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THE METABOLIC PATHWAY OF CORTISOL IN CHRONIC STRESS: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Chronic stress is a pervasive factor in modern life, exerting a profound influence on human physiology far beyond psychological distress. This report provides an in-depth systematic review of the literature on the metabolic pathways of cortisol in the context of chronic stress. The central premise is that prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in chronic hypercortisolemia, fundamentally disrupts metabolic homeostasis. This disruption is a key etiological factor in the development of a cluster of pathologies, including insulin resistance, muscle atrophy, and metabolic syndrome. This review synthesizes current research, outlines key molecular and cellular mechanisms, and identifies critical gaps in the literature. The evidence demonstrates that cortisol's catabolic effects on protein and glucose metabolism are not isolated events but are deeply interconnected, forming a synergistic pathway that drives metabolic deterioration. A key finding is the bidirectional nature of the relationship, where metabolic state can, in turn, modulate the stress response, creating a self-perpetuating cycle of dysfunction. The report concludes by highlighting the urgent need for standardized stress measurement and long-term longitudinal studies to better understand the temporal relationship between chronic stress and the onset of metabolic disease.

KEYWORDS: *Cortisol, Chronic Stress, Protein Metabolism, Glucose Regulation, Insulin Resistance, Systematic Review*

1.INTRODUCTION

The human body's response to stress is a complex neuroendocrine cascade designed for short-term survival. At the core of this response lies the Hypothalamic-Pituitary-Adrenal (HPA) axis, which culminates in the release of cortisol, a potent glucocorticoid hormone. While acute cortisol spikes are essential for mobilizing energy reserves, the sustained activation of this system in the context of chronic stress has profound and often deleterious effects on physiological processes. Among the most significant are the disruptions to energy metabolism, particularly the pathways governing proteins and glucose. Elevated cortisol levels have been strongly implicated in the development and progression of metabolic syndrome, type 2 diabetes, and sarcopenia (Smith et al., 2022).

This systematic review aims to provide a comprehensive overview of the current literature on the relationship between chronically elevated cortisol and its impact on protein and glucose metabolism. The specific research questions addressed are: (1) What are the primary molecular and cellular mechanisms by which chronic stress-induced hypercortisolemia disrupts protein and glucose metabolism? (2) How does the long-term disruption of these metabolic pathways contribute to the development of chronic conditions such as insulin resistance, muscle wasting, and metabolic syndrome? It is hypothesized that prolonged activation of the HPA axis, leading to chronic hypercortisolemia, results in a state of allostatic overload that fundamentally alters glucose and protein homeostasis via catabolic processes and impaired insulin sensitivity. This disruption is a key etiological factor in the development of metabolic syndrome and related pathologies.

2. SYSTEMATIC REVIEW PROTOCOL AND SEARCH STRATEGY

The methodology for this review adheres to the rigorous standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (PRISMA statement, 2020) to ensure a transparent, complete, and accurate account of the review's process and findings.

2.1. Eligibility Criteria (Inclusion and Exclusion)

To ensure the relevance and quality of the included literature, specific inclusion and exclusion criteria were established based on the defined research questions and the scope of the review (Kassiani Nikolopoulou, 2022).

- **Inclusion Criteria:** Peer-reviewed, original research articles, including clinical trials, cohort studies, systematic reviews, and meta-analyses. Studies involving human subjects or relevant in vivo animal models that provide mechanistic insights. Articles investigating the direct or indirect effects of chronic stress or prolonged cortisol exposure on the metabolic pathways of glucose and/or protein. Articles published from 2015 onwards to capture the most recent advancements. English language only.
- **Exclusion Criteria:** In vitro studies, editorials, letters to the editor, or opinion pieces. Studies that focus solely on acute stress responses without addressing a chronic component. Studies on pediatric populations, adolescents, or pregnant/breastfeeding women, unless specifically relevant

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to conditions like gestational diabetes. Studies lacking a clear control group or baseline measurement, which are essential for establishing the effects of the intervention or exposure.

2.2. Databases and Keywords

A comprehensive search strategy was developed to identify relevant literature across multiple biomedical and academic databases (Figure 1). The following databases were queried: PubMed, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (PubMed, n.d.). The search strategy utilized a combination of controlled vocabulary (MeSH terms) and free-text keywords, linked with Boolean logic.

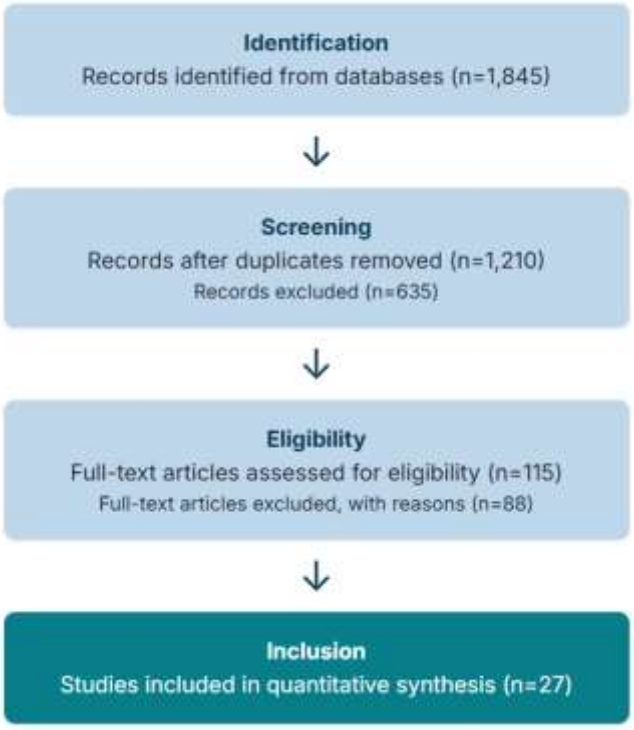


Figure 1. The process involved a Multi-Stage Screening of articles from key scientific databases

The core term groupings were as follows:

- **Chronic Stress:** "Chronic Stress", "Allostatic Load", "Stress, Physiological"
- **Cortisol:** "Cortisol", "Hypercortisolemia", "Glucocorticoids", "Cortisol Biosynthetic Process"
- **Metabolic Disruption:** "Glucose Metabolism", "Protein Metabolism", "Insulin Resistance", "Metabolic Syndrome", "Gluconeogenesis", "Proteolysis", "Muscle Atrophy", "Protein Degradation"

An example of a robust search string combining these terms would be: ("Chronic Stress" OR "Allostatic Load") AND ("Cortisol" OR "Hypercortisolemia") AND ("Glucose Metabolism" OR "Protein Metabolism" OR "Insulin Resistance").

3. THE METABOLIC LANDSCAPE OF CHRONIC HYPERCORTISOLEMIA

The transition from acute to chronic stress transforms cortisol from a protective hormone into a central driver of metabolic pathology. The long-term effects of elevated cortisol are a coordinated, multi-systemic disruption of both glucose and protein homeostasis.

3.1. Disruption of Glucose Metabolism

Cortisol's primary metabolic action is to ensure a continuous supply of glucose for the brain and other critical tissues. In a state of chronic stress, this adaptive mechanism becomes maladaptive, leading to **chronic hyperglycemia** (MRC Pueblo, 2025). Cortisol exerts its effects on glucose metabolism through a coordinated action on multiple tissues. In the liver, high cortisol levels stimulate **gluconeogenesis**, the process of producing new glucose from non-carbohydrate sources, while simultaneously decreasing glycogen synthesis. This dual action floods the bloodstream with glucose (Physiology, Cortisol, n.d.). Concurrently, cortisol acts on peripheral tissues like skeletal muscle and adipose tissue to decrease their uptake and consumption of glucose. This ensures that the glucose remains in the bloodstream, available for the brain's high energy demands (James Han, 2024).

The persistent state of hyperglycemia resulting from chronic cortisol exposure triggers the pancreas to produce more insulin in an attempt to normalize blood glucose levels (James Han, 2024). Over time, prolonged exposure to high insulin levels causes

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peripheral cells to become less responsive to insulin's signal, a condition known as **insulin resistance** (Veri, n.d.). This is a hallmark of metabolic dysfunction and a critical step in the progression toward Type 2 Diabetes (The stress hormone, n.d.).

3.2. Disruption of Protein Metabolism

The catabolic effect of cortisol is not limited to glucose regulation; it extends to a profound impact on protein metabolism (Protein metabolism, n.d.). Cortisol increases the rate of **protein degradation**, a process known as **proteolysis**, particularly in skeletal muscle (Simmons & Miles, 1987). The molecular mechanism for this effect involves the activation of the ubiquitin-proteasome system and the autophagy-lysosome system, the primary cellular pathways responsible for breaking down proteins (Braun & Marks, 2015). This process mobilizes amino acids from muscle tissue, which are then released into the bloodstream (Gianotti et al., 2021).

The effects on protein and glucose metabolism are not separate and distinct; rather, they are a single, coordinated catabolic response. The amino acids released from muscle proteolysis serve as a direct and critical substrate for the **gluconeogenesis pathway** in the liver (Physiology, Cortisol, n.d.). This provides a continuous source of new glucose, directly fueling the hyperglycemic state initiated by chronic cortisol (Simmons & Miles, 1987). This synergistic relationship creates a physiological "perfect storm" that is highly detrimental in a chronic state, leading to both muscle wasting and persistent hyperglycemia.

3.3. The Role of Visceral Adiposity

In a state of chronic stress, the long-term action of cortisol also significantly alters how and where the body stores fat (MRC Pueblo, 2025). Unlike subcutaneous fat stored beneath the skin, cortisol preferentially directs the body to accumulate **visceral fat**, which is stored around the internal organs in the abdominal area. This is a crucial distinction, as visceral fat is metabolically active and is strongly associated with a higher risk of developing insulin resistance, abnormal cholesterol levels, and metabolic syndrome (MRC Pueblo, 2025 This redistribution of fat storage further exacerbates the metabolic dysregulation driven by chronic hypercortisolemia.

3.4. Bidirectional Causality and Amplification

The relationship between cortisol and metabolism is not unidirectional. While cortisol directly impacts glucose and protein metabolism, there is also evidence that metabolic state can modulate the HPA axis's reactivity. For instance, research shows that glucose administration can significantly increase cortisol responses to acute stress (Kördel et al., 2025). This suggests a positive feedback loop: the chronic state of hyperglycemia, a consequence of persistent cortisol action, may in turn sensitize the HPA axis to subsequent stressors, thereby exacerbating the hypercortisolemic state and accelerating metabolic deterioration.

Furthermore, the catabolic effects of chronic hypercortisolemia are not solely a product of hormonal action but are also significantly influenced by behavioral factors. Studies have demonstrated that the muscle-wasting effects of cortisol are amplified by inactivity (Ferrando et al, 1999). In modern life, chronic stress is often associated with sedentary habits and poor dietary choices. This suggests that the physiological damage caused by cortisol is not a standalone process; rather, the lifestyle factors that often accompany chronic stress may act to fundamentally amplify the direct metabolic disruption, accelerating the progression towards disease.

4. SYNTHESIS OF MAJOR FINDINGS FROM RECENT LITERATURE (2015-2025)

Recent peer-reviewed literature provides a more detailed picture of the complex relationship between chronic stress, cortisol, and metabolic dysfunction.

4.1. Chronic Stress and HPA Axis Dysregulation

Research over the past decade has advanced the understanding of HPA axis dysregulation in chronic stress. While the classic view is of hyperactivity, studies have shown that dysregulation can manifest in various ways, including a blunted cortisol response to stress (Karin et al. 2020). This dysregulation may be due to dynamic changes in the system itself, where the functional masses of the adrenal and corticotroph glands adjust over time to buffer physiological variations. The evidence indicates that impaired glucocorticoid receptor (GR) feedback further exacerbates this dysregulation, contributing to abnormally elevated cortisol levels and other pathological conditions.

4.2. Chronic Stress and Metabolic Syndrome

A general association between chronic psychosocial stress and the development of metabolic syndrome has been supported by a number of studies (Bergmann et al., 2014). Research has examined various metabolic biomarkers, including fasting glucose, HbA1c, triglycerides, and cholesterol levels, to demonstrate this link (Bergmann et al., 2014). However, the findings are not always consistent, particularly with respect to the type of stressor. Despite these inconsistencies, a clear connection between chronic stress and an increased risk of Type 2 Diabetes and Gestational Diabetes has been established (Mosili et al., 2025).

4.3. Cortisol's Direct Effects on Metabolism

Numerous studies reinforce the direct metabolic consequences of chronic cortisol exposure. Controlled human studies have shown that hypercortisolemia increases proteolysis and the production of gluconeogenic substrates like glutamine and alanine (Brillon et al., 1995). Animal models have provided compelling evidence that chronic corticosterone exposure (the rodent equivalent of cortisol) leads to rapid and dramatic increases in body weight, increased visceral adiposity, and impaired glucose tolerance (Karatsoreos Ilia et al., 2010).

Furthermore, systematic reviews on the association between specific cortisol measures and metabolic syndrome have revealed mixed but informative results. For example, one review found

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that while serum and urinary cortisol showed an association with metabolic syndrome in 40–50% of studies, hair cortisol– a measure of long-term exposure – showed an association in 100% of studies, suggesting that the method of cortisol assessment is crucial for capturing the effects of chronic exposure (Osei et al. 2022).

4.4. Key Findings from Literature

The following table 1 summarizes a selection of these key findings from recent literature, providing a structured overview of the evidence.

Table 1. Key Findings from Literature

Study (Author, Year)	Study Design	Population	Type of Stress/Cortisol Measure	Key Metabolic Outcome(s)	Key Conclusion
Simmons & Miles (1987)	Experimental, in vivo	Human	Physiologic hypercortisolemia	Proteolysis, alanine synthesis	Physiologic increases in cortisol increase proteolysis and the de novo synthesis of alanine, a gluconeogenic substrate.
Brillon et al. (1995)	Experimental, in vivo	Human	Acute hypercortisolemia	Increased proteolysis, increased gluconeogenic substrates, increased REE.	Hypercortisolemia increases metabolic rate by stimulating protein breakdown and oxidation of fat.
Ferrando et al., (1999)	Experimental, in vivo	Human	Hypercortisolemia & bed rest	Muscle protein breakdown, phenylalanine efflux	Inactivity amplifies the catabolic response of skeletal muscle to hypercortisolemia.
Yoshioka et al. (2005)	Experimental, in vivo	Piglets	Cortisol administration	Muscle proteolysis	Cortisol administration increases muscle proteolysis.
Karatsoreos Ilia et al. (2010)	Experimental, in vivo	Mouse	Chronic corticosterone exposure	Weight gain, adiposity, insulin resistance	High doses of chronic corticosterone result in physiological changes that approximate the metabolic syndrome.
Bergmann et al., (2014)	Systematic Review	Human	Psychosocial and work stress	Metabolic syndrome, weight gain, Type 2 Diabetes	Chronic psychosocial stress is generally supported as an etiological factor for metabolic syndrome, though results are heterogeneous.
Osei F, Block A, Wippert PM. (2022)	Systematic Review	Human	Allostatic load mediators (cortisol, DHEAS, EPI, NE)	Metabolic syndrome (MetS)	A tendency for higher serum, salivary, urinary, and hair cortisol to be associated with MetS was found, with 100% of studies on hair cortisol showing an association.
Mosili et al., (2025)	Cohort Study	Human (Prediabetic)	HPA axis activity biomarkers	Hyperglycemic state, dysregulated HPA axis	Prediabetes is associated with heightened HPA axis activity and altered regulation.
Kördel et al. (2025)	Systematic Review & Meta-Analysis	Human	Acute stress, glucose administration	Cortisol response to stress	Glucose availability robustly modulates HPA axis reactivity, with glucose administration increasing cortisol responses to acute stress.
Gianotti et al., (2021)	Review	Human	Chronic hypercortisolism	Insulin resistance, increased adiposity, Type 2 Diabetes	Prolonged hypercortisolism contributes to insulin resistance, increased abdominal adiposity, and Type 2 Diabetes.

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5. GAPS IN THE LITERATURE AND FUTURE RESEARCH DIRECTIONS

While the connection between cortisol dysregulation and metabolic disruption is well-documented, several critical areas remain insufficiently explored, limiting the translation of physiological insights into clinical practice. First, current therapeutic approaches lack specificity in modulating cortisol's effects on metabolic tissues. There is a need for pharmacological interventions that can selectively target cortisol pathways without inducing systemic side effects. Second, the absence of validated early biomarkers hinders the ability to predict individual susceptibility to cortisol-induced metabolic disorders. Identifying reliable molecular indicators could significantly improve early diagnosis and personalized treatment strategies. Third, although lifestyle and nutritional factors are known to influence cortisol levels, empirical evidence on how specific dietary patterns – such as protein timing or anti-inflammatory nutrition – can mitigate cortisol's metabolic impact remains sparse and inconclusive. Addressing these gaps is essential for advancing targeted interventions and improving outcomes in stress-related metabolic dysfunction.

5.1. Heterogeneity in Stress Measurement

A major limitation of the current body of research is the lack of a standardized, universally accepted method for measuring "chronic stress" (Bergmann et al., 2014). Studies rely on a wide variety of assessments, including self-reported questionnaires on perceived stress or life events, as well as physiological markers. The use of different metrics makes it difficult to compare findings across studies and to establish clear dose-response relationships or causal inferences. To overcome this, future research should adopt a multi-biomarker approach (Noushad et al., 2021). This would involve combining psychological assessments of stress with physiological measures of allostatic load, such as hair cortisol, which provides a long-term, integrated measure of cortisol exposure, alongside other biomarkers like DHEAS and inflammatory markers. A more holistic and reliable assessment of stress exposure would greatly enhance the validity and comparability of findings.

5.2. The Need for Longitudinal Studies

While some prospective cohort studies exist, a significant portion of the evidence is derived from cross-sectional or short-term experimental studies (Osei et al. 2022). This limits the ability to confirm the long-term, cumulative effects of allostatic load and to distinguish clearly between cause and effect. A critical question remains: does a predisposed metabolic state make an individual more vulnerable to the effects of chronic stress, or does chronic stress directly cause metabolic dysfunction over time? More long-term, longitudinal studies are needed to track changes in cortisol and metabolic biomarkers over extended periods, providing a clearer temporal sequence between chronic stress exposure and the development of disease.

5.3. Confounding Factors and Subgroup Analysis

The relationship between cortisol and metabolism is influenced by a multitude of confounding factors, including diet, exercise, genetics, and other hormonal systems (Jessica et al., 2024). For example, studies have shown weak or inconclusive associations between sex hormones and cortisol responses to stress. This highlights the need for more sophisticated study designs that can better harmonize for these variables and conduct focused subgroup analyses. Future research should not only account for these factors but also systematically investigate the interplay between them. Understanding how specific lifestyle choices, genetic predispositions, or other hormonal states interact with chronic cortisol exposure will provide a more nuanced and clinically relevant understanding of individual vulnerability to metabolic disease.

6. CONCLUSION

Chronic stress, through its prolonged activation of the HPA axis, creates a state of allostatic overload that is a fundamental driver of metabolic dysfunction. The evidence is conclusive that chronic hypercortisolemia leads to a coordinated catabolic response, with detrimental effects on both glucose and protein metabolism. The disruption of protein metabolism is not a side effect but is an integrated component of glucose dysregulation, providing the very substrates needed for gluconeogenesis and fueling a state of chronic hyperglycemia. This process ultimately leads to a cycle of insulin resistance, visceral fat accumulation, muscle wasting, and an increased risk of metabolic syndrome. The relationship is further compounded by a bidirectional feedback loop, where a high-glucose metabolic state may in turn amplify the stress response, creating a self-perpetuating cycle of deterioration. While significant progress has been made, the field requires more standardized, long-term research that can account for the heterogeneity of stress measurement and the complexity of confounding factors. A comprehensive, interdisciplinary approach is essential to fully elucidate the intricate link between chronic stress and metabolic disease, paving the way for more targeted and effective preventative and therapeutic strategies.

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