REVIEW

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Association between burnout and immunological and endocrine alterations

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Abstract

Background: Weather a psychological construct or a clinical entity, numerous studies have been focused on the biological link between stress, burnout, and biomarkers. *Aim*: The purpose of our study was to search the existing literature and summarize the immunological and endocrine alterations found in burnout patients and, also, to provide updated data for clinicians to use. *Methods*: We performed a literature search in *PubMed* database using specific terms. *Results*: The primary focus of the literature seems to be the hypothalamic–pituitary–adrenal (HPA) axis, which may be affected due to chronic stress, which can be investigated by measuring hormonal responsiveness [corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, prolactin, thyroid hormones]. An important challenge that this field is faced with is the pulsatile and diurnal fluctuation of them, which may not always be considered and the heterogeneity of burnout measurements. Many studies have explored the linking pathways between the immune system and chronic stress, but only a few have specifically evaluated this process for future diagnostic or prognostic biomarkers. *Conclusions*: Burnout has cumulative effects on our body and stress does not affect us in a singular direction, on the contrary, significant clinical implications are found, not only microscopic, but affective symptoms leading to anxiety and depression.

Keywords: burnout, stress, immunology, endocrinology, depression, anxiety.

Introduction

The systematic research of burnout originated in the works of Freudenberger & Maslach, who described it as "the extinction of motivation or incentive, especially where one's devotion to cause or relationship fails to produce the desired results" [1]. Although not classified by International Classification of Diseases, 11th edition (ICD-11) as a medical condition, burnout is described as an "occupational phenomenon" with the potential to substantially influence the health status [2]. The *World Health Organization* (WHO) describes burnout as having three dimensions (emotional exhaustion, increased feelings of negativism towards one's job/depersonalization, and reduced efficacy/reduction of personal accomplishment). These phenomena are regarded in an occupational context, therefore it should not be used in another areas of functioning [3]. In this sense, many studies describe clinical patients with clear symptoms of burnout in populations with long-term exposure to stress and insufficient recovery [4, 5].

From a physiological point of view, whenever individuals face stressful situations, the endocrine system reacts through a hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–pituitary–thyroid (HPT) axis, accompanied by a distinct immunological response and secretion of anabolic or catabolic hormones [4]. These reactions are experienced differently in each individual faced with prolonged stress, in accordance with their personality, life experiences, and various other psycho-social variables [6]. Systematic attempts have been made to isolate biological markers specific to burnout, most of them being focused on the HPA axis using salivary cortisol awakening response and cortisol diurnal secretion [4]. In this respect, adrenocorticotropic hormone (ACTH) plays a dual role, as it may exert pro-inflammatory effects [*via* stimulation of interleukin-6 (IL-6), myeloperoxidase and homocysteine secretion, with a damaging effect on brain structures], but it also may stimulate the release of dehydro-epiandrosterone (DHEA) (which enhances the antioxidant system and prevents the formation of atherosclerosis) [7, 8]. A summary of these immuno-endocrine changes can be found in Table 1.

Table 1 – ***Biomarker detection in stress and burnout***

No.	Biomarker	Detection method	Origin	References
1.	Cortisol	Salivary Blood Hair	Hypothalamus (CRH)–pituitary (ACTH)–adrenal glands (Cortisol)	[9–31]
2.	CRH	Blood	Hypothalamus	[32]
3.	ACTH	Blood	Pituitary gland	[4, 33]
4.	DHEA	Blood	Hypothalamus (CRH)–pituitary (ACTH)–adrenal glands (DHEA)	[3, 8, 12, 34]

No.	Biomarker	Detection method	Origin	References
5.	BDNF	Blood	Endoplasmic reticulum from dense core vesicles localized in hippocampus, basal forebrain, and cortex	[11, 35]
6.	Thyroid hormones	Blood	Hypothalamus (TRH)–pituitary (TSH)–thyroid gland (T3, T4)	[3, 36–38]
7.	Prolactin	Blood	Pituitary gland	[39, 40]
8.	Serum S100B	Blood	Astrocytes and oligodendrocytes	[41]
9.	CRP	Blood	Micro-inflammation	[42]
10.	TNF-*α*	Blood		[43]
11.	IL	Blood		[3, 34, 42-47]

ACTH: Adrenocorticotropic hormone; BDNF: Brain-derived neurotrophic factor; CRH: Corticotropin-releasing hormone; CRP: C-reactive protein; DHEA: Dehydroepiandrosterone; IL: Interleukin; T3: Triiodothyronine; T4: Thyroxine; TNF-*α*: Tumor necrosis factor-alpha; TRH: Thyrotropin-releasing hormone; TSH: Thyroid-stimulating hormone.

Therefore, for this narrative review, we conducted an extensive literature search in the *PubMed* database from 1999 to 2021. The search was performed in May 2021, using the following terms: 'endocrine', 'endocrinology', 'immune', 'immunology', 'cortisol', 'CRH', 'ACTH', 'thyroid', 'inflammation', 'HPA axis', 'hormone', 'biomarker', 'dopamine', 'prolactin', cross-referenced with 'burnout'. We selected only articles based on human studies and written in English.

Cortisol

The assessment of the HPA axis function is the most common and sensitive method to reveal alterations in the physiological reaction to stress [9, 33, 48, 49]. In this sense, most studies originally used cortisol as a marker, but obtained inconsistent results, caused by its large circadian, as well as diurnal variations [9–11]. It is widely known that cortisol levels have an inter-individual, intra-individual variability. Cortisol can be higher when individuals' experiences are more negative and lower when they are less negative in comparison to their mean level, therefore, cortisol measurement studies have reported both higher, lower, and unchanged cortisol levels in the morning. These heterogeneous results can lead to the wrong conclusion that no relationship exists between the two [12–14].

Studies designed to investigate HPA dysregulations in burnout patients often used measurement of salivary cortisol (since awakening represents an endogenous HPA stimulation) and/or Dexamethasone (DEX) test [10, 11]. Some indicate a gender specific neuroendocrine profile in males with evidence of HPA axis hyporeactivity [15]. Grossi *et al.* (2005) divides the included subjects in the study by levels of burnout (low, moderate, and high) and compares morning salivary cortisol response at +15 minutes, +30 minutes, and +60 minutes after awakening and the most significant differences have been found between the highest levels of burnout and the lowest at +15 minutes and +60 minutes [16]. Lower evening values were reported by Osterberg *et al.* (2009) and reflecting the impact of lower everyday demands in the evening [17]. A study dated back in 1999 on teachers concluded that high levels of burnout are associated with blunted levels of cortisol during the first 60 minutes after awakening two days consecutively and increased suppression of cortisol after DEX (0.5 mg) the third day. Also, patients with the highest burnout scores have had the most bodily complaints and lowest self-esteem [18], difficulties of falling asleep and early awakenings [19]. This evidence of low cortisol is consistent with later findings [10, 12, 15, 20–22, 33]. Studies using DEX in a very low dose (0.25 mg) showed altered HPA axis sensitivity in higher burnout and vital exhaustion with stronger cortisol suppression [23]. Marchand *et al.* (2013) analyzed burnout subtypes (the three dimensions) and saliva samples from awakening, +30 minutes, 1400 hours, 1600 hours, and also at bedtime on workdays, but also repeated in leisure days for comparison and found that emotional exhaustion showed consistent negative cortisol association in afternoon and evening [24]. Another longitudinal study showed that levels of cortisol after awakening were positively associated with the exhaustion level and negatively associated with the change in the exhaustion scale over time [23]. Thus, awakening cortisol was positively associated with exhaustion [21, 25].

Since burnout is described as job-related chronic stress, some studies have focused their attention on the comparison of working and leisure time, identifying different patterns between the two. In a study by Söderström *et al.* (2006), the burnout group showed high awakening cortisol during workdays, compared to the weekend. A high frequency of arousal during sleep has been associated with high amplitude of cortisol during the daytime. These findings indicate that multiple sleep fragmentation due to arousals and awakening time influences cortisol. The comparison between workday and day off cortisol profiles has shown the importance of relaxation during leisure time, since the burnout group proved not to be able to recover during the weekend [26].

Taking into consideration that obtaining a long-term assessment of cortisol levels from blood or saliva has its limitations, newer research has discussed the hair analysis of this hormone (normally incorporated in the growing hair). This would provide a retrospective reflection of cortisol secretion in the past months. Based on this, researchers have commenced utilizing this method to answer questions on the changes in hair cortisol in different stress conditions and across time [13, 27–31]. Penz *et al.* (2018) found hypercortisolism in patients with burnout symptoms suggesting an increase in the basal glucocorticoid secretion in chronic stress [29]. These findings are similar to a cross-sectional study for parental burnout showing that their levels of hair cortisol were twice as high as the control group [30]. A recent populational study on healthcare workers during the coronavirus disease 2019 (COVID-19) pandemic evaluated stress and burnout and used hair cortisol concentration as a biomarker reporting that 40% of the investigated population presented abnormal values with a direct correlation between hair cortisol and emotional exhaustion [31].

Corticotropin-releasing hormone (CRH)

Since CRH is the one that stimulates the production of ACTH, recent studies have investigated the link between CRH or ACTH and burnout. For instance, CRH receptor 1 (*CRHR1*) gene codes a protein coupled with the receptor that binds CRH and the genetic variation of it have been associated with cortisol reactivity to stress. In fact, individuals with *AA* genotype of *CRHR1* have higher work stress susceptibility. He *et al.* (2019) reported that the same gene increases the emotional exhaustion and depersonalization dimensions in burnout [32].

Adrenocorticotropic hormone (ACTH)

Another level of investigating hypocortisolism in burnout patients is plasma ACTH level measurement. Since differences in the production of cortisol are easier to detect when we are testing the reactivity and not the resting levels, Lennartsson *et al.* (2015) exposed patients to a psychosocial stressor and in addition to the lower cortisol response in high burnout patients, they also reported lower ACTH response indicating that the cortisol level is not due to adrenal desensitization [33]. Plasma cortisol response was investigated in a group of healthy individuals after synthetic ACTH administration and it was related to emotional exhaustion, but not with the overall burnout score [4].

Dehydroepiandrosterone (DHEA)

Another physiological reaction to stress includes the release of anabolic hormones. Although few studies have focused on them, the most studied is DHEA [3, 8, 12, 34]. The level of DHEA peaks in adulthood, therefore studies correlating the hormone with clinically diagnosed patients have divided their search into age groups. Specifically, in the youngest groups presenting clinically diagnosed burnout (25–35 years), DHEA has been found to be much lower than in the control group. The shift in growth levels of this hormone could be caused by the effect of prolonged stress (in which case steroid synthesis may be focused on corticosteroid pathways for the secretion of cortisol [8].

Thyroid hormones

With exhaustion being one of the dimensions of burnout, all hormones involved in the mobilization of energy have been studied. The HPT axis stimulates the secretion of thyroid-stimulating hormone (TSH) with the production of thyroid hormones [triiodothyronine (T3), thyroxine (T4)]. Prolonged stress causes this axis to be less active, with significantly lower levels of hormones. This effect is higher in women, with significantly lower TSH and T3 levels as the result of high perceived stress. A cause for the low number of studies regarding the link between burnout and the thyroid gland dysfunctions might be the overlapping symptoms between the two [3, 36–38].

Dopamine and prolactin

The dopaminergic system controls energy expenditure, the vigorousness of responding and cognitive control functions (*e.g.*, the D2 receptors blockade can lead to fatigue), thus, burnout signs and symptoms suggest a decrease in dopaminergic function. Normally, dopamine secretion inhibits prolactin release, but in such cases where burnout occurs and the former hormone is decreasing, the latter one is increased. Studies found that treatment with cortisol normalizes the prolactin levels in subjects that scored high on attachment and in the burnout group by increasing the dopaminergic activity. The high basal prolactin levels or the reactivity of it may be the result of reduced dopamine levels, which increases D2 receptor sensitivity [39].

Elevation of prolactin levels are reported is acute stress with inter-individual differences by gender (since estradiol enhances the production of prolactin). All things considered, there have been studies investigating the levels in men diagnosed with burnout. Lennartsson *et al.* (2014) reported higher prolactin levels in male patients with burnout, but not in women [40].

The new research in the field of biomarkers has proven their practical usefulness for patients undergoing treatment using voltametric techniques for rapid determination of active compounds of pharmaceutical formulas [L-3,4-dihydroxyphenylalanine (L-DOPA) and Benserazide] [50] or a selective determination of dopamine in biological samples containing ascorbic acid [51].

Brain-derived neurotrophic factor (BDNF)

The increase in the HPA axis activity as a reaction to stress can lead to the hippocampal neurogenesis suppression, therefore, BDNF has been studied in conditions like depression and anxiety. Chronic stress can inhibit the feedback of the HPA axis, causing a decrease of the BDNF with impaired neurogenesis and eventual neuronal atrophy [35].

The review of the literature indicated a relationship between the limbic system and burnout. More specifically, chronic stress can produce neuroendocrine alterations (especially in the HPA axis) with some changes in the size and volume of brain structures (the limbic system) [52, 53]. Neuroimaging might show atrophy caused by the inhibition of control pathways in the HPA axis [54].

Onen Sertoz *et al.* (2008) conducted a study with 37 burnout patients investigating the role of BDNF and HPA axis. Firstly, the burnout group had lower BDNF levels than the control group (although there was no assessment of the sleep quality since it can also decrease BDNF; secondly, gender comparison revealed that female patients had lower BDNF and were more depressed [11].

Burnout, anxiety, depression and inflammation

Emotions hardly ever occur isolated. Burnout, as well as anxiety and depression following stress exposure, might concur and be accompanied by biological changes [55, 56]. However, these biological changes may remain discrete. Literature studies have described cases in which burnout syndrome, depression and anxiety were the only clinical expressions of organic causes such as cerebral tumors [57, 58]. In such situation, where somatic comorbidities are associated with feelings of guilt and shame, the syndrome might be aggravated [59].

In a longitudinal analysis of salivary cortisol concentration, the results showed that participants with high cortisol or a steep slope (morning to evening) had lower risk of developing depression two years later but considering the mean duration of a depressive episode (3–12 months), we cannot exclude the possibility that some participants developed and recovered from depression during the two-year gap [60].

Serum S100B is a protein that can be identified in and released by astrocytes and oligodendrocytes. It is both a growth and a differentiation factor linked with mood disorders. Postmortem studies investigating the histopathology of the brain in patients with mood disorders show a reduction of astrocyte density. Gulen *et al.* (2016) reported that S100B levels had a strong correlation with scores of depression and exhaustion [41].

There are a few studies that focused their search on immunological changes in burnout; however, chronic stress has been shown to alter levels of cytokines [3, 42–47]. Studies found a connection between burnout and high tumor necrosis factor-alpha (TNF-α) (anti-inflammatory cytokine) levels and decreased interleukin-4 (IL-4) (pro-inflammatory cytokine) levels, which suggests that chronic stress can influence both inflammatory cytokines [43]. The analysis of 167 patients in the study of von Känel *et al.* (2008) showed that high levels of burnout predicted higher TNF-α and lower IL-4 [43]. These findings suggest that not only was burnout associated with increased pro-inflammatory activity, but also with decreased anti-inflammatory activity. After comparing 56 burnout patients using endocrine and immune variables, Mommersteeg *et al.* (2006) concluded that interleukin-10 (IL-10) was increased compared to the control group, which could signify that vital exhaustion experienced by those patients is increasing the pathogen burden [34].

A study from 2005 showed that burnout and anxiety in women are linked with micro-inflammation [high fibrinogen and C-reactive protein (CRP)] [42]. Research suggests that in anxiety there is an active effort to cope with the stressful situation, whereas in depression the lack of resource mobilization is paramount [29, 42, 55].

All in all, the effects of burnout are severe and to keep employees in a healthy psychological environment, educational intervention need to occur in the workplace and general awareness of the consequences of job stress needs to be increased. Firstly, monitoring stress (work or personal) could be added to the regular health checks for primary prevention. Secondly, solutions to reduce stress at the workplace or during leisure time should be taken into consideration. Thirdly, persons affected by burnout would benefit from psychological interventions individually or in a group *via* psychotherapy or counseling, or at the organizational level [61, 62].

Conclusions

One challenge for future research consists in identifying which symptoms are associated with HPA dysregulation, thus making the studies more conclusive by reducing the search to smaller and more defined groups. The results of this study show that burnout has cumulative effects on our body and that stress does not affect us in a singular direction with significant clinical implication, not only microscopic, but affective symptoms leading to anxiety and depression. Our results indicate the possible changes that burnout can induce in neuroendocrine and immune pathways (especially the HPA axis), with alterations in size and volume of the brain.

Conflict of interests

The authors declare that they have no conflict of interests.

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