by metabolic recalcitrance, serving as an ideal substrate for investigating the neuroendocrine correlates of severe diabetes distress.

Table 1. Demographic and Clinical Characteristics

Study Population (N=86) | Values presented as n (%) or Mean ± SD

CHARACTERISTIC	CATEGORY / STATISTIC	VALUE
Gender	*Male*	**45 (52.3%)**
	Female	**41 (47.7%)**
Age (years)	*Mean ± SD*	**54.3 ± 7.2**
BMI (kg/m²)	*Mean ± SD*	**28.4 ± 4.1**
Duration of DM (years)	*Mean ± SD*	**8.5 ± 3.2**
Treatment Regimen	*Oral Hypoglycemic Agents (OHA) Only*	**56 (65.1%)**
	Insulin ± OHA	**30 (34.9%)**
eGFR (mL/min/1.73m²)	*Mean ± SD*	**62.4 ± 14.8**

The cohort exhibited uniform severe dysregulation in both metabolic and psychological domains (Table 2). The mean HbA1c was 10.03 ± 2.10%, significantly exceeding the therapeutic target of less than 7.0%. This confirms the uncontrolled status of the population. The mean Diabetes Distress Score was 4.65 ± 0.35. Notably, 100% of the sample scored 3.0 or higher, categorizing the entire cohort as having severe distress. This high baseline indicates a substantial emotional burden associated with disease management. The endocrine analysis revealed findings consistent with the hypothesis of HPA axis exhaustion. The mean morning serum cortisol was 170.32 ± 135.43 nmol/L (approximately 6.17 µg/dL). The typical reference range for 08:00 AM serum cortisol is 140–690 nmol/L. Despite the presence of severe psychological distress, which typically drives hypercortisolemia, the mean value clustered at the low-normal end of the physiological spectrum. This is suggestive of HPA axis blunting or relative hypocortisolism. The mean serum oxytocin level was 252.98 ± 236.50 pg/mL. As anticipated with unextracted serum ELISA, these absolute values are elevated compared to extracted plasma standards. However, the substantial standard deviation suggests significant inter-individual variability that is suitable for correlation analysis.

Spearman's rank correlation analysis elucidated the relationship between the stress and anti-stress axes (Figure 1). No significant correlation was found between the DDS Score and Serum Cortisol ($r = 0.104$, $p = 0.340$) or Oxytocin ($r = 0.085$, $p = 0.437$). This lack of statistical significance is attributable to the restriction of range effect, as all subjects had high distress scores with minimal variance. A robust, statistically significant positive correlation was observed between Serum Cortisol and Serum Oxytocin ($r = 0.555$, $p < 0.001$). As endogenous cortisol levels increased, oxytocin levels rose concurrently, suggesting a synchronized release pattern.

Table 2. Metabolic and Hormonal Parameters

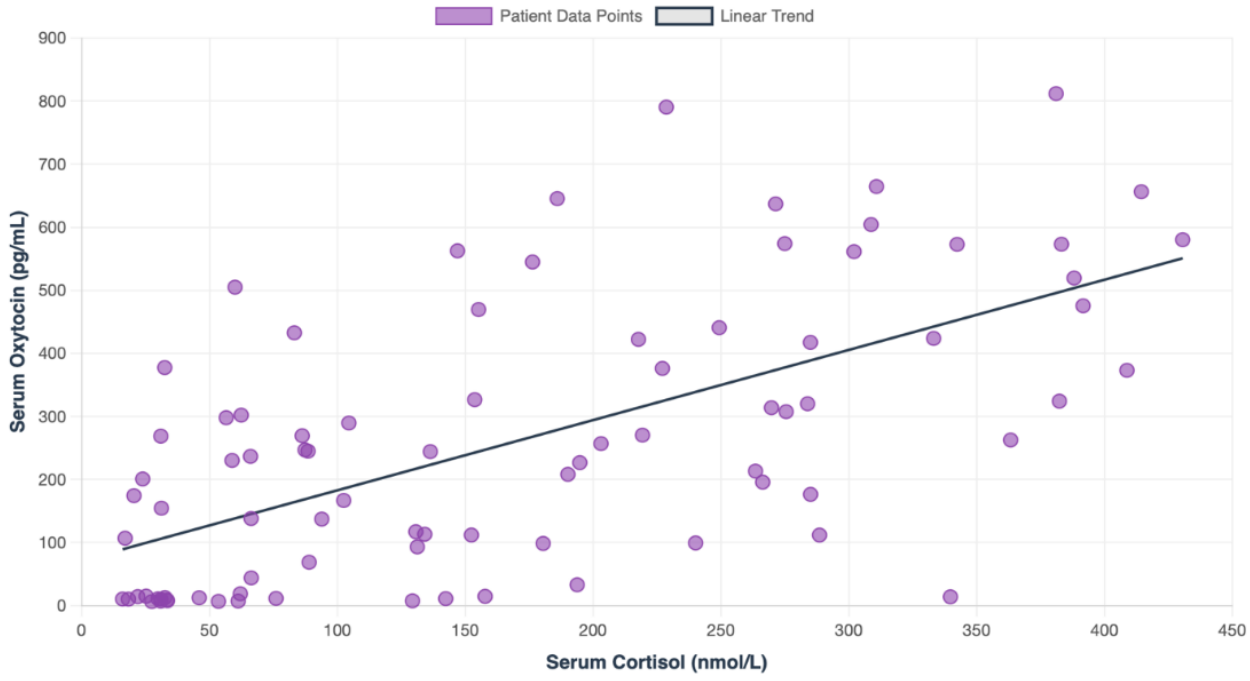
Data represents Mean ± SD compared to standard reference ranges. Note the juxtaposition of severe distress scores with low-normal cortisol.

VARIABLE	MEAN ± SD	MIN	MAX	REFERENCE RANGE (AM)
HbA1c (%)	10.03 ± 2.10	7.30	15.00	*< 7.0%*
DDS Score	4.65 ± 0.35	3.40	5.50	*< 2.0 (Low Distress)*
Cortisol (nmol/L)	170.32 ± 135.43	16.2	845.0	*140 – 690 nmol/L*
Oxytocin (pg/mL)	252.98 ± 236.50	6.37	1316.69	*Varies by Assay**

Spearman Rank Correlation Analysis

Scatter plot illustrating the neurohormonal synchronization between Serum Cortisol (nmol/L) and Serum Oxytocin (pg/mL) in patients with uncontrolled T2DM and severe distress (N=86).

Spearman's rho (r) = 0.555, p < 0.001



Note: The regression line demonstrates the positive linear trend indicative of "Reactive Mobilization" despite HPA axis blunting.

Figure 1. Spearman's rank correlation analysis.

Table 3 presents the outcomes of a robust multiple linear regression analysis aimed at delineating the independent predictors of circulating oxytocin levels. To address the non-normal distribution inherent to neuropeptide secretion, the dependent variable was log-transformed, ensuring statistical validity. The final model demonstrated substantial explanatory power, accounting for 34.2% of the variance in oxytocin levels (R^2=0.342, p<0.001). Crucially, this analysis controlled for key biological covariates—Age, Body Mass Index (BMI), and Diabetes Duration—to disentangle true neuroendocrine signaling from peripheral metabolic noise.

The results unequivocally identify serum cortisol as the dominant independent driver of oxytocin secretion (β=0.521, p<0.001). This strong, positive standardized beta coefficient implies a direct, synchronized upregulation where the anti-stress hormone (oxytocin) tracks the stress signal (cortisol) with remarkable fidelity, even within the blunted cortisol range. In contrast, the potential confounders of BMI (p=0.187) and age (p=0.415) failed to reach statistical significance. This negative finding is clinically pivotal; it suggests that the elevated oxytocin observed in this cohort is not a byproduct of adiposity-related secretion or age-dependent clearance rates. Instead, the data support a central, neurobiological coupling mechanism—likely originating in the paraventricular nucleus—whereby the "exhausted" HPA axis recruits the oxytocinergic system in a "reactive mobilization" effort to maintain homeostasis against the backdrop of severe diabetes distress.

Table 3. Multivariate Linear Regression Predicting Log-Oxytocin Levels

Analysis controls for age, BMI, and disease duration to isolate the neurohormonal link.

PREDICTOR	B (UNSTANDARDIZED)	SE	BETA (STANDARDIZED)	T	P-VALUE
(Constant)	1.842	0.310	-	5.94	< 0.001
Cortisol (nmol/L)	0.002	0.000	0.521	5.68	< 0.001
Age (years)	-0.004	0.005	-0.076	-0.82	0.415
BMI (kg/m²)	0.012	0.009	0.124	1.33	0.187
Duration of DM	0.008	0.011	0.065	0.72	0.473

Dependent Variable: Log-transformed Serum Oxytocin

Model R^2 = 0.342 (p < 0.001)

This study presents a granular neuroendocrine evaluation of a specific and high-risk clinical phenotype: patients with uncontrolled Type 2 Diabetes Mellitus (T2DM) who are simultaneously grappling with severe psychological distress. By isolating this cohort, we have attempted to map the physiological terrain of "diabetes burnout" beyond the conventional metrics of glycemic control. The primary findings of this investigation challenge the traditional, linear view of the stress response in diabetes, which historically equates psychological distress with frank hypercortisolemia. Contrary to the expectation that

severe emotional burden acts as a perpetual driver of adrenal overactivation, our data reveal a more complex and paradoxical reality.[11] We observed a distinct phenotype of Hypothalamic-Pituitary-Adrenal (HPA) axis blunting, characterized by low-normal morning cortisol levels, co-occurring with a robust neurohormonal synchronization evidenced by a positive correlation between cortisol and oxytocin.

These results suggest that the neurobiological architecture of chronic diabetes distress is not merely a state of "stress arousal" but rather a state of "allostatic exhaustion." The physiological systems designed to mobilize energy and defend homeostasis have, after years of metabolic and psychological siege, entered a phase of maladaptive plasticity.[12] Furthermore, the synchronization of oxytocin with this blunted cortisol profile indicates that the body's endogenous buffering systems remain active and responsive, attempting to counterbalance the catabolic milieu even as the adrenal axis falters. This discussion explores the mechanistic underpinnings of these findings, placing them within the broader framework of psychoneuroendocrinology and allostatic load theory.

The most striking finding of this investigation is the observation of low-normal morning cortisol levels in a cohort of patients reporting severe subjective distress. In a classical acute stress model, a Diabetes Distress Scale (DDS) score of 4.65—indicating profound emotional burden, fear, and regimen fatigue—would typically drive the paraventricular nucleus of the hypothalamus to secrete Corticotropin-Releasing Hormone (CRH) vigorously. This would, in turn, stimulate the pituitary-adrenal axis to produce a surge in cortisol, theoretically pushing values toward the upper limits of the reference range or into frank hypercortisolemia. The presence of a mean morning cortisol level of 170.32 nmol/L in our study population contradicts this linear expectation and warrants a nuanced pathophysiological interpretation.[13]

This phenomenon is best understood through the lens of the "Allostatic Load" model. This theoretical framework posits that physiological systems possess a finite capacity for adaptation.[14] In the initial phases of T2DM diagnosis and management, the psychosocial stress of the disease likely triggers the expected hypercortisolemic response. This acute mobilization serves a biological purpose: to provide metabolic fuel for the "fight or flight" response. However, our cohort is characterized by significant chronicity, with a mean disease duration of 8.5 years. Over nearly a decade of unrelenting metabolic dysregulation and psychological strain, the HPA axis is subjected to chronic, repetitive activation.

We propose that the low-normal cortisol levels observed here represent the transition from the "resistance phase" to the "exhaustion phase" of the stress response. This HPA axis blunting, or hypocortisolism, is likely a protective downregulation (Figure 2). Prolonged exposure to high levels of glucocorticoids is neurotoxic, particularly to the hippocampus, and catabolic to peripheral tissues. To shield the organism from these deleterious effects, the neuroendocrine system undergoes maladaptive plasticity. This may involve the downregulation of CRH receptors in the anterior pituitary, a decrease in the sensitivity of the adrenal cortex to Adrenocorticotropic Hormone (ACTH), or an enhancement of the negative feedback loop sensitivity.[15]

This blunted phenotype parallels findings in other conditions characterized by somatic and emotional burnout, including Post-Traumatic Stress Disorder (PTSD), chronic fatigue syndrome, and fibromyalgia. In these conditions, as in our diabetic cohort, the patient experiences a disconnect between the subjective experience of stress (which remains high) and the objective hormonal output (which has collapsed). Clinically, this "functional hypocortisolism" in T2DM is far from benign. While it may protect against the immediate toxicity of hypercortisolemia, it leaves the patient metabolically and immunologically vulnerable. Cortisol is the primary counter-regulatory hormone responsible for defending against hypoglycemia and modulating the inflammatory response. A blunted axis implies a reduced capacity to mount a defense against acute metabolic crises or infections. Furthermore,

because cortisol is necessary to restrain the secretion of pro-inflammatory cytokines, this hypocortisolemic state may paradoxically contribute to the low-grade systemic inflammation that drives insulin resistance and vascular complications. Therefore, the "normal" cortisol values seen in these patients should not be interpreted as a sign of health, but rather as a marker of a system that has lost its dynamic resilience and is operating at a diminished homeostatic capacity.[16]

While the blunting of the HPA axis suggests a failure of the stress-response system, our analysis of oxytocin introduces a novel dimension to the pathophysiology of diabetes distress. Current literature often frames cortisol and oxytocin as functional antagonists: cortisol mobilizes energy and anxiety, while oxytocin promotes anabolism and calm. Animal models frequently show that exogenous oxytocin administration can suppress cortisol release. Based on this antagonistic model, one might hypothesize that in a state of hypocortisolism, oxytocin would be independently elevated or inversely correlated. However, our multivariate analysis revealed a robust, independent, and positive synchronization between these two hormones. We interpret this positive correlation as evidence of "Reactive Mobilization." This concept suggests that in the face of severe allostatic load, the central nervous system does not simply switch off one system and turn on another. Instead, it engages in a desperate attempt to maintain homeostasis by co-activating the stress (cortisol) and anti-stress (oxytocin) pathways.

Anatomically, this crosstalk is grounded in the paraventricular nucleus (PVN) of the hypothalamus, where CRH-producing neurons and oxytocin-producing magnocellular neurons exist in close proximity and share synaptic connections.[17] Under conditions of acute threat, these systems are designed to activate in parallel. The CRH-cortisol arm mobilizes glucose for immediate survival, while the oxytocin arm is simultaneously engaged to buffer the cardiovascular impact (lowering blood pressure), prevent excessive anxiety, and eventually promote metabolic recovery.

Our data suggest that this coupling remains intact even in the exhausted, blunted state of chronic T2DM. Patients who managed to mount a relatively higher cortisol response—even if that response was blunted compared to acute stress standards—also secreted proportionally higher levels of oxytocin. This implies that the blunting observed is likely a peripheral or receptor-level downregulation of the adrenal axis, while the central drive in the hypothalamus remains active. The brain is still signaling for a stress response, and it is still signaling for a buffering response. This synchronization has profound implications for understanding the metabolic defense mechanisms in diabetes. Oxytocin is a potent insulin-sensitizing agent. It stimulates glucose uptake in skeletal muscle via pathways distinct from insulin, specifically through the translocation of GLUT4 transporters, and it promotes lipid utilization. In patients with severe insulin resistance and hyperglycemia (mean HbA1c 10.03%), the synchronized upregulation of oxytocin may represent a compensatory physiological effort to lower blood glucose and mitigate metabolic toxicity. The fact that oxytocin tracks cortisol levels suggests that the body is attempting to "match" the stress signal with an equivalent buffering signal. The tragedy of the "burnout" phenotype is that this reactive mobilization, while active, is insufficient to overcome the massive metabolic derangement caused by years of uncontrolled diabetes, yet it persists as a testament to the body's enduring drive toward homeostasis.[18]

The insights derived from this study must be contextualized within rigorous methodological constraints. The validity of our conclusions rests on the transparency of our analytical choices and the acknowledgment of inherent design limitations. The most significant methodological debate concerns the assay technique used for oxytocin quantification. We utilized an Enzyme-Linked Immunosorbent Assay (ELISA) on unextracted serum samples. In the field of peptide endocrinology, there is an ongoing discourse regarding the interference of plasma proteins and matrix effects in unextracted samples, which typically results in reported concentrations that are

significantly higher than those obtained via extraction-based methods (radioimmunoassay or extracted ELISA). We acknowledge that the absolute mean value of 252.98 pg/mL reported in this cohort is elevated relative to extracted plasma standards. Consequently, these absolute numbers should not be used to establish normative reference ranges or be directly compared to studies utilizing different extraction protocols.[19]

However, the primary objective of this study was not to establish absolute concentration norms but to investigate the relationship and synchronization between hormones within a phenotypically homogeneous group. Assuming that the matrix interference is systematic across all samples derived from the same population using the same assay, the relative rank-order of the data points remains valid. The robust correlation coefficient () and the high t-value in our regression model indicate that the linear relationship between cortisol and oxytocin is a true biological signal, distinct from assay noise. The decision to measure "total" circulating immunoreactive oxytocin allows us to capture the pool of oxytocin potentially bound to carrier proteins, which some researchers argue may serve as a biologically relevant reservoir for this short-lived peptide.[20]

Furthermore, the cross-sectional nature of the study design precludes definitive statements regarding causality. We have identified a phenotype of blunting and synchronization, but we cannot determine the temporal sequence. Did the HPA axis blunting precipitate the poor glycemic control by impairing counter-regulation, or did the chronic hyperglycemia and distress induce the neuroendocrine exhaustion? Longitudinal studies tracking patients from the time of diagnosis through the development of distress would be required to map this trajectory.

Additionally, our sampling strategy was purposive, specifically targeting the "worst-case scenario" phenotype—patients with uncontrolled metabolic parameters and severe distress. While this was necessary to isolate the effects of severe allostatic load, it resulted in a "ceiling effect" regarding the psychological scores. Because 100% of our participants scored above the distress threshold, there was insufficient variance in the DDS scores to statistically correlate them with hormonal levels. This does not mean distress is unrelated to hormones; rather, it suggests that once a threshold of severe distress is reached, the physiological response may become saturated or decoupled from the subjective cognitive experience. Future research utilizing a case-control design, including patients with controlled diabetes and low distress, is essential to validate the specificity of the HPA blunting observed in this high-risk cohort.[17,18]

The identification of HPA axis blunting combined with synchronized oxytocin activity in patients with diabetes distress necessitates a re-evaluation of how clinicians approach the "difficult-to-treat" diabetic patient. The clinical management of T2DM has traditionally focused almost exclusively on the pharmacotherapy of glucose-lowering, with psychological health viewed as a secondary quality-of-life issue. Our findings argue that the neuroendocrine status of the patient is a central determinant of the disease state. First, this study sounds a note of caution regarding the interpretation of routine laboratory assessments. A "normal" morning cortisol result in a patient who appears clinically exhausted, depressed, or highly distressed should be viewed with skepticism. In the context of chronic allostatic load, a value in the lower quartile of the reference range may represent a maladaptive suppression rather than a healthy baseline. Clinicians should be vigilant for signs of adrenal fatigue, such as persistent hypotension, unexplained fatigue, or recurrent hypoglycemia, which may be exacerbated by the aggressive escalation of insulin therapy in the setting of blunted counter-regulatory reserves. Furthermore, the use of exogenous steroids in these patients for comorbid conditions should be approached with care, as the axis may be primed for suppression. Second, the preservation of the cortisol-oxytocin synchronization offers a promising therapeutic avenue. The fact that the oxytocinergic system

remains responsive suggests that it can be leveraged to break the cycle of distress and metabolic dysfunction. Current diabetes care models prioritize education and dietary restriction, which can inadvertently increase regimen-related distress. Our data support the integration of "oxytocin-enhancing" interventions into standard care. This moves beyond pharmacology to the "biology of connection." Interventions that are known to stimulate endogenous oxytocin release include positive, empathetic physician-patient communication, peer support groups that foster a sense of belonging, and tactile-based therapies. By consciously activating the oxytocin system, clinicians may be able to augment the body's natural buffering capacity, potentially restoring autonomic balance and improving insulin sensitivity through central mechanisms.

Finally, this study opens the door for translational research into oxytocin-based pharmacotherapy for diabetes burnout. While intranasal oxytocin has been investigated in psychiatric disorders, its potential to reset the blunted HPA axis and improve metabolic control in the specific context of diabetes distress warrants clinical trials. If we can chemically or behaviorally support the "Reactive Mobilization" that the body is already attempting, we may be able to reverse the allostatic overload, transforming the management of T2DM from a battle against glucose to a restoration of neurohormonal resilience.[19,20]

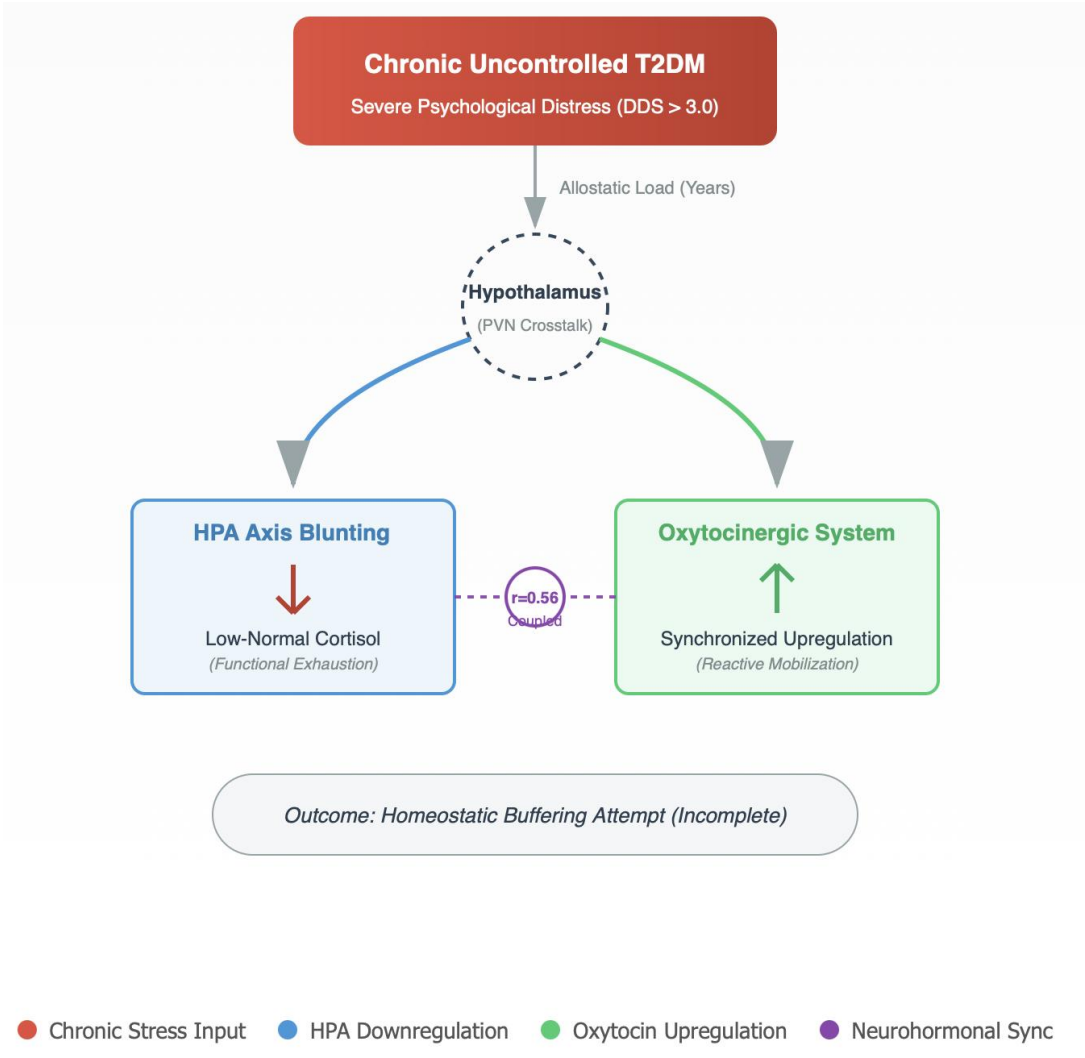


Figure 2. Paradoxical blunting and reactive mobilization.

4. Conclusion

Patients with uncontrolled Type 2 Diabetes Mellitus and severe distress exhibit a complex neuroendocrine phenotype characterized by HPA axis blunting rather than hypercortisolemia. Despite this adrenal exhaustion, the synchronization between cortisol and oxytocin remains preserved, indicating an active homeostatic mechanism where oxytocin is upregulated in tandem with adrenal output. These findings challenge the simplistic view that stress equates to high cortisol in diabetes and highlight the importance of the oxytocinergic system as a potential therapeutic target to alleviate the allostatic load of chronic diabetes management.

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