AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

CUSHING SYNDROME: PATHOPHYSIOLOGY, DIAGNOSIS, AND CONTEMPORARY MANAGEMENT

Xasanova Nargis Qodirovna

Department of Fundamental Medical Sciences of the Asian

International University, Bukhara, Uzbekistan

Abstract : Cushing syndrome is a rare but severe endocrine disorder characterized by chronic exposure to excess glucocorticoids, leading to significant morbidity and increased mortality. Despite advances in endocrinology, its heterogeneous etiology and overlapping clinical features continue to pose diagnostic and therapeutic challenges. Cushing syndrome is broadly classified into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms, each with distinct pathophysiological mechanisms. Advances in biochemical testing, imaging techniques, and invasive diagnostic procedures such as inferior petrosal sinus sampling have improved diagnostic accuracy. Surgical intervention remains the cornerstone of treatment, while medical therapies and radiotherapy serve as adjuncts or alternatives in selected cases. Persistent cardiovascular, metabolic, and neuropsychiatric complications may occur even after biochemical remission.

This review aims to provide a comprehensive overview of the current understanding of Cushing syndrome, focusing on its pathophysiology, etiological classification, diagnostic strategies, and contemporary management approaches based on recent literature.

Keywords : Cushing syndrome; hypercortisolism; ACTH-dependent; ACTH-independent; endocrine disorders; diagnostic approach; management

Etiology and Pathophysiology of Cushing Syndrome

Cushing syndrome encompasses a heterogeneous group of disorders resulting from prolonged exposure to excessive glucocorticoids. Etiologically, it is classified into ACTH-dependent and ACTH-independent forms, a distinction that is fundamental for both diagnostic evaluation and therapeutic decision-making.

ACTH-Dependent Cushing Syndrome

ACTH-dependent Cushing syndrome accounts for approximately 70–80% of endogenous cases and is characterized by excessive secretion of adrenocorticotropic hormone, leading to bilateral adrenal hyperplasia and cortisol overproduction.The most common cause is Cushing disease, which results from an ACTH-secreting pituitary adenoma, typically a microadenoma. Autonomous ACTH production overrides normal hypothalamic–pituitary–adrenal (HPA) axis feedback regulation, resulting in persistently elevated cortisol levels. A less frequent but clinically significant cause is ectopic ACTH syndrome, in which non-pituitary tumors—most commonly small cell lung carcinoma and neuroendocrine tumors—produce ACTH or corticotropin-releasing hormone (CRH). These tumors often lead to rapidly progressive

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

hypercortisolism with severe metabolic and electrolyte disturbances, particularly hypokalemic metabolic alkalosis.

ACTH-Independent Cushing Syndrome

ACTH-independent forms account for approximately 20–30% of endogenous cases and are characterized by primary adrenal cortisol overproduction with suppressed plasma ACTH levels.

Major causes include:

- Adrenal adenomas, the most common ACTH-independent etiology
- Adrenocortical carcinoma, often associated with severe hypercortisolism and poor prognosis
- Primary bilateral macronodular adrenal hyperplasia (PBMAH)
- Primary pigmented nodular adrenocortical disease (PPNAD), often associated with Carney complex

In these conditions, cortisol secretion is autonomous and no longer regulated by pituitary ACTH.

Exogenous (Iatrogenic) Cushing Syndrome

The most common overall cause of Cushing syndrome is iatrogenic exposure to exogenous glucocorticoids, used in the treatment of inflammatory, autoimmune, and neoplastic disorders. Chronic suppression of ACTH leads to adrenal atrophy, which has important implications for steroid withdrawal and adrenal insufficiency.

PATHOPHYSIOLOGY

The pathophysiology of Cushing syndrome is driven by sustained hypercortisolism and its widespread effects on virtually every organ system. Under normal physiological conditions, cortisol secretion is regulated by the HPA axis through a tightly controlled negative feedback mechanism. In Cushing syndrome, this regulatory system is disrupted.

Dysregulation of the HPA Axis

Excess cortisol production—whether ACTH-dependent or independent—leads to chronic activation of glucocorticoid receptors. In ACTH-dependent disease, excessive ACTH stimulation results in adrenal hyperplasia and increased cortisol synthesis. In ACTH-independent disease, autonomous adrenal cortisol secretion suppresses pituitary ACTH via negative feedback.

Loss of circadian rhythm and failure of cortisol suppression are hallmark features of pathological hypercortisolism.

Metabolic Effects

Cortisol excess induces profound metabolic alterations:

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

- Increased hepatic gluconeogenesis and insulin resistance
- Proteolysis leading to muscle wasting and proximal myopathy
- Lipolysis with abnormal fat redistribution, resulting in central obesity, moon facies, and dorsocervical fat accumulation

These effects contribute to the high prevalence of diabetes mellitus, dyslipidemia, and metabolic syndrome in patients with Cushing syndrome.

Cardiovascular Effects

Chronic hypercortisolism exerts deleterious cardiovascular effects through multiple mechanisms:

- Enhanced vascular sensitivity to catecholamines
- Activation of mineralocorticoid receptors, particularly when cortisol overwhelms 11β-hydroxysteroid dehydrogenase type 2
- Endothelial dysfunction and accelerated atherosclerosis

As a result, patients exhibit a markedly increased risk of hypertension, ischemic heart disease, stroke, and heart failure, which remains elevated even after biochemical remission.

Skeletal, Immune, and Neuropsychiatric Effects

Cortisol inhibits osteoblast function and enhances bone resorption, leading to osteoporosis and increased fracture risk. Immunosuppressive effects predispose patients to infections and impaired wound healing. Neuropsychiatric manifestations—including depression, anxiety, cognitive impairment, and sleep disturbances—reflect cortisol's effects on the hippocampus, amygdala, and prefrontal cortex.

CLINICAL MANIFESTATIONS OF CUSHING SYNDROME

The clinical presentation of Cushing syndrome is highly variable and reflects the systemic effects of chronic glucocorticoid excess. Manifestations may develop insidiously over months to years, often leading to delayed diagnosis. The severity and pattern of symptoms depend on the degree and duration of hypercortisolism, as well as the underlying etiology.

General and Metabolic Features

One of the hallmark characteristics of Cushing syndrome is abnormal fat redistribution, resulting in central obesity with relative sparing of the extremities. Patients typically develop moon facies, dorsocervical fat pad ("buffalo hump"), and supraclavicular fat accumulation.

Metabolic disturbances are common and include:

- Impaired glucose tolerance or overt diabetes mellitus
- Dyslipidemia
- Weight gain despite muscle wasting

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Proximal muscle weakness, particularly involving the hip and shoulder girdles, results from cortisol-induced proteolysis and is a frequent early complaint.

Dermatologic Manifestations

Cutaneous features are among the most distinctive clinical signs and often raise early clinical suspicion. These include:

- Thin, fragile skin with easy bruising
- Wide, violaceous striae, particularly on the abdomen, thighs, breasts, and arms
- Delayed wound healing
- Acne and seborrhea

In women, hirsutism and androgenic alopecia may occur, especially in ACTH-dependent forms due to adrenal androgen excess.

Cardiovascular Manifestations

Cardiovascular complications represent a major contributor to morbidity and mortality in Cushing syndrome. Arterial hypertension is present in the majority of patients and often exhibits resistance to standard antihypertensive therapy.

Additional cardiovascular manifestations include:

- Endothelial dysfunction
- Left ventricular hypertrophy
- Accelerated atherosclerosis
- Increased risk of ischemic heart disease, stroke, and venous thromboembolism

Notably, cardiovascular risk may persist even after successful treatment and biochemical remission.

Neuropsychiatric and Cognitive Manifestations

Neuropsychiatric symptoms are common and may significantly impair quality of life. Patients frequently experience:

- Depression and anxiety
- Emotional lability
- Cognitive dysfunction, including impaired memory and attention
- Sleep disturbances

In severe cases, psychosis and suicidal ideation have been reported. These manifestations reflect cortisol's effects on limbic and cortical brain structures.

Musculoskeletal and Skeletal Manifestations

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Chronic hypercortisolism leads to glucocorticoid-induced osteoporosis, with preferential involvement of trabecular bone. Patients are at increased risk of:

- Vertebral compression fractures
- Rib and hip fractures

Muscle atrophy and weakness contribute to decreased mobility and increased fall risk.

Immunologic and Infectious Manifestations

Cortisol-induced immunosuppression predisposes patients to recurrent and opportunistic infections. Clinical features include:

- Increased susceptibility to bacterial and fungal infections
- Masking of inflammatory signs, leading to delayed diagnosis
- Poor wound healing

Reproductive and Endocrine Manifestations

In women, hypercortisolism may cause:

- Menstrual irregularities
- Amenorrhea
- Infertility

In men, decreased libido and erectile dysfunction are common. Growth retardation may be observed in pediatric patients due to suppression of growth hormone secretion and direct effects on bone growth.

MANAGEMENT STRATEGIES OF CUSHING SYNDROME

The management of Cushing syndrome aims to normalize cortisol excess, treat the underlying etiology, reduce associated comorbidities, and improve long-term outcomes. Given the heterogeneity of disease causes and clinical presentations, an individualized, multidisciplinary approach is essential.

General Principles of Management

Effective management requires:

- Accurate etiological diagnosis
- Assessment of disease severity and comorbidities
- Consideration of patient-specific factors, including age, fertility status, and surgical risk

Early treatment is crucial, as prolonged exposure to hypercortisolism is associated with increased cardiovascular morbidity and mortality.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Surgical Treatment

Pituitary Surgery: Transsphenoidal pituitary adenomectomy is the first-line treatment for Cushing disease. Surgical remission rates are high in experienced centers, particularly for microadenomas.

Postoperative monitoring is essential to detect:

- Early remission
- Persistent disease
- Recurrence

Patients often require temporary glucocorticoid replacement due to postoperative adrenal insufficiency.

Adrenal Surgery: Unilateral adrenalectomy is the treatment of choice for cortisol-producing adrenal adenomas. In cases of adrenal carcinoma, surgery remains the primary therapeutic option, often combined with adjuvant medical therapy. Bilateral adrenalectomy may be considered in refractory cases but results in permanent adrenal insufficiency and requires lifelong steroid replacement.

Medical Therapy

Medical treatment is used as:

- Primary therapy in non-surgical candidates
- Bridging therapy before surgery
- Adjunctive treatment after incomplete surgical remission

Steroidogenesis Inhibitors

These agents reduce cortisol synthesis at the adrenal level:

- Ketoconazole
- Metyrapone
- Osilodrostat

They are effective in controlling hypercortisolism but require close biochemical monitoring due to potential hepatotoxicity and adrenal insufficiency.

Pituitary-Directed Therapies

These agents target ACTH secretion in Cushing disease:

- Pasireotide, a somatostatin analog
- Cabergoline, a dopamine agonist

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Response rates vary, and combination therapy may be required.

Glucocorticoid Receptor Antagonists

Mifepristone blocks cortisol action at the receptor level and is particularly useful in patients with severe hyperglycemia. However, biochemical cortisol levels cannot be used to monitor treatment efficacy, necessitating careful clinical assessment.

Radiotherapy

Pituitary radiotherapy is reserved for patients with persistent or recurrent disease after surgery or when surgery is contraindicated. While effective, its onset of action is delayed, and patients often require interim medical therapy. Potential long-term complications include hypopituitarism and secondary malignancies.

Conclusion:

Cushing syndrome represents a complex and potentially life-threatening endocrine disorder characterized by chronic exposure to excess glucocorticoids and widespread systemic consequences. Its heterogeneous etiology, variable clinical presentation, and overlapping features with more common metabolic conditions continue to pose significant diagnostic and therapeutic challenges. Importantly, normalization of cortisol levels does not invariably translate into complete clinical recovery. Persistent cardiometabolic risk, impaired quality of life, and long-term complications may remain even after biochemical remission, underscoring the need for early detection, comprehensive management of comorbidities, and long-term follow-up.

Used literature :

1. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, et al. Treatment of cushing's syndrome: An endocrine society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism. 2015;100(8):2807–2831. doi: 10.1210/jc.2015-1818.

2. Lindholm J, Juul S, Jørgensen JOL, Astrup J, Bjerre P, et al. Incidence and late prognosis of Cushing's syndrome: A population-based study. Journal of Clinical Endocrinology and Metabolism. 2001;86(1):117–123. doi: 10.1210/jc.86.1.117.

3. Arnardóttir S, Sigurjonsdóttir HA. The incidence and prevalence of Cushing's disease may be higher than previously thought: Results from a retrospective study in Iceland 1955 through 2009. Clinical Endocrinology. 2011;74(6):792–793. doi: 10.1111/j.1365-2265.2010.03961.x.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

4. Bolland MJ, Holdaway IM, Berkeley JE, Lim S, Dransfield WJ, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. Clinical Endocrinology. 2011;75(4):436–442. doi: 10.1111/j.13652265.2011.04124.x.

5. Newell-Price J, Trainer P, Besser M, Grossman A. The Diagnosis and Differential Diagnosis of Cushing's Syndrome and Pseudo-Cushing's States. Endocrine Reviews. 1998;19(5):647–672. doi: 10.1210/edrv.19.5.0346.

6. Giraldi FP, Moro M, Cavagnini F. Gender-related differences in the presentation and course of Cushing's disease. Journal of Clinical Endocrinology and Metabolism. 2003;88(4):1554–1558. doi: 10.1210/jc.2002-021518.

7. Lonser RR, Nieman L, Oldfield EH. Cushing's disease: Pathobiology, diagnosis, and management. Journal of Neurosurgery. 2017;126(2):404–417. doi: 10.3171/2016.1.JNS152119.

8. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 Years in Stoke-on-Trent, UK: Audit and meta-analysis of literature. Journal of Clinical Endocrinology and Metabolism. 2011;96(3):632–642. doi: 10.1210/jc.2010-1942.

9. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: An epidemiological approach. Clinical Endocrinology. 1994;40(4):479–484. doi: 10.1111/j.1365-2265.1994.tb02486.x.

10. Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jørgensen JOL. Mortality in Cushing's syndrome: A systematic review and meta-analysis. European Journal of Internal Medicine. 2012;23(3):278–282. doi: 10.1016/j.ejim.2011.10.013.

11. Van Haalen FM, Broersen LHA, Jorgensen JO, Pereira AM, Dekkers OM. Management of endocrine disease: Mortality remains increased in Cushing's disease despite biochemical remission: A systematic review and meta-analysis. European Journal of Endocrinology. 2015;172(4):R143–149. doi: 10.1530/EJE-14-0556.

12. Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, et al. Mortality in patients with Cushing's disease more than 10 years after remission: A multicentre, multinational, retrospective cohort study. The Lancet Diabetes and Endocrinology. 2016;4(7):569–576. doi: 10.1016/S2213-8587(16)30005-5.