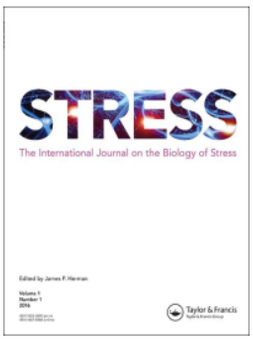

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REVIEW

Measuring stress: a review of the current cortisol and dehydroepiandrosterone (DHEA) measurement techniques and considerations for the future of mental health monitoring

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ABSTRACT

Psychological stress and its inevitable trajectory toward mental health deteriorations such as clinical and major depression has become an unprecedented global burden. The diagnostic procedures involved in the characterization of mental illnesses commonly follow qualitative and subjective measures of stress, often leading to greater socioeconomic burdens due to misdiagnosis and poor understanding of the severity of such illnesses, further fueled by the stigmatization surrounding mental health. In recent years, the application of cortisol and stress hormone measurements has given rise to an alternative, quantifiable approach for the psychological evaluation of stress and depression. This review comprehensively evaluates the current state-of-the-art technology for measuring cortisol and dehydroepiandrosterone (DHEA) and their applications within stress monitoring in humans. Recent advancements in these fields have shown the importance of measuring stress hormones for the characterization of stress manifestation within the human body, and its relevance in mental health decline. Preliminary results from studies considering multimodal approaches toward stress monitoring have showcased promising developments, emphasizing the need for further technological advancement in this field, which consider both neurochemical and physiological biomarkers of stress, for global benefit.

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Cortisol; stress hormones; stress monitoring; mental health; depression; cortisol/DHEA ratio; psychological stress; DHEA

1. Introduction

Mental health and specifically, clinical depression can be monitored using various techniques, which can be categorized into physiological monitoring and biochemical signal analysis. Biochemical biomarkers monitoring can facilitate the understanding of underlying neurobiological processes involved in several mental illnesses (McGorry et al., 2014), such as clinical depression and bipolar disorder, as well as neurological diseases, for example, Alzheimer's disease and dementia (Farah et al., 2018). The monitoring of specific biomarkers aids in the early detection and diagnosis of mental illnesses as well as simplifying the observation of illness progression (Farah et al., 2018). Clinical depression and major depressive disorder (MDD) are both highly associated with endocrine and metabolic dynamics (Schmidt et al., 2011). Intervention and deliberate influences on these factors often contribute to the treatment of this mental illness e.g. through use of antidepressants (Schmidt et al., 2011). Therefore, the observation of the endocrinology and metabolic markers is essential for the comprehension of psychological stress, its relationship to depression and the progression and treatment of the debilitating psychiatric disorder (Romero & Butler, 2007).

Psychological stress is often associated with fluctuations of stress hormones, such as cortisol and adrenaline (Tsigos & Chrousos, 2002). Cortisol is the primary stress hormone that is involved in governing the stress response from the moment of stress elicitation to recovery from stressful events. Alternatively, DHEA is a steroid hormone that has proven to express anti-glucocorticoid properties (Gallagher & Young, 2002). As two steroid hormones with inverse actions, the relationship between cortisol and DHEA is of great interest. The antagonistic relationship between cortisol and DHEA has been discussed at length in regard to their opposing actions on immune function, however, the relationship between cortisol and DHEA in stress management is seldom discussed (Buford & Willoughby, 2008). DHEA is primarily implicated in aging research, whereby an increase in cortisol/DHEA ratio can be a contributing factor of age-related declination in immune function (Buford & Willoughby, 2008). Evidently the biochemical interactions between cortisol and DHEA have proven to be of great importance in the determination of declining functions of biological systems. Therefore, observing the changes in these biomarkers with respect to stress and mental health monitoring could unveil vital details regarding stress management and mental health.

The key aims are to review the existing state-of-the-art technology comprehensively in the field of cortisol and dehydroepiandrosterone (DHEA) measurement and their applications within stress monitoring, whether it is in settings

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involving healthy participants or clinically depressed patients. Previous reviews within this field have focused primarily on the applications of cortisol monitoring for stress, albeit the importance of DHEA is seldom elaborated upon. Thereby, this review will consider the magnitude of DHEA in stress studies and discuss the strengths and shortcomings of measuring such stress biomarkers and whether it can impact the current perspective of mental health monitoring. The review will involve the evaluation of stress studies which focus on cortisol and DHEA measurements in various mediums, as well as its relationship with mental illnesses, primarily major depression. Stress studies include a broad set of studies involving either stress reactivity or chronic stress observations within adult populations. A broad set of stress studies were included to further comprehension regarding the cortisol/DHEA ratio and its implications in different modalities of stress.

2. Methods

The purpose of this review is to evaluate studies which have focused on the measurement of cortisol and DHEA, in different mediums e.g. saliva and plasma, simultaneously to comprehend the biochemical characteristics of psychological stress, and its trajectory to the manifestation of major depression. English-language articles were obtained from SCOPUS and PubMed databases. They were selected based on the search criteria of inclusion of specific words in their title, abstract or keywords. The searching criteria comprised of two fixed terms: ((“Cortisol”) AND (“DHEA”)), alongside two independent terms to obtain articles focusing on healthy subjects as well as depressed patients: (“Stress” OR “Depression”). Additional articles that were related were selected through reference lists and the “related articles” feature on SCOPUS and PubMed. After removal of duplicates, a total of 437 papers were obtained. Following the reading of paper abstracts, 98 papers were selected for further reading. The review focuses on the biochemical monitoring of psychological stress, therefore the most relevant papers that matched these criteria were selected. Ultimately, 31 papers were chosen for complete evaluation in this review. Figure 1 depicts a flow chart of the searching and selection process that was conducted for this review. Non-human studies were excluded from this review as the human stress response and stress hormones differ from other animals therefore the evaluation of animal studies would not be beneficial in the evaluation of stress biomarkers and the existing measurement techniques. Due to the implications of DHEA in aging function, the studies that were chosen for this review focus primarily on adults. Furthermore, papers involving participants with comorbid depression and other mental illnesses were excluded as these mental illnesses often have different and far more complex characteristics in stress hormone regulation which do not match the processes involved in acute or chronic psychological stress, nor major depression. The selection process was conducted by the primary author, upon shortlisting of articles a dual review was conducted with defined exclusion criteria to ensure minimization of bias and subjective errors. Exclusion criteria is noted in Figure 1. Various studies were selected for review, including cross-sectional case

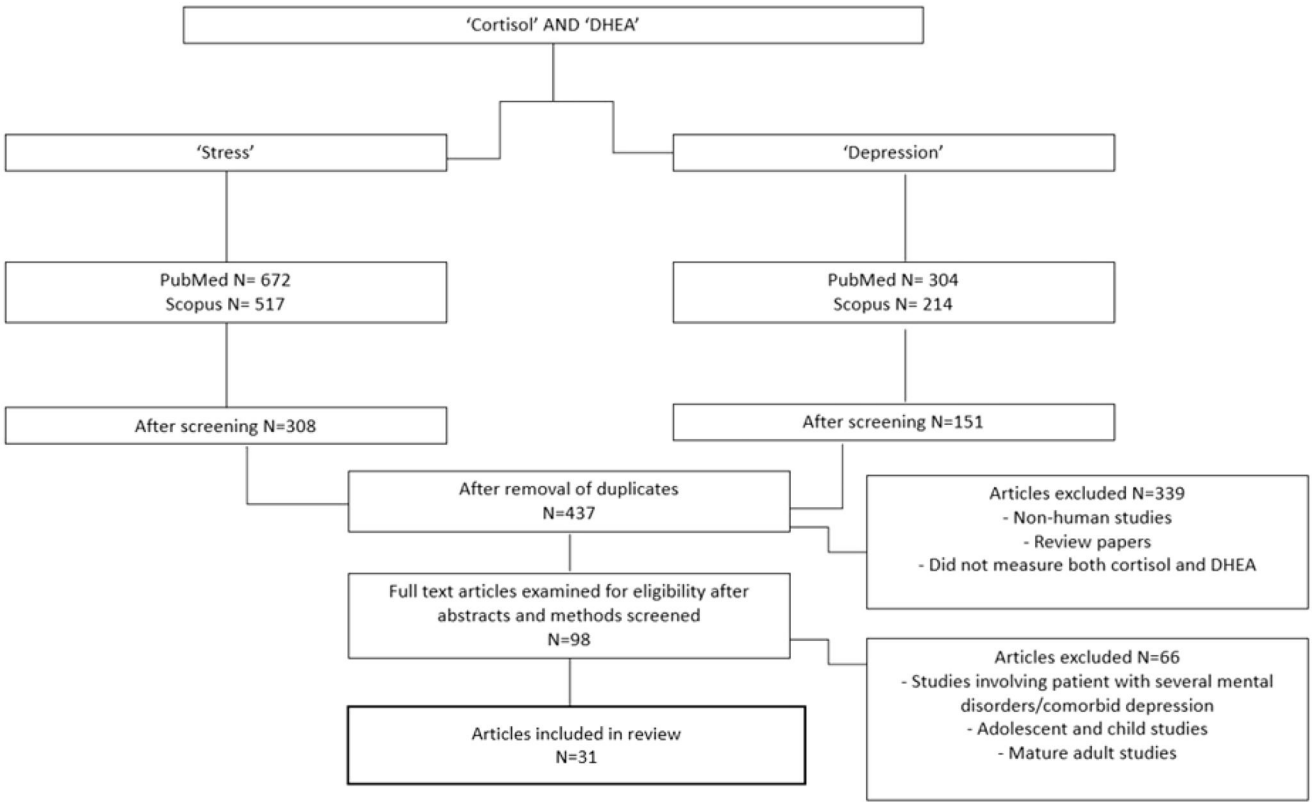

Figure 1. Flow chart of article selection process for comprehensive review of cortisol and DHEA monitoring for stress and depression.

control studies, randomized controlled trials and pilot studies. To ensure quality of the review was maintained, studies with lower sample sizes are explicitly mentioned in Table 1.

3. Cortisol and DHEA as biomarkers for stress and depression monitoring

Stress is characterized by the biological or physiological action that occurs in response to a stressor i.e. environmental conditions, external stimuli, biological agents that interrupt homeostasis (Evans, 1950). Upon perception of a stressor, a response (mediation or modulation) is generated through a course of circuits and pathways which are activated depending on the classification of the stressor, i.e. physiological or psychological (Kovács et al., 2005; Shors & Horvath, 2001). Historically, stress has been described through the general adaptation syndrome (G.A.S.), which encompasses the emergency responses of the parasympathetic nervous system and the adrenocortical system (Evans, 1950; Mcewen, 2005).

The general adaptation syndrome comprises of three stages: the alarm reaction; the resistance and the exhaustion stage. Immediately upon the body's perception of a stressor, the alarm reaction is triggered, i.e. the stress response or "fight or flight" response. The stress response is responsible for several physiological and biochemical changes in the body, to restore homeostasis (Mcewen, 2005). Once triggered, catecholamines (adrenaline and noradrenaline) are released into the bloodstream via the sympathetic-adrenal-medullary (SAM) axis for mobilization of energy required for the "fight or flight" responses (Juster et al., 2010; Romero & Butler, 2007). In parallel, corticotrophin-releasing hormone (CRH) is released from the hypothalamic-pituitary-adrenal (HPA) axis, which subsequently leads to the synthesis and release of glucocorticoids, such as cortisol, into the bloodstream (Sapolsky et al., 2000; Schmidt et al., 2011). As a result of the biochemical responses, there are several physiological changes that occurs, such as an increase in heart rate and blood glucose levels, muscular tension and perspiration (Charmandari et al., 2005; Evans, 1950). Furthermore, there are adaptive redirections of behavior such as increased arousal and alertness and, focused attention (Charmandari et al., 2005). These characteristics and responses contribute to the restoration of homeostasis interrupted by a short-term stressor.

In the resistance/maintenance stage, the body continues to activate afferent pathways in a series of allostatic mechanisms, leading to further physiological changes with increased metabolic activity, to restore balance in the organism from the perceived stress (Juster et al., 2010; Mcewen, 2005). In cases of persistent stressors, i.e. chronic stress, the exhaustion stage is reached wherein the energy and resources for prolonged adaptive responses to the stressor are depleted thus, efforts are ceased (Evans, 1950; Mcewen, 2005; Romero & Butler, 2007). Deterioration and "wear and tear" of the body, known as allostatic overload, can lead to immunosuppression, development of metabolic diseases e.g. diabetes and, progression of clinical depression or major depressive disorder (MDD) (Jefferies, 1991; Juster et al., 2010; Mcewen, 2005).

3.1. Cortisol

Cortisol is often considered the key logical indicator of stress and, in many cases, depression is characterized by the stable and sustained elevation of cortisol levels (Monroe, 2008; Schmidt et al., 2011). Hypercortisolaemia and reduction of the cortisol awakening response are characteristics of depression. These qualities are often monitored in the assessment of biomarkers of HPA axis activity and for neuroendocrinal analysis of depression and major depressive disorder.

Additionally, in studies where cortisol levels are monitored during treatment of first-episode psychosis, it was found that a decline in cortisol and cortisol/dehydroepiandrosterone sulfate (DHEAS) ratio directly correlated to an improvement in depressive and psychotic symptoms (Garner et al., 2011). As the most common HPA biomarker associated with depression, cortisol and its relationship with dexamethasone suppression is considered a promising neuroendocrine marker for analysis of treatment response, albeit not robust for clinical applications (Strawbridge et al., 2017).

The implication of cortisol level dynamics on the depressive symptoms of psychosis and other mental illnesses showcases that cortisol is a critical factor in the development of several mental illnesses, especially those involving depressive and negative symptoms (Knight et al., 2010). Thus, cortisol can be considered as the ideal biomarker for analysis and clinical staging in psychiatry (McGorry et al., 2014). The dexamethasone suppression test is categorized as the most promising neuroendocrine marker for treatment response in depression, although is it not considered robust for clinical applications (Strawbridge et al., 2017). In the dexamethasone test, post administration of dexamethasone resulting in non-suppression of cortisol translates to a lower likelihood of remission of the illness, post-treatment. Dysfunction in neuroendocrine hormone function is regularly associated with depression, specifically the dynamics of the hypothalamic pituitary adrenal (HPA) axis, is considered the primary contributing factor to the development of depression via endocrinal means (Stephens et al., 2014). Thus, the necessitation of further analysis of cortisol and a plethora of other potential biomarkers can facilitate greater comprehension of major depressive disorder and associated psychiatric illnesses (Strawbridge et al., 2017).

HPA activity leads to the release of neurohormones, such as CRH into general circulation (Schmidt et al., 2011). This triggers a hormonal cascade in which ACTH is released, which induces glucocorticoid synthesis and secretion of glucocorticoids into circulation. The central nervous system (CNS) and the endocrine system are tightly interconnected to coordinate glucocorticoid activity (Stephens et al., 2014). After a stressful event activates the HPA axis, the increase of cortisol and other glucocorticoids facilitate the body's recovery from the stressor (Gjerstad et al., 2018). Cortisol regulates its secretion through a negative feedback mechanism involving the activation of the glucocorticoid receptor in the anterior pituitary gland. This mechanism is necessary to eliminate the HPA axis response to stress, i.e. to aid the body's recovery from the stressor, as well as the maintenance of optimal

Table 1. Studies involving the measurement of cortisol and DHEA for stress and psychological evaluation in depressed and non-depressed groups.

Author	Year	*N* (Number of Participants)	Age in years (mean±*SD*)	Aim	Methods	Major findings/limitations
Asadikaram, G. (Asadikaram et al., 2019)	2019	79 MDD patients, 71 healthy controls	36.1 ± 16.6 (MDD); 34.5 ± 19.8 (Controls)	Analyze differences in hormonal alterations between healthy participants and MDD patients.	Cortisol, ACTH, Testosterone, TSH, DHEA-S, T4, T3, FT4I, T3RU were evaluated via blood samples under fasting conditions between 7 and 8 am using ELISAs. MDD confirmed through clinical interview.	Patients with other mental illnesses e.g. bipolar disorder were excluded. Depressed patients had substantially decrease in TSH, increase in FT4I compared to matched controls. ACTH levels were also higher in MDD patients. DHEA-S differences between healthy men and women were found but there were no differences between MDD and HC. MDD patients had considerably higher cortisol/DHEA-S ratio compared to HC. MDD testosterone was lower than HC. Small sample size, sex differences, blood sampling.
Assies, Johanna (Assies et al., 2004)	2004	13 MDD, 13 healthy controls	39.8 ± 11.3 (MDD) 40.7 ± 10.1 (Controls)	Measurement of salivary DHEAS and cortisol in MDD patients vs healthy controls	Salivary morning and evening DHEA-S and cortisol levels measured via ELISA. DSM-IV for MDD evaluation.	All depressed patients were medicated. No differences in cortisol levels between patients and controls. DHEA-S levels were elevated in MDD medicated patients vs healthy controls. It is possible that treatment may have normalized HPA axis dysfunction. DHEA-S levels may more adequately reflect 'state-related' HPA axis dysregulation than cortisol. Small sample size and only one day study.
Bae, Yoon Ju (Bae et al., 2019)	2019	33 TSST, 34 placebo (control)	18–35	Determine which stress biomarker had highest discriminatory power amongst groups of healthy males undergoing a stress test vs a placebo/control	67 healthy male participants, 33 of which completed TSST, 34 completed placebo TSST. Blood and saliva collected at 14 time points along with STAI and HR. Serum steroids, salivary cortisol and alpha amylase were analyzed using LC-MS/MS, chemiluminescent immunoassays, intraassay and enzymatic colorimetric testing.	Salivary cortisone had highest discriminatory power 10 mins after peak salivary cortisol and meaningful correlations with subjective and autonomic stress measures. Salivary cortisone is superior surrogate marker for serum free cortisol compared to salivary cortisol due to irreversible conversion from cortisol to cortisone in saliva. Only tested stress response in healthy males.
Boudarene, M (Boudarene et al., 2002)	2002	40 subjects	42 ± 12 years	Define relationships between biological and physiological aspects of stress response.	Stressed out participants but not mentally ill were asked to complete cognitive tasks with audio-visual cues. Amiel Lebrige questionnaire was filled as well as STAI. Serum cortisol and DHEA measured using radioimmunology and radio-immunoassays.	Most subjects had high STAI scores and life events impact. 25 subjects exhibited high level of STAI. 11 subjects had increase in cortisol plasmatic concentrations. Close correlation between DHEA and cortisol concentrations suggesting antagonistic relationship between the two hormones. High level of anxiety associated with increase in cortisol, low anxiety correlates to exclusive rise of DHEAs. Low sample size.
Cutshall, S.M. (Cutshall et al., 2016)	2016	21 female subjects	30–55	Assess the efficacy of functional medicine approach to improving stress, energy, fatigue, digestive issues and QoL in women	Measured salivary DHEA and cortisol via commercial salivary test kits.	Cortisol/DHEA ratio increased considerably from the beginning to the end of the study. Shows possible reversal of HPA dysregulation. Mean salivary DHEA levels also increased and SF pain subscale scores decreased. Small sample size, multiple intervention methods were applied.
Du, C.-L. Chung-Li C.-L. Chung-Li (Du et al., 2011)	2011	63 city bus drivers and 54 staff		Validation of physiological stress biomarkers.	24-h urine cortisol testing and blood draws for DHEAs.	Elevated cortisol level was associated with worker's relationship with supervisor and life changes in recent 3 months. DHEAS levels were higher in drivers of young age and in drivers with more concerns relating to their salary and bonuses. Non-drivers showed no association between urine cortisol and blood DHEA levels. Serum cortisol should have been taken. A standardized stress test was not used, subjective understanding of stress.
Ebrahimpour, Z. (Ebrahimpour et al., 2011)	2011	10 female volleyball players	21.44 ± 1.13	Determine levels of salivary cortisol and DHEA in response to competition.	Salivary cortisol and DHEAs samples were collected 5 and 30 min before the match, between the sets and immediately and 30 min after the	No substantial differences between DHEA concentrations and salivary cortisol. Slight increase in salivary cortisol during middle of the match but it was not statistically significant. Cortisol concentration increases more drastically during loss versus win in amateur players. Small sample size.

(*continued*)

Table 1. Continued.

Author	Year	*N* (Number of Participants)	Age in years (mean±*SD*)	Aim	Methods	Major findings/limitations
					match, for 2 matches. ELISA used for concentration determinations	
Ge, Fiona (Ge et al., 2016)	2016	218 couples	28.4	Investigated the extent to which individual differences in HPA axis activity are associated with depressive symptoms among newlywed couples	Five saliva samples provided before and after discussion of major areas of disagreement in relationship. Samples assayed for cortisol and DHEA-S concentrations. Depressive symptoms assessed initially and 19, 37 months later with IDS-SR	Concordant levels of cortisol and DHEAS were concurrently and prospectively associated with higher depression scores. This effect was observed for wives only. Study was correlational so cannot determine whether differences in HPA axis functioning led to depressive symptoms.
Ghiciuc, Cristina (Ghiciuc et al., 2011)	2011	102 healthy males		Investigate presence of awakening response for various salivary biomarkers of adrenocortical activity including DHEAs, alpha amylase and cortisol	Saliva was collected upon waking and 15, 30, 45, 60 min afterwards and then at 8 pm.	Salivary alpha amylase and DHEAS also produce awakening responses, similar to cortisol. Salivary cortisol and alpha amylase have opposite diurnal fluctuation patterns, Salivary cortisol and DHEAS represent HPA whereas alpha amylase represents sympathetic activity. Cortisol and DHEAS concentrations are inversely correlated to alpha amylase levels.
Grillon, C. (Grillon et al., 2006)	2006	30 healthy male and female participants		Investigate relationship between cortisol/DHEAS ratio and fear-potentiated startle	30 subjects participated in differential aversive conditioning experiment with one of two stimuli (shock or no shock). Conditioned Responses were assessed with startle reflex. DHEAS and cortisol levels assayed from blood samples collected at baseline and after aversive conditioning session. State anxiety also assessed throughout testing.	Fear potentiated startle was higher in individuals with high/low cortisol/DHEA ratio. Multiple regression analysis showed that fear potentiated startle was positively associated with cortisol and negatively associated with DHEAS. No meaningful correlation between DHEAS and cortisol levels.
Heuser, I. (Heuser et al., 1998)	1998	15 male MDD patients, 11 female MDD patients, 22 healthy males, 11 healthy female volunteers	47.7 ± 14.8 (MDD males); 48.2 + − 18.1 (MDD females); 53.1 + − 18.2 (healthy males); 47.9 + − 21.6 (healthy females)	Studied differences in diurnal plasma concentrations of DHEA in depressed patients vs healthy controls	Studied 24 h DHEA plasma concentration in severely depressed patients and controls. Depressed patients were included after assessment using DSM-3-R and Hamilton Depression Scale.	Depression increases diurnal minimal and mean DHEA plasma concentrations but has no effect on diurnal maximal plasma concentrations or amplitude of DHEA. Novel finding of parallel increases in diurnal DHEA and cortisol plasma concentrations in depressed patients.
Irshad, Lylah (Irshad et al., 2020)	2020	58 healthy adults	18–35	Investigate impact of exam period stress on salivary free light chains alongside stress biomarkers	Saliva samples and questionnaires were filled during periods without exams to analyze baseline vs start of exam period. Saliva samples were assessed for FLCs, IgA, cortisol and DHEA.	Cortisol concentration substantially increased during exams. DHEA did not change, leading to increase in cortisol/DHEA ratio.
Izawa, S. (Izawa et al., 2008)	2008	33 male students	22.6+−3.6	Investigate DHEA secretion in response to acute psychosocial stress and relations of DHEA and cortisol, cardiovascular activity and negative mood changes.	33 participants were subjected to TSST, collections of saliva, BP measurements, HR and mood assessments were taken via visual analog scales. These were conducted before, during and immediately after the TSST.	Peak DHEA concentration preceded cortisol concentration by 10 min. Lower DHEA and elevated cortisol/DHEA ratio during TSST significantly correlated with increased negative mood during and after TSST. Indication that acute increase in DHEA concentration under stressful situations might be partly mediated by the activity of the HPA axis—could have some significance in improvement of negative mood.
Izawa, S. (Izawa et al., 2012)	2012	33 women	19.5+−3.3	Investigates variation in salivary levels of cortisol and DHEA in prolonged stressful situation (2-week teaching practice).	Saliva samples taken at awakening, 30 min after, and bedtime at 2 weeks before practice, first week of practice, second week of practice and few days after practice.	Linear mixed model indicated that cortisol levels considerably increase during the first and second week of the practice compared with those before and after the practice period. DHEA levels decreased after the practice period compared with those at the other time points. Cortisol awakening

(*continued*)

Table 1. Continued.

Author	Year	*N* (Number of Participants)	Age in years (mean±*SD*)	Aim	Methods	Major findings/limitations
					Completed questionnaires for perceived stress and subjective moods on each day. Cortisol and DHEA analyzed via enzyme immunoassays.	response reduced substantially compared to other time points of saliva collection. Perceived stress and mood scores were higher during practice period. Negative feedback of the HPA axis may cause diminished cortisol awakening response and lower DHEA levels after the stress period. Limitations: not enough saliva samples taken, nonstandardized stress test.
Jeckel, Cristina M Moriguchi (Jeckel et al., 2010)	2010	41 caregivers, 33 non-caregivers	60.56+−16.56 (caregivers); 60.27+−14.11 (non-caregivers)	Assessed neuroendocrine and immunological correlates of realistic chronic stress experience by strictly healthy caregivers of Alzheimer's disease and age-matched controls.	Salivary cortisol and DHEAS were assessed at multiple points by radioimmunoassay. Peripheral T cell proliferation and cellular sensitivity to glucocorticoids were evaluated by colorimetric assays.	Caregivers were drastically more stressed, anxious and depressed than controls. Similar cortisol levels between cohorts but caregivers had reduced DHEAS levels thus, increased cortisol/DHEAS ratio as well as impaired HPA axis response to DEX intake. Caregivers had higher T proliferation compared to controls.
Jozuka, H. (Jozuka et al., 2003)	2003	17 MDD patients, 10 controls	40.3+−15.1	Compared NK cell activity and blood levels of IL-2 to DHEA, DHEAS and cortisol in MDD patients vs healthy controls	Depression severity measured with Zung Self-rating depression scale. NK cell activity and IL-2 levels measured with chromium-51 release test and ELISA. Radioimmunoassay used to measure serum cortisol, DHEA and DHEAS.	NK cell activity and cortisol and DHEA levels were reduced in MDD patients compared with controls. IL-2 levels were increased. No differences in DHEAS levels. Reduction in NK levels and DHEA with increase in IL-2 is indicative of MDD.
Kim, M.-S. (Kim et al., 2010)	2010	74 participants	41.39+−10.22	Determine day-to-day differences in cortisol levels and molar cortisol/DHEA ratio in working subjects	Cortisol and DHEA levels measured from saliva samples via radioimmunoassay 30 min after awakening for 7 consecutive days.	Cortisol levels from samples collected after awakening on workdays were radically different from cortisol level on Sunday. DHEA levels were not much different between the days of the week. DHEA levels on Monday and Tuesday were relatively lower than the levels on the other weekdays with levels on Thursday and Friday being the highest. Cortisol/DHEA ratios on Sunday were lower than those on workdays. Limitations: Short testing phase of only one week. No subjective measures of state anxiety taken.
Lac, G. (Lac et al., 2012)	2012	41 subjects suffering from bullying vs 28 healthy controls	46.3+−8.45 (Bullied); 46.0+−10.4 (Controls)	Measure salivary DHEAS and cortisol in individuals suffering from bullying at work	Bullied subjects screened for mental distress and institute of occupational health. Conditions causing bullying were recorded. Hospital anxiety and depression scale, Beech questionnaire and Visual analog scale of stress used to determine psychological state. Saliva samples taken at awakening, 30 min and 60 min after awakening and every 2 h until bedtime. Cortisol and DHEA measured using commercial ELISA kits.	Bullied subjects had higher HAD scale scores, higher stress on the VAS and Beech questionnaire. Substantially higher salivary DHEA in bullied subjects but no meaningful differences between groups in cortisol levels at any time. Discrepancy probably arises from the stability and longer half-life of DHEA vs cortisol.
Laudenslager, Mark L M.L. (Laudenslager et al., 2013)	2013	31 healthy subjects	43.5+−12.4	Constructed convenient and novel collection device for collecting saliva for determination of cortisol and DHEA	Saliva collected four times a day on 3 consecutive days using filter paper collection device. Subjects were asked to provide saliva at awakening, 30 min after, before lunch and 600 min after awakening. Cortisol and DHEA were measured from filter paper using EIA kits	Cortisol and DHEA revealed diurnal declines in similar patterns. Subjects did not adhere to collection times so caused disparities in the results.

(*continued*)

Table 1. Continued.

Author	Year	*N* (Number of Participants)	Age in years (mean±*SD*)	Aim	Methods	Major findings/limitations
Lennartsson, A.-K. (Lennartsson et al., 2022)	2022	81 healthy subjects divided into low stress and high stress	20–50	Investigate the DHEA and DHEAS production capacity in relation to prolonged stress.	Participants underwent TSST. Blood samples drawn before, during and after the stress test. Concentrations of cortisol, DHEA and DHEAS measured via LC-MS/MS, radioimmunoassay and immuno-chemiluminescence assays.	High stress group had appreciably higher pretest cortisol to DHEAs ratio than low stress group. Higher perceived stress in previous month related to attenuated DHEAS response during acute psychosocial stress. Limitation—only categorized using one question regarding perceived stress.
Lennartsson, A.-K. (Lennartsson et al., 2012)	2012	20 men, 19 women	30–50	Study investigates effect of psychosocial stress on serum concentrations of DHEA and DHEAS in healthy subjects	Physiological measurements were performed before, directly after test and 30 min after recovery. Blood samples were analyzed via electrochemiluminescence assays, LC-MS/MS and radioimmunoassay for cortisol, DHEA and DHEAS respectively. Participants underwent TSST.	In both men and women, there was notably elevated DHEA and DHEAS in response to stressor. Large inter-individual variation in the magnitude of the response, especially for DHEA—no statistical difference between men and women. Magnitude of change in DHEA levels positively associated with magnitude of change in ACTH, cortisol and heart rate. Suggests capacity to secrete DHEA and DHEAS during acute psychosocial stress declines with age. Limitations—blood samples taken but there were only four time points available to measure DHEA and DHEAS levels.
Lennartsson, A.-K. (Lennartsson et al., 2013)	2013	36 healthy subjects	37+−5	Investigate whether prolonged psychosocial stress is related to capacity to produce DHEA and DHEAS during acute psychosocial stress	Perceived stress at work measured using Stress-Energy Questionnaire. Participants divided into three groups based on their means scores (low stress, medium stress, high stress). Participants underwent TSST and blood samples were collected before, directly after test and after 30 min recovery. Same methods of concentration analysis as above	Higher perceived stress at work associated with attenuated DHEAS response during acute psychosocial stress. Cortisol/DHEAS ratio during acute stress test were higher in individuals reporting higher perceived stress at work vs individuals reporting lower perceived stress. No statistical difference in DHEA response between groups. All participants had relatively low perceived stress level as no individuals suffering from severe stress issues were included in the study—biased sample.
Mazgelyte, E. (Mazgelyte et al., 2006)	2021	40 subjects	21–53	Evaluate activity of the HPA axis by measuring salivary cortisol, cortisone, DHEA levels and their ratios to examine association with HRV measures in healthy adults.	Participants completed self-reported questionnaire on sociodemographic and lifestyle characteristics as well as the perceived stress scale and state trait anxiety inventory. Saliva samples were collected and resting HR and HRV were recorded during three data collection sessions. Salivary samples were analyzed using ultra-high-performance liquid chromatography. HR measures were made by high-frequency IR earlobe sensor.	Statistically significant associations between HRV measures and higher salivary cortisol and lower DHEA levels. Decreased DHEA/cortisol ratio.
Michael, A. (Michael et al., 2000)	2000	44 MDD, 35 partially depressed and 41 healthy controls	20–64	Examine whether levels of DHEA are abnormal in depressed patients vs healthy controls	Salivary cortisol and DHEA samples were taken at 8 am and 8 pm for 4 days. Assayed with immunoassays	DHEA was lower at 8 am and 8 pm in depressed patients compared to controls. DHEA levels at 8am correlated negatively to severity of depression, were not related to drug treatment but decreased with age as expected. Cortisol was elevated in depression in the evening. Molar cortisol/DHEA ratio differentiated between those with depression vs the control group. Lower DHEA levels are additional state of abnormality in adult depression. DHEA may antagonize some effects of cortisol. Results could be affected by cortisol and DHEA awakening responses.
Mocking, R.J.T. (Mocking et al., 2015)	2015	187 remitted recurrent MDD	18–65	Tested whether low DHEAS and high cortisol/DHEAS ratio in MDD reflects a trait or	Salivary samples taken morning and evening for 8 weeks, repeated after 3 months and 2 years. Measured	Steeper diurnal DHEAS decline and flatter profile of cortisol/DHEAS ratio throughout follow up in remitted patients. Higher morning cortisol/DHEAS ratio predicted

(*continued*)

Table 1. Continued.

Author	Year	*N* (Number of Participants)	Age in years (mean±*SD*)	Aim	Methods	Major findings/limitations
		patients, 72 matched controls		depressive state and its association with previous MDD episodes/effects of cognitive therapy	clinical symptoms during 10 year follow up. MDD reviewed with DSM-IV and HDRS. Saliva samples assayed via radioimmunoassay analysis.	shorter time till recurrence over 10 year follow up. Cognitive therapy did not influence DHEAS or ratio.
Noser, E. (Noser et al., 2018)	2018	121 male participants	40–75	Investigate whether men with different degrees of vital exhaustion differ in terms of allostatic load, chronic stress and social support	Salivary cortisol, DHEAS, waist to hip ratio, systolic and diastolic BP were measured. Long-term cortisol and DHEAS were measured in hair. Chronic stress and social support assessed via questionnaires.	Men who reported mild-severe levels of exhaustion had highest scores of cumulative indices of biological stress. Hair cortisol was unrelated to vital exhaustion. Hair DHEA was highest in men with substantial levels of exhaustion.
Osran, H (Osran et al., 1993)	1993	9 MDD patients, 9 healthy matched controls		Observe abnormalities in adrenal androgen and cortisol metabolism in depressed patients	Serum levels of cortisol and DHEA measured at 8 am and 4 pm	Hypercortisolaemia and loss of diurnal DHEA variation but not cortisol variation in depressed patients. Suggests that in depression the adrenal androgens are partially regulated by mechanisms independent of ACTH. Very small sample size.
Ota, A. (Ota et al., 2015)	2015	115 healthy female nursery school teachers	30.8+−8.5	Examine associations of job strain and social support with daytime secretion amounts of DHEA and cortisol and daytime variations of cortisol/DHEA ratio.	Salivary DHEA and cortisol were measured with LC-MS/MS. Samples taken at 9 am, 12 pm and 3 pm. Job strain measured via Job Content Questionnaire.	Social support scores were negatively associated with daytime DHEA secretion, not associated with cortisol/DHEA ratio. There were no major associations between job strain and the salivary measures.
Pérez-Valdecantos, Daniel (Pérez-Valdecantos et al., 2021)	2021	97 healthcare professionals	20.6+−+79.4	Assessed stress response in emergency health workers through measurement of cortisol, DHEA and salivary alpha amylase	Saliva samples obtained at 8am, 12 pm, 3 pm and midnight. Samples assayed by ELISA immunoassays.	Cortisol levels decreased throughout working day, similar pattern as DHEA. Alpha amylase values increased throughout the working day. Baselines not calculated, only measured for single working day.
Persson, Roger (Persson et al., 2006)	2006	50 with 84 h working week; 25 workers with 40 h working week	21–65	Examines degree to which long workhours influenced stress biomarkers, metabolic processes and diurnal rhythm.	Blood samples obtained in the morning immediately prior to start of work on days 1, 5 and 7. Psychosocial circumstances assessed with questionnaire.	84-h group had higher melatonin concentrations and reported higher job control scores than 40-h group. Both groups had lower melatonin, cortisol and cholesterol concentrations on workday 5 than workday 1. DHEA and uric acid concentrations remained stable across all days.
Ter Horst, D M (Ter Horst et al., 2019)	2019	73 unmedicated recurrent MDD patients; 46 matched controls	35–65	Determine whether alterations in HPA axis activity and fatty acids in recurrent MDD remain during remission.	Measurements of salivary cortisol and DHEAS were taken at awakening, evening and after sad-mood induction. Assayed via radioimmunoassay. Depressive symptoms measured using HDRS.	Patients had higher cortisol awakening responses and lower evening cortisol/DHEA ratios compared to healthy controls. Fatty acids did not differ between patients and controls.

levels of cortisol secretion in basal conditions (Gjerstad et al., 2018).

Cortisol increases blood pressure as well as blood glucose levels due to induction of insulin resistance (Kamba et al., 2016). Furthermore, excessively high cortisol levels in the body often result in suppression of the immune system (Jefferies, 1991). HPA axis dysfunctionality and dysregulation of the biological stress response system has been linked with risk of depression (Dienes et al., 2013). As the primary coordinator of the stress response, cortisol secretion patterns can indicate HPA axis dysfunction, in response to laboratory stressors and other interventions. Cortisol reactivity studies have shown that depressed individuals often have higher levels of cortisol during the recovery period post-stressor (Burke et al., 2005).

Commonly known as the "hormonal endpoint" of the HPA axis, cortisol is primarily responsible for the body's reactions to stressors (Tsigos & Chrousos, 2002). Cortisol follows a circadian rhythm which is linked to the sleep/wake pattern in humans; therefore, basal levels of cortisol vary between the daytime and the evening (Tsigos & Chrousos, 2002). The rate of its secretion is dependent on the level of circulating corticotrophin, under extreme stimulating conditions, the level of cortisol in the human body can exceed 250 mg a day, approximately an 125% of its typical level of 20 mg (Garrod, 1958). In healthy and normal individuals, there are very low/-undetectable levels of cortisol at midnight. This gradually builds up and peaks in the morning, known as the cortisol awakening response. After this peak, cortisol levels decline throughout the rest of the day (Chan & Debono, 2010). Comparatively, disturbances in this circadian rhythm are highly prevalent in individuals with depression (Germain & Kupfer, 2008). In normal individuals, there is a decline in mood in the evening, compared with the morning whereas in depressed individuals, there are mood improvements in the evening, which is associated with increased dorsal neural network activity. Sustained activity in the brainstem and hypothalamus involved with the sleep/wake cycle and, increased brain glucose metabolism is also observed throughout the day, which is reversed in healthy individuals (Germain & Kupfer, 2008). Due to these disturbances in the cortisol circadian rhythm in depressed individuals, irregularities in sleeping patterns and the sleep/wake cycle are commonly observed. 90% of depressed patients have complained about difficulties with sleeping, staying asleep and early morning awakening, compared to only 6% with complaints about hypersomnia (Almeida & Pfaff, 2005; Roberts et al., 2000). Thus, cortisol monitoring can simplify the comprehension of the circadian rhythms and chemical balances of depressed individuals compared to healthy subjects.

3.2. DHEA

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are steroid hormones that are regulated by the ACTH and possess anti-glucocorticoid properties (Gallagher & Young, 2002). DHEA is produced by the zona reticularis area in response to the ACTH. It has a regenerative role in the body, often associated with aging (Dutheil et al., 2021; Rutkowski et al., 2014). The primary function of DHEA is its involvement as a metabolic intermediate in sex hormone biosynthesis, i.e. to produce androgen and oestrogen (Mo et al., 2006). DHEA is known to improve physical well-being through reduction of total cholesterol, and prevention of bone mineral density. The steroid has an antagonistic relationship with cortisol, the primary stress hormone in humans (Gallagher & Young, 2002). This relationship can translate to reduced stress and improved psychological well-being. The cortisol-to-DHEA ratio has been considered as a precise method of assessing HPA axis functionality (Gallagher & Young, 2002). Several studies have shown an association between DHEA levels and stress intensity, as well as focusing on the cortisol/DHEA ratio. Although the magnitude of fluctuations in DHEA levels caused by stress is known to decrease with age (Dutheil et al., 2021). As a well-established biomarker of acute stress, the metabolism of DHEA and its release patterns in the human body are of great interest in stress studies. Several studies have noted that DHEA levels often appear as a peak at the end of a stressful period, and progressively return to baseline levels after recovery from stress (Dutheil et al., 2021). However, these factors are sex and age dependent therefore, it is imperative to delve deeper into the functionality of DHEA in the human body and the roles it plays within the stress response.

There are clear gender differences in circulating DHEAS levels, higher levels are found in men than in women, with peak levels around ages 25–30 (Dutheil et al., 2021). After this, there is an age-dependent decline in levels, which can also be influenced by drastic developmental changes. The reactivity to developmental changes in unique to DHEA secretion and not commonly observed for other steroid hormones. DHEA is a naturally occurring C-19 adrenal steroid synthesized by the adrenal cortex from cholesterol. The adrenal cortex secretes 75–90% if the body's DHEA with the remainder produced by the sex organs, i.e. testes and ovaries (Webb et al., 2006). Clinical studies have shown that DHEA secretion has several effects on the human body such as, reduced inflammation, improved sexual function, cognitive function and memory enhancement (Traish et al., 2011). Furthermore, studies have shown that low DHEA and DHEAS levels are associated ischemic heart disease, endothelial dysfunction, atherosclerosis as well as psychological distress (Dutheil et al., 2021; Lennartsson et al., 2013; Traish et al., 2011).

4. Current state of the art monitoring techniques for cortisol and DHEA

The manifestation of stress and its effects on the human body are considerable for the comprehensive and quantitative evaluation of depression, and severe mental illnesses such as major depressive disorder. The relationship between stress hormones and clinical depression have been highlighted in a plethora of studies. Such studies have showcased the importance of cortisol monitoring for a better understanding of the neurobiological processes and their dysfunctionalities, which often lead to the development of

depression. Evidently, Ter Horst et al. demonstrated the differences which exist between patients suffering from recurrent depression and healthy participants in their 2019 study (Ter Horst et al., 2019). This study highlighted HPA axis irregularities and subsequent hormonal imbalances which exist in depressed patients. Higher cortisol awakening responses were observed alongside lower cortisol/DHEA ratios, which have been noted as key characteristics commonly found in depressed patients.

The monitoring of stress-related biomarkers is well established in the field of stress studies, in cases of healthy participants as well as patients suffering from major depressive disorder. It is evident that the techniques used to measure cortisol, DHEA and other stress-related biomarkers often require the utilization of highly complex and expensive equipment, and highly skilled specialists to comprehend and evaluate the quantification of the biomarkers and its translation into psychological and neurobiological changes in the human body (Assies et al., 2004). Common techniques for the measurement of cortisol and DHEA include enzyme-linked immunoassays (ELISA) and liquid chromatography tandem mass spectrometry (Laudenslager et al., 2013; Lennartsson et al., 2022; Ota et al., 2015; Shors & Horvath, 2001).

The cortisol/DHEA ratio was first coined in 2001 by Goodyer et al. in a selective review which related the three aspects of behavioral endocrinology i.e. the developmental changes of cortisol and DHEA and their roles in psychopathology and neurobiological mechanisms (Goodyer et al., 2001). Goodyer observed that there exist medial changes in brain sensitivity following an excess in cortisol exposure, which often leads to dysfunctionalities and impairments in mental and behavioral function. Furthermore, it was noted that steroid hormones, therefore, contribute drastically to the shaping of behavioral and mental functions during early development and such dysfunctionalities act as risk factors for psychopathology. The cortisol/DHEA ratio is a measure of the relative activity of both steroids and can be indicative of psychopathological issues (Goodyer et al., 2001). Decreased ratios are often associated with dysfunctionality of the HPA axis. The two hormonal profiles that are common in depressed patients are either higher cortisol levels with normal levels of DHEA: or normal cortisol levels with lower levels of DHEA. Both of which lead to a lower cortisol/DHEA ratio. The cortisol/DHEA ratio has been a successful indicator of predicting recurrent major depressive disorder in adolescents (Goodyer et al., 1998). Such studies have shown the clinical relevance of the cortisol/DHEA ratio and its impact in the prediction and evaluation of major depression. Several studies have demonstrated the efficacy of monitoring cortisol and DHEA for the assessment of stress and major depressive disorder. Comparatively, some studies have showcased the shortcomings in monitoring the stress and gonadal hormones and its correlations with psychological changes in the body, therefore it is imperative to critically discuss the benefits and limitations of studies highlighting such methodologies for more robust application of biomarker monitoring technologies for stress evaluation. The complete evaluation of these studies can be seen in Table 1.

5. Discussion

Several studies have demonstrated the benefits of utilizing the cortisol/DHEA ratio as an objective and quantitative measure of stress in depressed and healthy participants (Asadikaram et al., 2019; Bae et al., 2019; Cutshall et al., 2016; Ge et al., 2016; Jeckel et al., 2010; Kim et al., 2010; Lennartsson et al., 2013, 2022). Moreover, some studies have noted the decline in cortisol levels, i.e. hypercortisolaemia and in DHEA levels were characteristic in patients suffering from depression, compared to controls (Osran et al., 1993; Ter Horst et al., 2019). Michael et al., 2000 study observed that a negative correlation relationship existed between DHEA awakening response levels and the severity of depression in a study consisting of 44 MDD patients and 35 partially depressed participants (Michael et al., 2000). They went on to suggest that lower DHEA levels are an additional state of abnormality in adult depression, alongside hypercortisolaemia, i.e. blunted cortisol response (Osran et al., 1993). Additionally, the results of Jozuka et al., 2003 study further justify this argument (Jozuka et al., 2003). In this study the cortisol and DHEA levels were observed to be radically lower in MDD patients compared to healthy controls, albeit in a smaller sample size of 17 MDD patients and 10 healthy participants. These studies suggest that the abnormalities found in secretion patterns of cortisol and DHEA may be indicative of the dysfunctionalities of the HPA axis, as well as irregularities in the antagonistic relationship between cortisol and DHEA, which would evidently be reflected in the cortisol/DHEA ratio.

In studies that compared the hormonal differences between depressed patients and healthy participants, such as Assies et al. (2004) study on salivary cortisol and DHEAS, it was observed that DHEAS levels were elevated in MDD patients, whereas no noteworthy differences existed in salivary cortisol levels amongst MDD and healthy cohorts (Assies et al., 2004). Although this led to indications that MDD patients had greater cortisol/DHEA ratios, which correlate with existing literature, the behavior of salivary cortisol and DHEA and its fluctuations did not corroborate with the hormonal patterns expected from MDD patients. Comparatively, Boudarene et al. (2002) study on the roles of cortisol and DHEA during the stress response showcased high levels of anxiety and stress were linked with higher cortisol levels and close correlations between DHEA and cortisol (Boudarene et al., 2002). As this study was conducted on healthy participants, it brings forward the question of whether the cortisol fluctuations in the Assies et al.'s study were a result of blunted cortisol responses, commonly observed in MDD patients (Assies et al., 2004; Mcewen, 2005; McEwen, 2000; Tsigos & Chrousos, 2002). Moreover, parallel increases in plasma cortisol and DHEA levels of depressed patients were found in a 1998 study conducted by Heuser et al. whereby it was found that the mental disorder led to large increases in diurnal minimal and mean plasma DHEA concentrations in a comparative study between depressed patients and healthy control participants (Heuser et al., 1998).

Evidently, stress studies which have been conducted on healthy participants have demonstrated results which further

support this theory. In healthy human studies, such as those conducted by Izawa et al. and Irshad et al. the analysis of salivary biomarkers revealed the increase in salivary cortisol levels after stressful events (Irshad et al., 2020; Izawa et al., 2008). In both cases the presence of a stress-inducing event led to the increase in cortisol levels whereas, in Irshad et al.'s study there were no substantial changes in DHEA levels (Irshad et al., 2020). However, in Izawa et al.'s study, a peak in DHEA concentration was observed 10 minutes prior to peak cortisol concentration (Izawa et al., 2008). Both studies showcased increases in cortisol/DHEA ratios as a result of stress induction, albeit with different hormonal profiles. Although Izawa et al.'s study reveals the antagonistic nature of the relationship between salivary cortisol and DHEA, the results of Irshad et al.'s study suggests that further evaluation is required to fully assess the manner in which the fluctuations of cortisol and DHEA influence each other within the human body (Irshad et al., 2020; Izawa et al., 2008).

Thus, an argument can be derived that is dependent on the behavior of the stress-related biomarkers in the body and its roles in mental/psychological changes in humans. The cortisol/DHEA ratio can be considered as an objective indicator of mental stress in healthy humans. This is because the fluctuations of cortisol and DHEA are expected to follow a known pattern in response to stressors, i.e. stressor leads to an increase in cortisol levels, which results in a higher cortisol/DHEA ratio, as seen in several studies. Whereas, in studies involving depressed patients, a lower cortisol/DHEA ratio can be expected due to declines in cortisol or DHEA, which coincides with existing literature regarding blunted cortisol responses in patients suffering from MDD due to reaching the "exhaustive" stage of the stress or "fight or flight" response (Mcewen, 2005; McEwen, 2000; Tsigos & Chrousos, 2002).

It is therefore imperative to consider the methods in which cortisol and DHEA are measured from serum and saliva samples in stress studies. As previously mentioned, the primary methods of monitoring cortisol and DHEA involve immunoassay-based techniques or high-performance chromatography-based methods (Jeckel et al., 2010; Lennartsson et al., 2012). Although such methods yield highly accurate results regarding cortisol and DHEA concentrations, they require laboratory-based protocols and expensive equipment that are not easily accessible. Furthermore, in cases with high-risk individuals, such as those at risk of suicide, the time taken to obtain results is of utmost importance. The standard time taken to generate results from the gold standard salivary cortisol evaluation technique, i.e. ELISA testing is minimally 24–48 hours. Ideally, in high-risk cases, the existence of a rapid and continuous cortisol and DHEA monitor is compulsory for the betterment and improvement to quality of life for depressed patients.

Additionally, only one study considered the physiological changes which arise during stress, as well as the hormonal fluctuations which are implicated by the cortisol/DHEA ratio. Mazgelyte et al. investigated the associations between salivary steroid hormone fluctuations and time domain heart rate variability (HRV) indices in healthy individuals (Mazgelyte et al., 2021). Participants were asked to provide saliva samples during three collection sessions, which also involved a sociodemographic and lifestyle questionnaire, state trait anxiety inventory and the perceived stress scale. Salivary samples were analyzed for cortisol and DHEA concentrations via high performance liquid chromatography whilst HRV measures were taken issuing a high frequency infrared earlobe sensor. The results of this study demonstrated statistically significant associations between HRV measures and salivary cortisol and DHEA levels (Mazgelyte et al., 2021). The results coincided with previously mentioned studies whereby an increase in stress on the perceived stress scale correlated with an increased cortisol/DHEA ratio. Other studies involving multimodal measurements of stress include Ahrens et al.'s study on stress responses in recurrent MDD patients versus healthy participants through HRV, as well as serum and, salivary cortisol measurements (Ahrens et al., 2008). However, such studies did not consider the presence of DHEA in response to stress elicitation, therefore it was not considered within the scope of this review. The importance of physiological biomarkers of psychological stress in tandem with the evaluation of biochemical measurements is evidently essential for the comprehension of the stress response, as well as the relationship between steroid hormones and mental health deterioration in humans.

5.1. Considerations

The implication of monitoring stress-related biomarkers such as cortisol and DHEA has been highlighted throughout this comprehensive review. Evidently, the quantification of the relationship that exists between cortisol and DHEA is an important characteristic for the objective measurement of stress, and its manifestations in the human body. Various studies have shown promising findings which corroborate with the existing literature (Mazgelyte et al., 2021). Whereby, spikes in cortisol concentration leads to increased cortisol/DHEA ratios in healthy subjects, whilst blunted cortisol responses and irregularities in DHEA secretion led to subsequent declines in cortisol/DHEA ratios in depressed individuals (Osran et al., 1993; Ter Horst et al., 2019). Alternatively, several studies have demonstrated the insufficiencies in measuring only two steroid biomarkers for the understanding of the stress response. Evidently, the lack of standardized stress testing in stress studies involving healthy participants has led to diminished legitimacy in the results as there is no clear boundaries of stress elicitation in these individuals. The utilization of standardized stress tests such as the TSST validifies that individuals were subjected to stress and genuine stress response were elicited. For example, in Bae et al.'s. 2019 study, the TSST was used to investigate the stress biomarkers which had the highest discriminatory power between healthy cohorts undergoing stress tests versus controls (Bae et al., 2019). It was observed that salivary cortisone and salivary cortisol had substantial correlations with the subjective and autonomic stress measures, which were monitored via questionnaires and heart rate, respectively. Therefore, it is imperative to consider standardized

stress tests such as the TSST when conducting stress studies as it is a reliable method for stress response elicitation.

5.2. Multimodal approaches

Undertaking a multimodal approach for monitoring of stress and depressive symptoms may lead to great advances for the complete quantification of psychophysiological stress evaluation (Ahmed et al., May 2022). Particularly, Mazgelyte et al.'s study showcases promising results in the use of chemical biomarker monitoring alongside physiological monitoring techniques such as HRV measures in the discrimination between stress responses versus resting state responses in healthy adults (Mazgelyte et al., 2021). Notably, the application of HRV measures in parallel with the cortisol/DHEA ratio established statistically significant associations between the physiological stress measures and biochemical stress biomarkers, which could be a promising characteristic to incite further investigations in stress measurement. In a recent review of studies involving the measurement of cortisol in tandem with physiological measurements of stress, promising results were obtained which further bridges the gap in knowledge in the quantification of psychological stress (Ahmed et al., May 2022). Therefore, efforts in the investigation of DHEA and the cortisol/DHEA ratio in similar studies would ideally lead to a greater understanding of the fluctuations of stress hormones during the stress response, and the physiological markers that are expressed during an episode.

6. Conclusion

To conclude, the prominence of cortisol and DHEA monitoring for the evaluation of psychological stress and its discriminatory power between patients of major depressive disorder and healthy individuals is inevitable. Further investigations with an emphasis on multimodal techniques could lead to a greater understanding regarding the relationship between the cortisol/DHEA ratio and physiological measures of stress such as HRV and electrodermal activity. Thus, leading to the robust quantification of stress. With this understanding and the aide of standardized stress testing, it could direct efforts away from existing subjective stress monitoring practices and drive research toward the complete quantification of psychological stress in the human body, for the improvement of quality of life for stressed individuals as well as those suffering from chronic stress or, clinical depression.

Author contributions

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We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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