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Laboratory Markers of Chronic and Acute Stress: Diagnostic Value and Clinical Implications (Part 2: Neuroendocrine, Immunological and Metabolic Biomarkers of Chronic Stress in the Context of Its Influence on Cardiovascular System)

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Abstract: *Chronic stress (CS) is a powerful factor that silently, but persistently undermines human health by dysregulating the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). Its manifestation goes far beyond emotional experiences, shaping profound physiological changes that affect the endocrine, immune and metabolic systems. Modern biomarkers allow us both to visualize these changes and measure their intensity, making them quantifiable and clinically relevant. A comprehensive literature review was conducted, encompassing 76 English-language sources identified through PubMed, Scopus, Web of Science and Google Scholar. The analysis focused on the interplay between the hypothalamic–pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and stress-related conditions (CS). The search strategy targeted peer-reviewed publications from 2020 to 2025 using the following keywords: "cardiovascular system", "acute stress", "chronic stress", "cortisol", "epinephrine", "norepinephrine", "dehydroepiandrosterone", "dopamine", "aldosterone", "tumor necrosis factor alpha", "interleukin-1", "interleukin-6", "C-reactive protein", "cholesterol", "albumin" and "glycosylated hemoglobin". Inclusion criteria comprised original research articles, systematic and narrative reviews, meta-analyses and clinical guidelines, while non-peer-reviewed sources and non-English publications were generally excluded. The article summarizes key laboratory markers of stress, from classical hormones (cortisol, epinephrine, ACTH) to immune and metabolic indicators (cytokines, C-reactive protein, oxidative stress markers), with particular attention to hair cortisol as an innovative tool for long-term stress assessment. Stress-related biomarkers provide an integrated view of CS pathophysiology, demonstrating how neuroendocrine, immune and metabolic dysregulation drives hypertension, cardiovascular events, insulin resistance, systemic inflammation and neuropsychiatric disturbances. Early detection and management of CS are essential to prevent cumulative damage that can progress to obesity, metabolic syndrome, atherosclerosis, neurodegeneration and increased morbidity and mortality.*

Key words: Cortisol, Oxidative Stress, Immune System, Endocrinology, Biomarkers, Chronic Stress.

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Introduction

Stress is an unavoidable part of life that in small doses enhances focus and adaptation, but when prolonged, becomes harmful, destabilizing core regulatory systems and raising the risk of cardiovascular, endocrine, psychiatric and autoimmune disorders. Elevated cortisol levels promote the generation of reactive oxygen species (ROS) [1], which can induce damage to DNA, RNA and proteins, thereby accelerating cellular aging and predisposing to age-related pathologies [2]. Oxidative stress, further amplified by sustained catecholamine activity, contributes to vascular inflammation and facilitates the progression of atherosclerosis [3,4]. Additionally, chronic stress (CS) induces neurobiological alterations that may underlie anxiety and depression [5], disrupts reproductive function [6] and plays a role in the pathogenesis of autoimmune and inflammatory disorders [7, 8]. The diagnosis of CS requires a multifaceted approach that integrates neuroendocrine, immunological and metabolic biomarkers. Hair cortisol is especially promising, as it provides a long-term record of stress exposure while remaining non-invasive and practical. Such comprehensive biomarker analysis enhances diagnostic accuracy, supports individualized prevention and therapy, and reframes stress as a measurable process that can be effectively managed.

Materials and methods

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science and Google Scholar to gather relevant articles for this manuscript. The keywords “cardiovascular system“, “acute stress“, “chronic stress“, “cortisol“, “epinephrine“, “norepinephrine“, “dehydroepiandrosterone“, “dopamine“, “aldosterone“, “tumor necrosis factor alpha“, “interleukin-1“, “interleukin-6“, “C-reactive protein“, “cholesterol“, “albumin“ and “glycosylated hemoglobin“ were utilized. The search was restricted to peer-reviewed articles published between 2020 and 2025. However, older articles were also considered and included when deemed relevant to the topic. The inclusion criteria encompassed original research studies, systematic and narrative reviews, meta-analyses, and clinical guidelines, while non-peer-reviewed articles and publications in languages other than English were mainly excluded. Articles were initially screened based on their titles and abstracts, and those meeting the inclusion criteria were further assessed through a full-text review to ensure relevance to the manuscript’s objectives.

Laboratory Markers of Stress: Overview

The identification of specific biomarkers is crucial for assessing stress levels, understanding individual susceptibility and developing targeted therapeutic interventions. Biomarker-based diagnostics offer objective and quantifiable insights into stress-related pathophysiological changes, allowing for early detection of maladaptive responses and guiding clinical decision-making. Stress biomarkers are classified into three primary categories based on their physiological roles: neuroendocrine markers, immunological markers, and metabolic markers [9] (Table 1). These categories correspond to key physiological systems that mediate the stress response, including the HPA axis, the ANS and immune/metabolic pathways.

Neuroendocrine biomarkers primarily reflect the activation of the HPA axis and the sympathetic nervous system, which are central to the physiological response to stress [10, 11].

Cortisol is the primary glucocorticoid hormone released by the adrenal cortex in response to ACTH stimulation [12, 13, 14]. This hormone regulates glucose metabolism, immune function and blood pressure. CS leads to a dysregulated cortisol secretion, manifesting as either hypercortisolemia or hypocortisolemia [15, 16]. Cortisol is the main stress hormone that takes a vital role in the regulation of various physiological processes, including metabolism, immune response, and blood pressure [17, 18]. Its concentration serves as a reliable biomarker for assessing both acute and CS [19]. In clinical diagnostics acute stress is typically evaluated through cortisol levels in saliva or blood, as these fluids reflect immediate hormonal responses triggered by the activation of the HPA axis [20]. Cortisol levels can be measured in saliva, blood serum, sweat, urine and hair [21]. The measurement of free cortisol

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Table 1. Laboratory markers of CS

Name	Sample	Units of measurement	Method for detection	Time of material collection	Number of samplings	References
Neuroendocrine markers (the main ones)						
Cortisol	Hair	pg/mg	ELISA[a], LC-MS[b]/MSc RIA[d]	Anytime	Single sample	10, 11, 12
	Saliva	ng/mL	ELISA, LFIA[e]	Anytime	Single sample	11, 13
	Serum	µg/dL	CLIA[f], RIA	Morning (7:00-9:00)	Single sample	14, 15
	Sweat	µg/L; µM	ELISA, FET[g]	Anytime	Single sample	16, 17
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	18
Dehydroepia ndrosterone sulfate (DHEA-S)	Serum	µg/dL	ELISA, LC-MS/MS	Morning (7:00-9:00)	Single sample	19
	Saliva	pg/mL	ELISA	Morning	Single sample	20
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	21
	Hair	pg/mg	RIA	Anytime	Single sample	12
Cortisol/DHEA-S	Saliva	Ratio	ELISA	Morning	Single sample	12, 20
Epinephrine (adrenalin)	Plasma	pg/mL	HPLC[h], LC-MS/MS	Morning (fasting)	Single sample	22, 23
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 25, 26
Norepinephrine (norepinephrine)	Plasma	pg/mL	HPLC, LC-MS/MS	Morning (fasting)	Single sample	27, 23
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 25, 26
Dopamine	Plasma	pg/mL	HPLC, LC-MS/MS	Morning (fasting)	Single sample	22, 28
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 29
	Cerebro-spinal fluid	pg/mL	HPLC, LC-MS/MS	Lumbar puncture	Single sample	30
Aldosterone	Serum	ng/dL	RIA, CLIA	Morning (upright position)	Single sample	31, 32
	Plasma	ng/dL	RIA, CLIA	Morning (upright position)	Single sample	33

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Name	Sample	Units of measurement	Method for detection	Time of material collection	Number of samplings	References
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	34
Immunological biomarkers (additional ones)						
TNF-α	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	35
IL-1	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	36
IL-6	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	36
CRP	Serum	mg/L	Immuno-turbidimetry	Morning (fasting)	Single sample	36
ILG-1	Serum	ng/mL	ELISA	Morning (fasting)	Single sample	35
Metabolic biomarkers (additional ones)						
Cholesterol	Serum	mg/dL	Enzymatic colorimetric	Morning (fasting)	Single sample	36
Albumin	Serum	g/dL	Bromocresol Green	Morning (fasting)	Single sample	36
Glycosylated hemoglobin	Serum	% (mmol/mol)	ELISA, HPLC	Anytime	Single sample	36

Legend of the table: [a]The enzyme-linked immunosorbent assay; [b]Liquid chromatography-mass spectrometry; [c]Mass spectrometry; [d]Radioimmunoassay; [e]Lateral flow immunoassay; [f]Chemiluminescent Immunoassay; [g]Aptamer-field-effect transistor; [h]High-performance liquid chromatography.

in response to awakening should be considered a potential biomarker of CS, and salivary cortisol is a suitable medium for this purpose [22, 23]. Utilizing salivary cortisol as a stress biomarker enhances the reliability and informativeness of cortisol assessments obtained through saliva samples [24, 25, 26, 27, 28]. Previous studies have demonstrated that salivary cortisol levels are elevated in individuals experiencing CS compared to those without such stress exposure [29]. However, in cases where cortisol is assessed through saliva, serum, or urine, these methods face limitations due to the significant diurnal fluctuations in cortisol levels, making it difficult to rely on a single measurement [30]. Hair cortisol serves as a retrospective indicator of cumulative HPA axis activity over previous months, similar to how hemoglobin A1c reflects average glucose levels over the past three months. The purpose of this review is to explore hair cortisol as an innovative and practical biomarker for assessing long-term cortisol exposure linked to CS in older adults. Measuring cortisol in hair enhances our understanding of aging by providing a more accurate marker for CS both as a contributor to disease progression and as a means of evaluating the success of stress-reduction strategies [31]. Conversely, CS assessment is more accurately achieved through hair cortisol analysis. Given that human hair grows at approximately one centimeter per month, segmented hair samples allow for retrospective evaluation of cortisol exposure over extended periods [32]. Among biological matrices, saliva and blood are primarily used to measure short-term cortisol fluctuations, while hair provides insight into long-term hormonal accumulation [33]. Hair cortisol measurement offers several distinct advantages: it allows for long-term stress monitoring, involves a non-invasive sample collection process, and ensures sample stability over time, facilitating

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both storage and transportation. The use of hair cortisol as a diagnostic tool holds considerable promise in medical practice. It enables continuous stress monitoring, supports the prevention and management of stress-related disorders, and provides a means to evaluate the effectiveness of therapeutic interventions [33, 34]. Furthermore, it contributes to psychosocial research by linking physiological stress markers to psychological and social variables. Thus, cortisol remains a critical biomarker for stress evaluation, and its measurement in hair presents significant opportunities for advancing the diagnosis and treatment of stress-associated conditions in clinical settings [34]. As a key regulator of cortisol secretion, ACTH levels provide insights into upstream HPA axis function. Elevated ACTH with normal or low cortisol levels suggests adrenal insufficiency, while suppressed ACTH with high cortisol may indicate HPA axis hyperactivity [34]. It is confirmed that under prolonged exposure to stressors, the level of ACTH significantly increases alongside epinephrine and corticosterone, while monoaminergic transmitters (5-hydroxytryptamine (5-HT), dopamine, norepinephrine) simultaneously decrease [35]. There is a documented association between plasma ACTH levels and the severity of suicidal ideation in patients with major depressive disorder who are resistant to antidepressant therapy, as well as with the overall severity of depression. This finding highlights the potential role of ACTH in understanding the consequences of stress and mental disorders [36]. Because of its connection with the level of cortisol and possible relation to development of mental problems, ACTH stays an important marker of CS too.

Dehydroepiandrosterone sulfate (DHEA-S) is a steroid hormone synthesized in the zona reticularis of the adrenal cortex in response to ACTH, and it plays an immunomodulatory role that counteracts the effects of cortisol. It contributes significantly to tissue regeneration and protective functions that support overall health. Both elevated and reduced DHEA-S levels are often linked to various health conditions and clinical outcomes. DHEA-S is most commonly assessed in saliva, urine, and blood serum, though studies have also explored its measurement in hair samples [36]. In CS DHEA-S levels progressively decline despite cortisol fluctuations, and although its reliable assessment requires frequent time-specific sampling, the cortisol/DHEA-S ratio remains a valuable indicator of the HPA axis imbalance and prolonged stress-related neurodegeneration risk [36]. Prolonged activation of stress pathways can contribute to immunosuppression or chronic inflammation. That is why the importance of immunological markers is present.

Epinephrine and norepinephrine mediate the sympathetic nervous system's response to stress [27]. CS induces adaptive changes in hormonal regulation, where responsiveness to epinephrine decreases due to habituation, yet overall levels may remain elevated because of slower metabolism [38]. Although epinephrine reliably rises under stress, its diagnostic value is limited by non-specificity, as it also increases during general arousal and mental activity. Nevertheless, catecholamines remain important for understanding how prolonged stress contributes to oxidative damage, cellular senescence and long-term health risks [38]. Acute or short-term stress can alter dopamine levels and midbrain dopaminergic neuronal activity. These changes typically enhance reward-related neural circuits, such as improving the learning of cue-reward associations. Such stress episodes do not usually lead to depressive behavior. In contrast, chronic and repeated stress exposure has been consistently shown, especially in animal studies, to induce behaviors resembling depression. Established models for studying CS include chronic restraint stress, chronic social defeat stress, and chronic unpredictable mild stress. Acute stress appears to temporarily heighten sensitivity to rewards, facilitating the engagement of reward-related neural networks. However, prolonged exposure to CS dampens this sensitivity, which may lead to anhedonia – a core symptom of depression, marked by diminished pleasure and motivation. Prolonged, uncontrollable, and unpredictable stressors exert an inhibitory effect on dopamine release, contributing to the neurochemical foundation of stress-induced mood disorders [39].

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A key acute-phase protein and marker of systemic inflammation. Having been traditionally utilized as a marker of infection and cardiovascular events, there is now growing evidence that CRP plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly interleukin-6 and tumor necrosis factor-α [40]. CS is associated with persistently elevated CRP levels, which correlate with an increased risk of cardiovascular disease and metabolic syndrome [41].

CS profoundly alters immune regulation by elevating pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β [42], while simultaneously suppressing anti-inflammatory mediators like IL-10 and TGF-β, thereby promoting neuroinflammation, mood disorders and autoimmune susceptibility [42]. In parallel, CS disrupts lymphocyte homeostasis, as reflected by a decreased CD4+/CD8+ ratio and diminished natural killer (NK) cell activity, which together weaken immune surveillance and heighten vulnerability to infections and chronic disease [42]. Stress also influences metabolic homeostasis through alterations in glucose metabolism, lipid profiles and oxidative stress regulation. Acute stress induces transient hyperglycemia due to increased hepatic gluconeogenesis and insulin resistance. CS contributes to persistent insulin resistance, predisposing individuals to type 2 diabetes mellitus [43]. Dysregulation of lipid metabolism caused by stress is characterized by increased levels of triglycerides and decreased levels of high-density lipoprotein cholesterol, which contribute to the development of fatty plaques in the blood vessels and elevate the risk of cardiovascular disease [44]. CS also promotes oxidative damage by increasing the production of highly reactive molecules that can damage cells. Elevated levels of malondialdehyde indicate lipid peroxidation, while decreased levels of superoxide dismutase and glutathione reflect a weakened antioxidant defense system, leading to increased cellular damage [45].

Conclusions

CS disrupts neuroendocrine, immune and metabolic regulation, thereby increasing the risk of cardiovascular and systemic diseases. Laboratory biomarkers, including cortisol, DHEA, catecholamines, cytokines and oxidative stress indicators, are essential for translating the physiological burden of stress into measurable parameters. Hair cortisol provides a particularly valuable long-term marker, complementing conventional biofluids in both research and clinical practice. The integration of diverse biomarkers enhances early diagnosis, supports individualized interventions and strengthens strategies for the prevention and management of stress-related disorders.

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Conflict of interests

The authors declare no conflict of interest.

Consent to publication

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AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

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Лабораторні маркери хронічного та гострого стресу: діагностична цінність та клінічні наслідки (Частина 2: Нейроендокринні, імунологічні та метаболічні біомаркери хронічного стресу у контексті його впливу на серцево-судинну систему)

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Анотація: *Хронічний стрес (ХС) є потужним чинником, який непомітно, але наполегливо підриває здоров’я людини шляхом порушення регуляції гіпоталамо-гіпофізарно-надниркової (ГГН) осі та автономної нервової системи (АНС). Його прояви виходять далеко за межі емоційних переживань, формуючи глибокі фізіологічні зміни, що впливають на ендокринну, імунну та метаболічну системи. Сучасні біомаркери дають змогу не лише візуалізувати ці зміни,*

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а й вимірювати їхню інтенсивність, роблячи їх кількісно оцінюваними та клінічно значущими. Було здійснено ґрунтовний огляд літератури, що охопив 76 англомовних джерел, відібраних у базах даних PubMed, Scopus, Web of Science та Google Scholar. Аналіз був зосереджений на взаємодії ГГН осі, АНС та ХС. Стратегія пошуку включала рецензовані публікації за 2020-2025 роки з такими ключовими словами: «серцево-судинна система», «гострий стрес», «хронічний стрес», «кортизол», «епінефрин», «норепінефрин», «дегідроепіандростерон», «дофамін», «альдостерон», «фактор некрозу пухлини альфа», «інтерлейкін-1», «інтерлейкін-6», «С-реактивний білок», «холестерин», «альбумін» та «глікозильований гемоглобін». Критерії включення охоплювали оригінальні наукові статті, систематичні та наративні огляди, метааналізи й клінічні настанови, тоді як нерецензовані матеріали та публікації іншими мовами, окрім англійської, загалом виключалися. У статті подано огляд основних лабораторних маркерів стресу: від класичних гормонів, таких як кортизол, адреналін та адренокортикотропний гормон (АКТГ), до імунних і метаболічних показників, включаючи цитокіни, С-реактивний білок і маркери оксидативного стресу. Особливу увагу приділено визначенню рівня кортизолу у волоссі як інноваційному методу довгострокової оцінки стресу, що відкриває перспективи для вдосконалення ранньої діагностики, профілактичних стратегій, терапевтичного моніторингу та персоналізованих медичних втручань. Оцінка стрес-асоційованих біомаркерів дає змогу всебічно зрозуміти патофізіологію ХС, демонструючи, як порушення регуляції нейроендокринної, імунної та метаболічної систем сприяє розвитку гіпертензії, серцево-судинних подій, інсулінорезистентності, системного запалення та нейропсихіатричних порушень. Відтак раннє виявлення та контроль ХС мають вирішальне значення, оскільки своєчасні втручання можуть запобігти його кумулятивним наслідкам, які інакше призводять до ожиріння, метаболічного синдрому, атеросклерозу, нейродегенерації та суттєвого зростання захворюваності й смертності.

Ключові слова. Хронічний стрес, кортизол, оксидативний стрес, імунна система, ендокринологія