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Work Stress and Biochemical Changes-An Updated Review Article.

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Abstract

Background: Stress, as a psychophysiological response, arises when individuals encounter challenging or adverse situations. Extensive research over the past decades has demonstrated stress's profound effects on both the nervous system and overall health, showing associations with memory impairments, cognitive decline, and physiological damage in chronic cases. Stress-induced biochemical changes impact critical systems, including the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and immune responses. These physiological responses influence various biomarkers and immune functions, increasing vulnerability to chronic diseases.

Aim: This review aims to update and synthesize findings on the biochemical biomarkers involved in stress responses, particularly the role of cortisol and related biochemical indicators in both acute and chronic stress conditions.

Methods: A comprehensive review of peer-reviewed literature was conducted, focusing on studies investigating stress biomarkers. Data were sourced from multiple databases, covering research on cortisol measurements in hair, saliva, blood, and other biological samples, and studies exploring the physiological responses regulated by the HPA axis, ANS, and immune system.

Results: Findings highlight cortisol as a significant biomarker in stress, with measurement methods, including hair and salivary cortisol, offering reliable indicators for chronic stress levels. Chronic stress influences hormone levels, such as those produced by the HPA axis, and leads to increased pro-inflammatory cytokines like IL-6, TNF-alpha, and C-reactive protein. Additionally, elevated oxidative stress markers, such as glutathione peroxidase and superoxide dismutase, reveal the body's antioxidant response under stress. Studies also link stress responses to various long-term health outcomes, including metabolic disturbances, immunosuppression, and age-related physiological changes.

Conclusion: This review underscores the biochemical changes triggered by stress and emphasizes cortisol as a key chronic stress biomarker. The cumulative evidence suggests that biochemical monitoring of stress can aid in early identification of stress-induced health risks. Future research should focus on refining stress measurement techniques and exploring interventions that target these physiological markers to improve health outcomes.

Keywords: Stress biomarkers, cortisol, hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), immune response, chronic stress, oxidative stress, inflammatory cytokines.

1. Introduction

When the body is exposed to unfavorable, difficult, and demanding circumstances or stressors, it frequently creates stress, a psychophysiological reaction [1–3]. The effects of stress on the neurological system have been studied for more than 50 years [4], and studies have shown that stress has negative consequences on the human brain [5]. Long-term stress is linked to anatomical changes, like brain shrinkage [6], which affects memory and cognitive processes [5] and leads to changed reactions. These consequences, which cause long-lasting structural damage to the brain and psychological alterations, vary in intensity depending on how long the stress lasts [5,7]. Stress can be triggered by any traumatic event, such as being in a vehicle accident that leaves you permanently disabled. Simply being present at a distressing occurrence can occasionally have long-lasting effects on one's mental health and general well-being [6]. Furthermore, it has been determined that parental separation is a powerful stressor that impacts people from the postnatal stage into adulthood [5].

While chronic stress is a longer-lasting condition associated with maladaptive reactions that negatively affect body systems, acute stress is a short-lived, adaptive state [3,8]. Long-term stress causes the body to release specific hormones and chemicals, which can have detrimental effects on important organs like the liver, heart, and brain as well as communicate the body's ongoing stress. The hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and the immune system are among

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the physiological systems that control stress levels, either alone or in concert [9,10]. Cortisol, a hormone that primes the body for fight-or-flight scenarios and is an essential stress biomarker, is released by the HPA axis in response to stressors [9]. The HPA axis is primarily sensitive to psychological stress and has close interactions with the ANS and immune system [9,10]. Because it affects cognition, metabolism, behavior, and immunological responsiveness [9,15], it is essential to comprehend how stress impacts disease processes. Although cortisol levels are normally higher at some periods of the day, such as the morning, they indicate a dangerous stress condition if they remain high throughout the day. Numerous biological samples, including blood, urine, hair, and saliva, can be used to test these cortisol levels [9].

By regulating body functions through autonomic reflexes in response to internal (homeostasis maintenance, such as temperature, blood glucose, water balance, and weight) and external (environmental, visual, olfactory, and tactile) stimuli, the ANS also contributes to the creation and management of both acute and chronic stress [12,16–19]. Acetylcholine (ACh), norepinephrine, and adrenaline are important neurotransmitters that are released by the sympathetic and parasympathetic ANS. The fight-or-flight response is modulated by catecholamines rising and acetylcholine falling under stress [13,20]. While some immunological indicators regulated by the ANS and HPA axis aid in the immune response to stress, other non-immunological biomarkers, such as arginine vasopressin (AVP) and dehydroepiandrosterone, are regulated by these systems and do not directly involve immune responses. The fight-or-flight response is one way the immune system reacts to stressors by starting processes including the release of immune cells in reaction to wounds or infections [21]. Due to immunological dysregulation, both acute and chronic stress increase inflammatory responses. Pro-inflammatory cytokines rise in both situations, raising the risk of chronic illnesses and the frailty that goes along with them [22–24]. Compared to acute stress, chronic stress has more detrimental long-term impacts on health, such as viral reactivation, which puts an additional burden on the immune system [25]. Individual differences exist in the severity of these stress reactions, with some people exhibiting a heightened immunological response [26,27].

Cytokines, such as interleukin-6 (IL-6) [9,28,29], IL-1 beta [9], C-Reactive Protein (CRP) [9,30], tumor necrosis factor-alpha (TNF-alpha) [9,28], and natural killer cells (NK) [31–33], are the main components of immunological biomarkers. In addition to aiding in the body's defense against infections, these immunological markers—in particular, cytokines and CRP—are important in triggering stress reactions in response to social and psychological stimuli [34]. In addition to these biomarkers, the relationship between chronic stress and chronic diseases is investigated using metabolic indicators including fasting glucose, glucose tolerance [35,36], glycosylated hemoglobin (HbA1c) [37], triglycerides, and cholesterol levels [38,39]. In addition to stress-related hormones, blood samples are used to measure chronic stress levels by analyzing endocrine hormones such as prolactin [40,41], estradiol [42], oxytocin [40], growth factors (GF), and dehydroepiandrosterone sulfate (DHEA-S) [43,44]. Therefore, how a person responds to extended stress is greatly influenced by interactions between the immunological, endocrine, and neurological systems. Enzymatic and non-enzymatic antioxidants, such as glutathione peroxidase (GTPx), ascorbic acid, superoxide dismutase (SOD), catalase, and malondialdehyde (MDA), are also part of the body's intricate defense mechanism. Reactive oxygen species (ROS) cause oxidative stress, and this antioxidant defense system acts as a natural defense against their negative consequences [45–47].

HPA-Axis Biomarkers: Cortisol

Research has focused on cortisol, ACTH, and BDNF as key biomarkers linked to the HPA-axis under chronic stress. The use of cortisol readings from hair samples as a trustworthy indication of chronic stress is supported by data from nine research. Corticotropin-releasing hormone (CRH) is released in the hypothalamus to initiate the HPA-axis activation. This triggers the anterior pituitary to release adrenocorticotropic hormone (ACTH), which in turn stimulates the synthesis of cortisol [9]. In response to biochemical stress, the adrenal cortex's zona fasciculata produces cortisol, the main glucocorticoid made from cholesterol [15,48,49]. Both bound and unbound forms of cortisol are present; unbound cortisol is lipophilic and can permeate cells, making it easier to find in body fluids [50]. Given that cortisol levels normally peak in the early morning and fall by the evening, particularly during the early stages of sleep, time of measurement is crucial [50]. Research on cortisol as a chronic stress biomarker and quantification techniques employing urine, saliva, and hair samples are the main objectives of this work. It is noteworthy that Rauel et al. were the first to use hair samples for cortisol analysis [51].

Hair Cortisol

The relationships between baseline levels and the length of time a baby was ventilated in the NICU [52] indicate that hair cortisol is a possible clinical biomarker for evaluating chronic stress in babies. According to a different study, hair cortisol is a useful measure of stress in both moms and babies, and it may be useful in detecting chronic stress in the first year after giving birth [53]. Furthermore, hair cortisol is a promising indicator of long-term stress in expectant mothers, with significant clinical research implications [54]. Additional research supports hair cortisol as a valid biomarker, highlighting its significance in evaluating stress in pregnant women and other populations [54–57]. Research has shown that children who experience high levels of stress throughout their early school years have higher levels of scalp hair cortisol concentration (HCC), which has been beneficial for measuring stress over the long term [58]. Moreover, obesity in children with impairments is positively correlated with elevated hair cortisol [59]. Studies on maternal stress also provided evidence for the validity of HCC, demonstrating its efficacy as a biomarker of chronic stress [60]. Children and adolescents that experience chronic stress as a result of low socioeconomic status (SES) trigger the HPA-axis, which results in consistently high cortisol levels. Children and adolescent groups with lower socioeconomic status frequently exhibit these high levels [61]. Chronic cortisol increase is correlated with age-related stress, raising the risk of stress-related illnesses in the elderly. Research indicates that HCC is positively associated with age, female sex, alcohol use, and smoking, which leads to markedly higher cortisol levels in older adults [62], and elevated hair cortisol levels have been found in Walpole Island First Nation members, suggesting a strong association between HCC and chronic stress in particular communities [63].

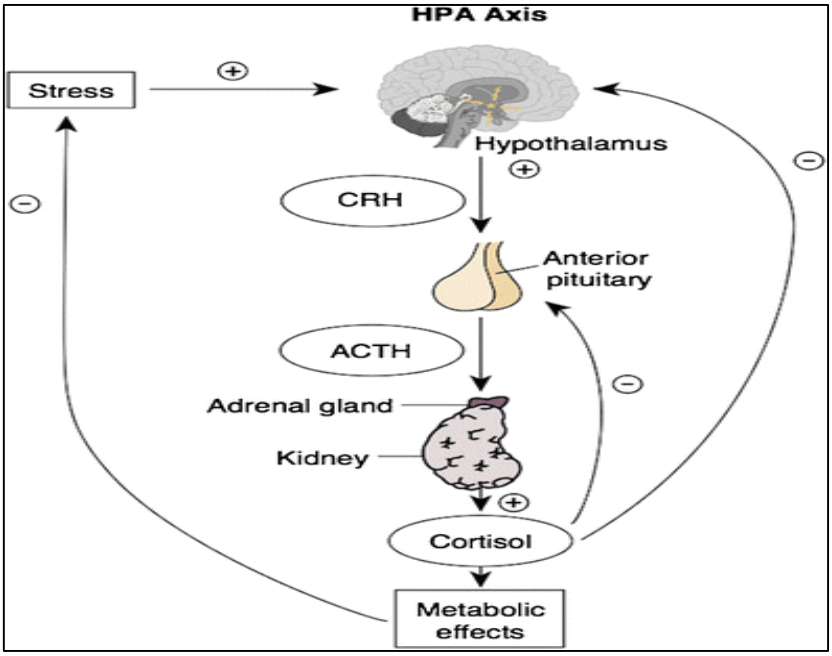

Figure 1: HPA axis.

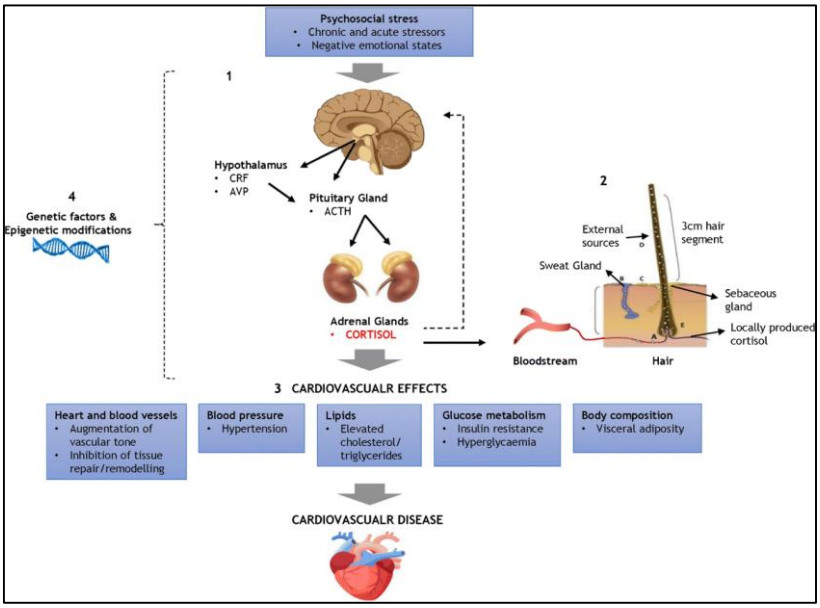

Figure 2: Hair Cortisol Markers.

The studies on hair cortisol concentration (HCC) reveal its utility as a biomarker of chronic stress across various populations and life stages. Yamada et al. (2007) found a potential link between hair cortisol levels and chronic stress in infants born after 25 weeks (n=60), suggesting early-life stress markers. Liu et al. (2016) studied infants (n=47) and mothers (n=41), finding that hair cortisol could serve as a chronic stress biomarker within the first year after birth and postpartum. Kalra et al. (2007) focused on pregnant women aged 18-45 (n=25) and proposed HCC as a viable marker of gestational stress. Janssen et al. (2017) explored HCC in adults (n=102) with a mean age of 43.4, indicating that while HCC might not be fully reliable for job stress, it could still detect early symptoms of stress-related conditions like depression.

For caregivers and children with disabilities, Chen et al. (2015) observed a positive association between caregivers' HCC and obesity in children (n=87), highlighting a stress-related factor. In a mother-daughter study, Ouellette et al. (2015) found a strong association between HCC levels and negative parenting experiences (n=60 per group). Vliegenthart et al. (2016) identified elevated cortisol in children and adolescents (n=270) from lower socioeconomic backgrounds, noting HCC's potential for analyzing chronic stress in these groups. Feller et al. (2014) confirmed associations between HCC and age, gender, alcohol use, type 2 diabetes, and newly identified smoking risks, all of which elevated cortisol levels in older participants (n=654). Lastly, Henley et al. (2013) reported higher HCC in Walpole Island First Nation individuals (n=55) compared to non-First Nation volunteers, potentially due to socioeconomic and health disparities that contribute to chronic stress. These findings collectively demonstrate HCC's relevance in assessing stress in diverse

populations, although factors such as age, health, and socioeconomic background may influence cortisol levels.

Salivary Cortisol

Salivary cortisol has been confirmed as a reliable biomarker for chronic stress in seven investigations. The responsiveness of salivary cortisol measurement to stress assessment in saliva samples emphasizes its usefulness [64–70]. Research indicates that individuals with stress-related burnout had higher cortisol levels in the first hour after waking up than do non-stressed individuals, suggesting a link between morning cortisol and chronic stress [64]. Burnout patients exhibited a greater waking cortisol response during the workweek as opposed to the weekend, according to Soderstrom et al. (2006) [66]. Research on the free cortisol response after awakening by gender indicates that males with moderate burnout have higher levels of this hormone, especially 60 minutes after awakening, whereas females with significant burnout have a higher reaction [67]. Free cortisol is a promising biomarker for chronic stress, as evidenced by this response pattern. Furthermore, in chronic stress instances, somatic and physiological arousals have been associated with higher salivary cortisol levels, especially in middle-aged women who had high nighttime cortisol levels and first-morning testosterone levels. Nevertheless, there was no correlation seen between catecholamines and overnight urine cortisol [69]. Salivary cortisol, then, offers a sensitive and easily accessible way to detect the effects of chronic stress on a range of physiological indicators.

The studies on cortisol levels in relation to chronic stress and burnout provide insights into how these factors influence physiological responses across various populations. De et al. (2003) found that burnout patients (n=22) exhibited higher cortisol levels within the first hour after awakening compared to healthy participants (n=23). Schulz et al. (1998) observed that chronically stressed individuals, particularly women, showed elevated post-awakening cortisol levels compared to non-stressed individuals, indicating gender-based differences in stress responses (n=100). Soderstrom et al. (2006) identified that participants with high burnout scores experienced increased cortisol levels upon waking on workdays compared to weekends, coupled with heightened mental fatigue, diminished recovery, and elevated pre-sleep arousal (n=20). Grossi et al. (2005) found that female burnout patients exhibited higher morning cortisol levels, while in men, elevated cortisol was associated only with moderate burnout, not severe cases (n=64). Melamed et al. (1999) linked chronic burnout to higher somatic arousal and salivary cortisol levels among non-shift blue-collar workers (n=111). In studying the impact of marital stress, Powell et al. (2002) reported that women experiencing divorce or separation had higher evening salivary cortisol levels than those in stable marriages (n=40). Lastly, Siddiqui et al. (2019) associated chronic psychological stress with increased oxidative stress and inflammation in newly diagnosed diabetic patients (n=250), underscoring the impact of sustained stress on metabolic health. Together, these findings emphasize cortisol's role as an indicator of stress and burnout, with variations influenced by gender, stress type, and health status.

Other Cortisol Markers:

Research indicates a notable presence of urinary free cortisol in individuals experiencing chronic stress or burnout when compared to healthy controls, though hormonal and biochemical parameters appear unchanged between the two groups. These findings imply the occurrence of hypocortisolism among stressed individuals [71]. Powell et al. (2002) utilized high-performance liquid chromatography with electrochemical detection to examine chronically stressed women undergoing divorce or separation (n=20) and compared them to non-stressed women in stable marriages (n=20). Although no significant trend was observed, stressed women showed a tendency towards elevated platelet catecholamines [69]. Moch et al. (2003) found reduced urinary free cortisol in women with burnout (n=16) when compared to controls (n=16) using high-pressure liquid chromatography. Importantly, a stress management intervention did not reverse hypocortisolism, even as clinical and psychological improvements were reported in burnout patients. Other studied hormonal and biochemical parameters showed no notable differences [7]. Adrenocorticotropic hormone (ACTH), which is regulated by corticotrophin-releasing hormone (CRH), plays a pivotal role in modulating endocrine, autonomic, and immune responses to stress. In two studies measuring ACTH to assess chronic stress [71,72], Moch et al. (2003) confirmed reduced urinary free cortisol in burnout patients and noted no significant restoration of this state post-intervention [71]. Borders et al. (2015) found that non-Hispanic Black (NHB) women (n=55) had elevated CRP and ACTH levels in the later stages of pregnancy when compared to non-Hispanic White (NHW) women (n=57), revealing racial disparities in stress responses during gestation [72]. Furthermore, brain-derived neurotrophic factor (BDNF), essential for neuron development, survival, and physiological maintenance [35], was markedly lower in subjects with burnout. These reduced BDNF levels were associated with symptoms such as mood alterations and cognitive changes, highlighting significant physiological effects of chronic stress compared to healthy controls [36].

Brain-derived neurotropic factor (BDNF):

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic adrenergic medullary (SAM) axis are the two physiological channels that mostly control biomarkers of the autonomic nervous system (ANS). Rapid adaptation to stress is made possible by the SAM axis's instantaneous reaction to stressors, while the HPA axis reacts more slowly. SAM activation triggers physiological reactions, including elevated blood pressure and heart rate, as well as the release of catecholamines, especially norepinephrine and adrenaline, which improve a person's capacity to cope with stressful situations [9,10,65]. With epinephrine and norepinephrine produced by central noradrenergic neurons and mostly discharged from the adrenal medulla into the bloodstream, catecholamines are important biomarkers for ANS activity and indicate the body's reaction to stress [20]. The physiology of stress is also significantly influenced by metabolic indicators such as insulin, glucose, cholesterol, and glycosylated hemoglobin (HbA1c). With high levels of glucose, HbA1c, and other metabolic markers suggesting inadequate stress regulation, these biomarkers shed light on the body's levels of chronic stress. For example, McCurley et al. (2015) discovered that among Hispanic individuals at risk for diabetes, long-term stress had a direct effect on glucose regulation, independent of mediation by inflammatory markers [41]. According to Aguilo et al. (2017), caregivers of cancer patients had greater levels of perceived stress and increased plasma glucose than those who cared for elderly

patients with chronic illnesses [40]. According to Grossi et al. (2003), women who are burnt out have higher levels of TNF-α and HbA1c, which suggests increased oxidative stress and inflammatory reactions [73]. Male participants' raised cholesterol, uric acid, glucose, and slightly higher triglycerides were linked to "tense burnout" by Melamed et al. (1992) and decreased well-being [74]. Finally, Siddiqui et al. (2019) observed that newly diagnosed diabetes patients with significant chronic stress had elevated HbA1c and glucose levels, as well as enhanced oxidative stress and inflammation [70]. These results highlight the important part stress plays in metabolic dysregulation and its possible effects on the development of chronic diseases.

Other Mediators:

Prolactin, oxytocin, growth hormone, and dehydroepiandrosterone sulfate (DHEA-S) are endocrine hormones that are important biomarkers for evaluating physiological reactions to stress in a variety of populations. [75,76]. In contrast to cortisol, the steroid hormone DHEA-S, which is generated in the zona reticularis of the adrenal cortex in response to ACTH, has an immunomodulatory role. Variations in DHEA-S levels are frequently linked to particular health issues and outcomes, and this hormone helps maintain health through its regenerative and protective qualities [43,45,77]. Antioxidants: Enzymes like superoxide dismutase (SOD) and catalase help the body fight off reactive oxygen species (ROS), reducing oxidative stress linked to aging and illness. Studies reveal that night and evening shift workers have higher SOD levels, suggesting that it plays a part in how they react to stress at work [78,79]. Although it is not directly related to chronic stress, malondialdehyde (MDA), a consequence of lipid peroxidation, is associated with elevated stress levels, especially in night shift workers, and functions as an indication of oxidative stress [29,82].

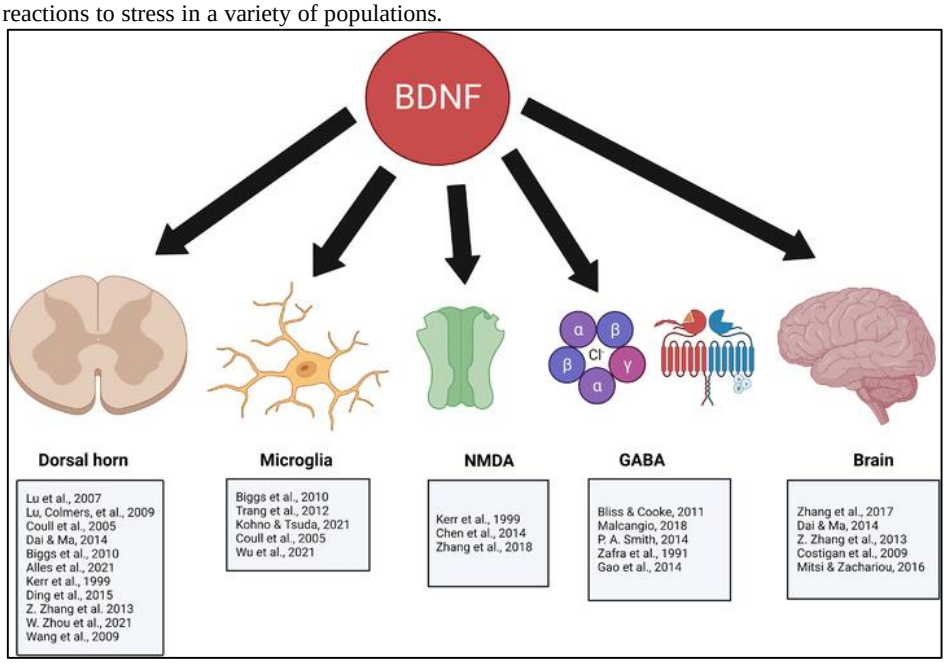

Figure 3: Brain-derived neurotropic factor (BDNF).

Immune system biomarkers: By bridging the neuroendocrine and immune systems, immunological biomarkers shed light on chronic illnesses linked to stress [84]. Growth factors, interleukins, and interferons are examples of cytokines that are essential to immune responses and have functions in infection, inflammation, and damage. Pro-inflammatory (like IL-6 and IL-1β) and anti-inflammatory (like IL-10) cytokines have both been studied as markers of immunological alterations brought on by stress. For example, pro-inflammatory TNF-alpha is higher than anti-inflammatory IL-4 in instructors who are burnt out, suggesting increased systemic inflammation [32,85-88]. Leukocytes and Natural Killer (NK) Cells: According to some research, burnout is associated with higher amounts of leukocytes and T-cells, which are correlated with stress levels. Large-scale variations in leukocyte counts, however, are not always associated with burnout stress [28,89,90]. Fibrinogen and C-reactive Protein (CRP): While CRP relationships with burnout are still inconsistent across research, chronic stress and everyday stressors, especially in caregivers, are associated with higher levels of IL-6 and CRP. While some studies find no significant changes, others reveal higher CRP levels in burnout cases, indicating that CRP is a variable stress signal [42,74,91]. When taken as a whole, these indicators offer important insights into how the body reacts to stress and guide strategies for treating health problems associated with stress.

Studies and Discussions:

The 37 papers under examination, which span the last 40 years, are novel investigations centered on certain biomarkers associated with chronic stress. Cortisol, ACTH, and BDNF are among the HPA-axis biomarkers that have been frequently studied. Although other mediums, including blood, urine, and saliva, are also utilized, albeit with certain limitations, nine investigations supported the use of hair cortisol as a valid biomarker for chronic stress (33). Recent developments have made hair cortisol the favored technique. Hair cortisol is a more reliable assessment than urine or saliva samples, according to Kimberly et al., who found cortisol to be a potential biomarker under maternal stress. Because it provides a reliable indicator of HPA-axis activity during pregnancy and represents total cortisol release over time, hair cortisol concentration (HCC) is a useful measure for evaluating long-term cortisol levels (56). Studies on the working population have shown a relationship between hair cortisol concentration and chronic stress, suggesting that hair

cortisol is a useful biomarker for work-related stress and could help detect depression early (57). Hair cortisol is a more significant indicator for evaluating stress than salivary cortisol (58). Furthermore, studies on ACTH as a marker of chronic stress revealed that Black Hispanic pregnant women had higher mean levels of ACTH and C-reactive protein (CRP) in the second and third trimesters (72). On the other hand, another study did not find any connection between blood samples' chronic stress indicators and ACTH (72). According to BDNF research, people who are under stress have much reduced BDNF levels (35, 36).

Catecholamines were investigated as ANS biomarkers, whereas glucose, HbA1c, triglycerides, and cholesterol were investigated as metabolic process biomarkers. Results show that there is no correlation between chronic stress and ANS-regulated hormones, and earlier research has not found any discernible changes between stressed and healthy people (70, 72). As a result, ANS markers might not be reliable markers for identifying chronic stress. One study that looked at the impact of stress using metabolic, endocrine, and immunological biomarkers found substantial increases in glucose and HbA1c in two distinct caregiver groups, but no significant changes in endocrine and immune markers (41). According to another study, women who experience burnout have higher levels of TNF-alpha and HbA1c, which may indicate that they are more prone to oxidative stress and inflammatory reactions (74). Elevated levels of glucose, cholesterol, triglycerides, and uric acid, which indicate a decrease in health condition, further illustrated the connection between burnout and cardiovascular risk factors (75).

Prolactin, oxytocin, and dehydroepiandrosterone sulfate (DHEA-S) were among the endocrine hormones that were examined. While cortisol levels stayed constant, three studies analyzing blood sample DHEA-S levels discovered a link between higher DHEA-S and burnout. While there were no differences in cortisol levels, burnout patients had higher DHEA-S levels (78). Stress participants between the ages of 25 and 34 had lower DHEA-S levels than healthy persons, with the difference being particularly noticeable in females. On the other hand, stress individuals between the ages of 35 and 44 and 45 and 54 did not vary from controls (28). Health benefits were correlated with changes in DHEA-S levels in stress patients throughout the first year of treatment, indicating that changes in DHEA-S are linked to effective stress management (33). SOD and catalase, two antioxidant indicators, were also examined; one study found that workers who worked night and evening shifts had higher SOD activity, suggesting that they were under more oxidative stress (80).

NK cells, leukocytes, CRP, fibrinogen, cytokines, and pro- and anti-inflammatory indicators were among the immunological biomarkers that were reviewed. According to one study, chronic stress raises IL-6 levels, which may indicate that long-term stress causes immunological adaptations that persist even after stressors are eliminated, potentially impairing immune function in those who experience chronic stress (31,86). IL-6 levels were found to be four times greater in caretakers than in non-caregivers in another study that linked IL-6 levels to chronic stress. This may be a mechanism that connects immunological aging and age-related diseases to long-term stress (30). The results also point to a connection between inflammation, oxidative stress, and chronic stress that may increase the risk of type 2 diabetes (71). Burnout patients showed elevated IL-10, suggesting an anti-inflammatory reaction to long-term stress (80). Furthermore, interleukin-8 was found to be a strong biomarker of chronic stress, with high levels associated with negative psychological effects and cardiovascular disease (87). Chronic stress has been linked to alterations in NK cell numbers and activity. One study found that male office workers with high burnout and depersonalization levels had lower NK cell activity (89). These results suggest that leukocytes and NK cells may not be as accurate as other indicators and that their function in chronic stress responses is yet unknown. However, studies repeatedly demonstrate that chronic stress settings result in higher levels of CRP, making it a noteworthy indicator of inflammation (80, 92, 93). Gender differences in stress biomarkers were highlighted by the positive correlation found between burnout and fibrinogen and hs-CRP levels in women but not in men (94-95).

Conclusion:

The significant role of biochemical markers in understanding stress responses is increasingly clear, with cortisol and related biomarkers offering insights into how the body reacts to both acute and chronic stress. Cortisol, as a primary indicator of HPA axis activity, remains a crucial marker due to its ability to reflect stress levels in various biological samples such as saliva, hair, and blood. Elevated cortisol levels, especially chronic stress, are associated with adverse health outcomes, including cardiovascular disease, metabolic syndrome, immune suppression, and neurocognitive impairment. Additionally, the rise in inflammatory cytokines, such as IL-6 and TNF-alpha, along with markers of oxidative stress like glutathione peroxidase, reflects the body's pro-inflammatory and antioxidant responses, further linking prolonged stress exposure to inflammation-related diseases and accelerated aging. The synthesis of existing studies on stress biomarkers reveals that chronic stress induces a cascade of physiological responses that impact multiple systems, not only through direct hormonal changes but also by disrupting immune balance and oxidative stress. This cumulative physiological toll underscores the need for reliable, non-invasive methods to assess stress biomarkers. Salivary and hair cortisol levels, in particular, offer promising approaches for evaluating chronic stress, providing an accessible way to monitor long-term HPA axis activation. Regular assessment of stress biomarkers could serve as an early warning system for individuals at risk of stress-induced health issues, supporting preventive measures to mitigate these risks. Future research should aim to refine the techniques for assessing cortisol and other biomarkers, explore the full range of immune and oxidative stress markers affected by chronic stress, and investigate interventions that might stabilize these biochemical responses. Interventions such as mindfulness, exercise, and pharmacological approaches have shown potential in modulating HPA axis activity and reducing inflammatory responses. Research on these interventions can help develop targeted strategies to counteract the physiological effects of stress. In conclusion, stress biomarkers provide a valuable tool in understanding and managing the health impacts of stress. Enhanced monitoring and intervention strategies based on these biomarkers may lead to improved health outcomes, particularly for those at high risk of stress-related disorders. By identifying stress-induced biochemical changes early, healthcare providers can play a

proactive role in managing stress to support both mental and physical well-being.

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