"GLOBAL HEALTH AND MODERN MEDICINE: INNOVATIONS AND PERSPECTIVES"
International Conference titled

Website:https://worldsiencepub.com/index.php/isngcs September edition,2026

CORTISOL PHYSIOLOGY, CAUSES OF ELEVATION, CLINICAL MANIFESTATIONS, AND MODERN TREATMENT APPROACHES

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ABSTRACT: Cortisol is the principal human glucocorticoid and a key effector of the hypothalamic-pituitary-adrenal (HPA) axis. It maintains cardiovascular tone, glucose availability, immune modulation, and adaptive responses to physical and psychological stress. Persistent cortisol excess, however, produces a multisystem disorder characterized by central adiposity, hypertension, glucose intolerance, muscle weakness, osteoporosis, skin changes, reproductive dysfunction, and increased susceptibility to infection. This thesis summarizes cortisol physiology, major physiological and pathological causes of elevation, the clinical pattern of hypercortisolism, current diagnostic principles, and contemporary treatment options. Particular attention is paid to distinguishing transient stress-related cortisol elevation from endogenous Cushing syndrome and from exogenous glucocorticoid exposure.

Keywords: cortisol; HPA axis; hypercortisolism; Cushing syndrome; ACTH; adrenal cortex; glucocorticoids; treatment.

ANNOTATSIYA: Kortizol inson organizmidagi asosiy glyukokortikoid bo‘lib, gipotalamus-gipofiz-buyrak usti bezi o‘qi faoliyatining muhim yakuniy gormoni hisoblanadi. U yurak-qon tomir tonusi, glyukoza almashinuvi, immun javob va stressga moslashuvni boshqaradi. Kortizolning uzoq muddat yuqori bo‘lishi markaziy semirish, arterial gipertenziya, glyukoza intolerantligi, mushak kuchsizligi, osteoporoz, teri o‘zgarishlari va reproduktiv buzilishlarga olib kelishi mumkin. Ushbu tezisda kortizol fiziologiyasi, uning ko‘payishining asosiy fiziologik va patologik sabablari, klinik belgilari, diagnostika tamoyillari va zamonaviy davolash usullari yoritilgan.

Kalit so‘zlar: kortizol; HPA o‘qi; giperkortizolizm; Kushing sindromi; AKTG; buyrak usti bezi; glyukokortikoidlar; davolash.

АННОТАЦИЯ: Кортизол является основным глюкокортикоидом человека и конечным эффектором гипоталамо-гипофизарно-надпочечниковой оси. Он участвует в поддержании сосудистого тонуса, регуляции обмена глюкозы, иммунного ответа и адаптации к стрессу. Длительный избыток кортизола может приводить к центральному ожирению, артериальной гипертензии, нарушению углеводного обмена, мышечной слабости, остеопорозу, изменениям кожи и репродуктивным нарушениям. В тезисе обобщены физиология кортизола, причины его повышения, клинические проявления, современные диагностические принципы и методы лечения.

Ключевые слова: кортизол; ГГН-ось; гиперкортицизм; синдром Кушинга; АКТГ; надпочечники; глюкокортикоиды; лечение.

INTRODUCTION

Cortisol is synthesized in the zona fasciculata of the adrenal cortex from cholesterol and is secreted in response to adrenocorticotropic hormone (ACTH). The HPA axis operates through a negative-feedback loop: corticotropin-releasing hormone (CRH) from the hypothalamus stimulates pituitary ACTH, ACTH stimulates adrenal cortisol production, and circulating cortisol inhibits both CRH and ACTH release (1,2). Cortisol secretion is pulsatile and strongly circadian, with the highest concentrations around awakening and a progressive decline toward late evening and midnight. This

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temporal organization is clinically important because loss of the late-night nadir is a characteristic feature of endogenous hypercortisolism (3,4).

Physiologically, cortisol supports gluconeogenesis, mobilizes amino acids and fatty acids, maintains vascular responsiveness to catecholamines, and restrains excessive inflammatory signaling. Short-lived cortisol elevation is therefore adaptive during acute illness, trauma, exercise, hypoglycemia, and psychological stress. In contrast, persistent cortisol excess causes a catabolic and cardiometabolic state with substantial morbidity. The aim of this thesis is to summarize cortisol physiology, explain the major causes of increased cortisol exposure, characterize the clinical manifestations of hypercortisolism, and review evidence-based diagnostic and therapeutic approaches (3,5).

MAIN PART

Physiology and mechanisms of cortisol elevation. More than 90% of circulating cortisol is protein-bound, mainly to corticosteroid-binding globulin and albumin; the unbound fraction is biologically active. Cortisol acts through intracellular glucocorticoid receptors that regulate gene transcription in nearly all tissues. Its metabolic effects include increased hepatic glucose production, reduced peripheral glucose utilization, enhanced protein catabolism, altered adipocyte differentiation, and permissive effects on vasoconstrictor systems. At the immune level, cortisol suppresses cytokine production and leukocyte trafficking, which is beneficial during excessive inflammation but may increase infection risk when exposure is chronic (1,2,6).

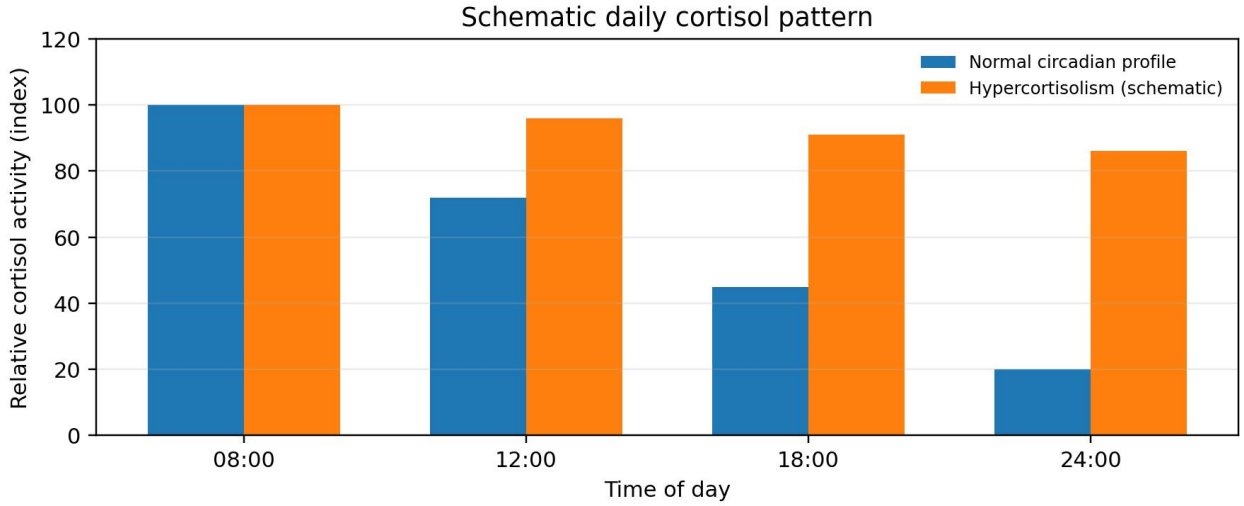
Table 1. Major causes of increased cortisol exposure and characteristic clues

Category	Typical causes	ACTH pattern	Clinical clue
Physiological / pseudo-Cushing states	Acute illness, major stress, severe depression, alcohol excess, intense exercise, pregnancy	Usually preserved	Potentially reversible; biochemical abnormalities may fluctuate
ACTH-dependent endogenous hypercortisolism	Pituitary corticotroph adenoma (Cushing disease); ectopic ACTH secretion	Normal-high or high	Loss of circadian nadir; progressive catabolic signs
ACTH-independent endogenous hypercortisolism	Adrenal adenoma, adrenal carcinoma, bilateral adrenal disease	Suppressed	Adrenal lesion with low ACTH
Exogenous glucocorticoid excess	Oral, injectable, inhaled, topical or intra-articular glucocorticoids	Suppressed endogenous ACTH/cortisol	Cushingoid phenotype despite suppressed endogenous cortisol

An important distinction is that a patient may have glucocorticoid excess without a high endogenous cortisol concentration. Iatrogenic Cushing syndrome caused by prescribed glucocorticoids is common and typically suppresses ACTH and endogenous cortisol secretion. Conversely, endogenous hypercortisolism is classified as ACTH-dependent or ACTH-independent. Pituitary Cushing disease is the most common ACTH-dependent form, while ectopic ACTH secretion is less frequent but may be severe. ACTH-independent forms arise from adrenal cortisol-producing lesions or bilateral adrenal disorders (4,5,7).

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Figure 1. Schematic comparison of normal circadian cortisol decline and hypercortisolism



Note: relative indices are illustrative and are not diagnostic cut-off values.

Clinical manifestations. Chronic cortisol excess affects nearly every organ system. Common findings include progressive central weight gain, facial rounding, supraclavicular or dorsocervical fat accumulation, thin skin, easy bruising, broad violaceous striae, acne, proximal muscle weakness, hypertension, dyslipidemia, impaired glucose tolerance or diabetes, osteoporosis, and increased fracture risk. Neuropsychiatric manifestations may include insomnia, emotional lability, anxiety, depression, and impaired concentration. Gonadal dysfunction can present as menstrual irregularity, reduced fertility, decreased libido, or hypogonadism. In children, weight gain accompanied by slowing of linear growth is particularly suggestive (4,5,7).

Diagnostic principles. Evaluation should begin with a careful medication history to identify exogenous glucocorticoids, including inhaled, topical, intra-articular, and "herbal" products that may contain steroids. In patients with a compatible phenotype, recommended first-line biochemical tests include late-night salivary cortisol, 24-hour urinary free cortisol, or an overnight 1-mg dexamethasone suppression test. Because false-positive results can occur in acute illness, depression, alcohol misuse, obesity, and disrupted sleep, abnormal screening usually requires confirmation and interpretation in clinical context. Once endogenous hypercortisolism is established, plasma ACTH helps separate ACTH-dependent from ACTH-independent disease, after which targeted pituitary, adrenal, or thoracoabdominal imaging is selected (4,5,8).

Treatment approaches. Definitive therapy is directed at the source of cortisol excess. Transsphenoidal surgery is the preferred first-line treatment for most resectable pituitary corticotroph adenomas, whereas adrenalectomy is used for cortisol-producing adrenal tumors. Resectable ectopic ACTH-producing tumors should be removed when feasible. When surgery is not curative, is contraindicated, or must be delayed, medical therapy may be used. Steroidogenesis inhibitors include osilodrostat, metyrapone, ketoconazole/levoketoconazole, and in selected settings mitotane; etomidate can provide rapid cortisol control in critically ill patients. Pituitary-directed agents such as pasireotide or cabergoline may be useful in Cushing disease, while mifepristone blocks the glucocorticoid receptor and is particularly relevant when hyperglycemia is prominent (5,8,9).

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Management must also address complications: hypertension, diabetes, dyslipidemia, osteoporosis, infection risk, psychiatric symptoms, thromboembolic risk, and hypogonadism. Bilateral adrenalectomy can provide rapid and definitive control of cortisol production in selected severe or refractory cases but creates lifelong adrenal insufficiency and requires permanent glucocorticoid/mineralocorticoid replacement. Radiotherapy is an option for persistent pituitary disease, although the cortisol-lowering effect may take time. Long-term follow-up is essential because recurrence may occur years after apparent remission (5,8,9).

CONCLUSION

Cortisol is indispensable for normal metabolism, vascular homeostasis, immune regulation, and adaptation to stress, yet chronic excess produces a characteristic multisystem syndrome. The most important clinical task is to distinguish transient physiological cortisol elevation and pseudo-Cushing states from true endogenous Cushing syndrome and from exogenous glucocorticoid exposure. A stepwise approach based on medication review, validated screening tests, ACTH-based classification, and targeted imaging improves diagnostic accuracy. Modern management is etiology-specific and combines surgery, pharmacotherapy, radiotherapy, and aggressive treatment of comorbidities. Early recognition and sustained follow-up are essential to reduce cardiovascular, metabolic, skeletal, infectious, and neuropsychiatric complications (5,8,10).

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