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Review Article

A Cortisol dynamics in the elderly: Systematic Review

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Abstract: The elderly are defined as individuals aged ≥65 years, increasing rapidly in the United States and are expected to reach 84 million by 2050. One of the main biological processes of systemic damage that contributes to the development of organ dysfunction in aging is immunosenescence (gradual decline in age-related protective immunity) and inflammation (chronic subclinical systemic inflammation). Cortisol, a steroid hormone, is synthesized from cholesterol. Cortisol release is under the control of the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is released by the paraventricular nucleus (PVN) of the hypothalamus. Normal aging is associated with multiple endocrine changes, including those related to changes in the structure and function of the adrenal glands. A literature search was carried out using three main databases, namely ScienceDirect, Google Scholar and PubMed in journals covering the last ten years (2013-2023) using PRISMA guidelines. Based on the analysis of inclusion and exclusion criteria, there are 8 reference journals that match the research topic. The results of this study show that there is a dynamic regulation of cortisol in the elderly with an increase in cortisol levels in the elderly and these levels are higher in individuals with comorbidities. Based on the systematic review carried out in this study, it was concluded that there are changes in the dynamics of cortisol secretion in the elderly with a significant increase in secretion in certain groups of elderly which is related to the level of stress and comorbidities status.

Keywords: cortisol; dynamics; elderly

1. Introduction

The elderly, defined as individuals aged ≥65 years, are rapidly increasing in the United States and are projected to reach 84 million by 2050. Although there are differences between chronological and physiological aging, the older adult population tends to have a weaker physiological phenotype compared to the younger population. In addition, older adults account for nearly 50% of intensive care unit (ICU) admissions and 60% of all ICU days. [1]

One of the major biological processes of systemic damage that contributes to the development of organ dysfunction in aging is immunosenescence (age-related gradual decline in protective immunity) and inflammation (chronic subclinical systemic inflammation). Both of these deleterious processes decrease the effectiveness of the immune system, leading to increased susceptibility to infection and susceptibility to inflammatory conditions, and thus increased susceptibility to critical illness and poor outcomes. Other cellular processes such as increased oxidative

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stress and apoptosis, and decreased autophagy are hallmarks of the degenerative processes of aging that contribute to susceptibility to infection and poorer outcomes in critical illness. Reactive oxygen species are produced in normal aging at the cellular level in all systems as mediators of cell differentiation and growth, and are taken up by antioxidant enzymes to maintain homeostasis. The aging process is associated with less efficient free radical scavenging processes and excessive free radical production, resulting in increased oxidative stress, cell damage, and death or necrosis. Aging is also associated with higher rates of apoptosis, programmed death, and decreased autophagy, a cellular process by which dysfunctional and cytotoxic cell components are digested and removed by lysosomes. These detrimental processes contribute to the development of comorbidities in older adults such as cardiovascular disease, neurodegenerative diseases, physical disabilities, and cancer. [2,3]

Stress is a condition caused by various factors and characterized by an imbalance in body function, nervous system disorders, and tension. A person who experiences stress due to an unpleasant event responds to the situation with physiological and emotional changes and changes in perception and behavior. Although people may think that they are not too affected by an event, they may develop reactions without realizing it. Stress most often occurs in situations that are uncontrollable, and undesirable, and when a person has a greater workload than he or she can handle. Chemical or physical imbalances that occur in cells or tissue fluids as a result of changes in the body or the external environment are called physiological stress. There are 3 components of physiological stress. These are exogenous or endogenous stress factors and chemical or physical imbalances caused by stress factors and the body's adaptive response to these conditions. The results of researchers examining the relationship between stress and the immune system and the monoaminergic system show that 2 endocrine response systems that are sensitive to stress are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic adrenal medulla system [5]. When a person is faced with a stressor that cannot be controlled by existing coping mechanisms, the HPA axis is activated through the association of the cortex, amygdala, and hippocampus, which causes blood cortisol levels to increase and brain function is affected through neurons in the brain and glucocorticoid receptors in glial cells. Cortisol is a steroid-structured hormone released from the outer part of the cortex of the suprarenal glands and exhibits glucocorticoid effects. [4.5]

Cortisol, a steroid hormone, is synthesized from cholesterol. It is synthesized in the zona fasciculata layer of the adrenal cortex. Cortisol release is under the control of the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is released from the paraventricular nucleus (PVN) of the hypothalamus. It then acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then acts on the adrenal cortex. In a negative feedback loop, sufficient cortisol inhibits the release of ACTH and CRH. The HPA axis follows a circadian rhythm. Thus, cortisol levels are high in the morning and low in the evening. [6] Normal aging is associated with multiple endocrine changes, including those related to changes in adrenal gland structure and function. The various morphological changes in the adrenal glands that occur during aging are associated with changes in hormonal output, such as a gradual increase in glucocorticoid secretion and a decrease in adrenal androgen levels. [4.7]

Dysregulation of the HPA axis could theoretically be achieved through several pathways. It may start with chronic stress causing prolonged high activity in the HPA axis. Prolonged exposure to high cortisol levels can lead to decreased sensitivity of the glucocorticoid receptor (GR) in the brain, which would result in less negative feedback, since negative feedback relies on GR to hear the cortisol "signal." Disruption of negative feedback can even lead to increased cortisol in the long term, thus prolonging the cycle. The second pathway may start with individuals who have fewer GR or less accessibility to GR for any number of reasons, whether genetic, early life experiences, ongoing stressors causing short-term changes, etc. Fewer or less accessible GR can result in lower negative feedback, which can then lead to high cortisol, as discussed above. Importantly, however, chronic stress has been associated with both high and low GC levels. GC levels may reflect the effects of chronic stress such as financial hardship, work overload, and burnout. In addition, the HPA axis is closely linked to the immune, nervous, and other endocrine systems. Therefore, HPA response and inactivation are important both directly and indirectly for health. [7]

The increased circulating cortisol levels in aging individuals are of particular interest because of the impact of cortisol on several systems, including cognition, and the inherent relationship between chronic stress, elevated cortisol, and aging. Normal aging and chronic stress appear to affect the body through shared mechanisms related to glucocorticoid function. The chronicity of the aging process, particularly related to changes in adrenal gland structure and function, and stress can have a detrimental effect on an individual's general well-being. Existing evidence supports that the synergy of aging and chronic stress, through the common endpoint effector cortisol, can have a detrimental effect on the function of various vital systems, leading to neurological and cognitive changes, osteopenia, diabetes mellitus, visceral obesity, and altered immunocompetence, among others. 8 Given the impact of cortisol function dysregulation in individuals, especially the elderly, with decreased body homeostasis, researchers are interested in elaborating cortisol dynamics in the elderly using a systematic review method.

2. Method

The second way is to combine theory with related literature and explain each theory in one sub-chapter. This study is a study with a systematic review approach to explore cortisol dynamics in the elderly. This systematic review follows the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines which can be seen in chart 1. The literature search was carried out using three main databases, namely ScienceDirect, Google Scholar and PubMed. The search strategy used the Boolean technique with a combination of keywords, namely: ("Cortisol") AND / OR ("Dynamic") AND / OR ("Elderly")) AND ((("Cortisol") AND / OR ("Dynamic") AND / OR ("Elderly")). The literature search was carried out using the last ten years (2013-2023) due to the limited literature with a quantitative approach or RCT on this topic. Articles that met the criteria were then reviewed thoroughly after the titles and abstracts of the selected studies were evaluated.

The literature included in this study is literature that discusses the dynamics of cortisol in the elderly. Studies were included if they met the following inclusion criteria: 1) published in the last ten years (2013-2023); 2) quantitative studies and

RCTs; 4) free full text. Studies excluded in this study were: 1) did not have outcomes in the form of cortisol levels in the elderly; 2) did not have a DOI or PMID. Article selection begins with identifying articles in the database using appropriate keywords, followed by eliminating duplicate article results. The author will review the abstract and title to filter articles that meet the criteria for further review of the full text of articles that meet the inclusion criteria. Data extraction was carried out by one reviewer, in this case the researcher himself. General information on each study (author name, year of publication, country, research design) and characteristics (research results and conclusions) were collected.

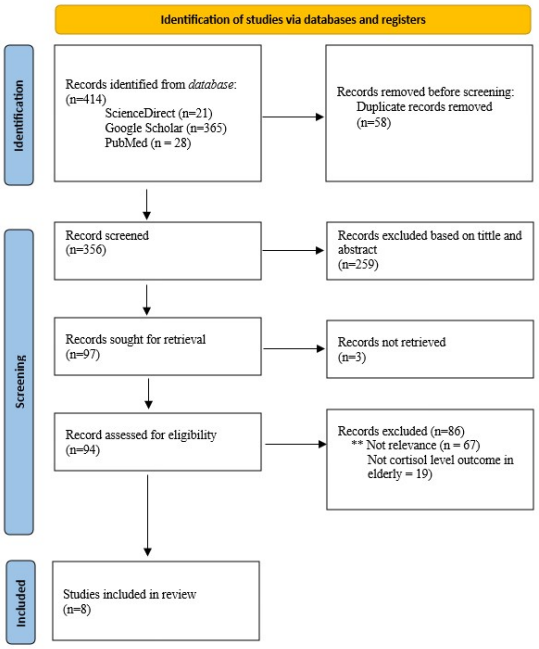

Figure 1. Documentation

3. Results

In the initial search, there were 414 journal articles identified from 3 main databases, namely Google Scholar, ScienceDirect and PubMed. A total of 356 articles were taken for the screening process by excluding 51 duplicate articles. Article screening was carried out based on title and abstract, obtaining 97 articles for review. After review, our study was included in the final analysis after 86 were excluded after evaluation because they did not meet the inclusion criteria or met the exclusion criteria. Of the 356 articles excluded from the final analysis, 67 articles were off-topic and 19 articles did not show the main outcome of cortisol levels in the elderly, so the literature analysis was carried out on 8 literatures that met the criteria (figure 1).

In the 8 studies included in the literature study, the population included in the study were mostly individuals aged ≥ 65 years. In this literature study, several studies used a sample comparison of the elderly with comorbidities.

such as sarcopenia, psychological disorders and others compared to control individuals or healthy elderly. The results of this study indicate that there is a dysregulation of cortisol dynamics in the elderly with an increase in cortisol levels in the elderly and these levels are higher in individuals with comorbidities.

Table 1. Characteristics of Literature in Research

Author and Year	Country	Study Design	Research methods	Results	Conclusion
Hek et al. (2013) [9]	Rotterdam	Cohort	The study population consisted of 1,788 older adults from a population-based cohort. The Munich Composite International Diagnostic Interview is used to diagnose anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, agoraphobia, and panic disorder). The cortisol awakening response and total cortisol secretion throughout the day were calculated from cortisol levels in four saliva samples taken over the course of one day (upon awakening, 30 minutes after awakening, at 5:00 p.m., before bedtime).	Older adults with anxiety disorders (n = 145, median duration since first symptoms 41 years) had lower cortisol awakening responses (p = 0.02) than those without the disorder (n = 1643). This association was most pronounced in those with generalized anxiety disorder (p = 0.008), but was not related to the level of chronicity of the anxiety disorder.	Older adults from the general population with long-term anxiety disorders have lower cortisol awakening responses than those without anxiety disorders. This is consistent with the notion that chronic anxiety may result in downregulation of HPA axis activity.
Marcos-Perez et al. (2019) [10]	English	Cross Sectional	This study was a cross-sectional study of 252 elderly adults (≥65 years) classified based on their frailty status. Plasma cortisol	The results showed a significant increase in cortisol concentration along with frailty burden, but there	Although it has been previously reported that frailty may be associated with higher oxidative stress and possibly lower antioxidant

			and biomarkers associated with oxidative stress including reactive oxygen/nitrogen species, oxidative DNA damage, and total antioxidant capacity were determined in non-frail, pre-frail, and frail subjects.	was no significant relationship between oxidative stress biomarkers and frailty status. Additionally, dependence on daily activities and 10-year mortality risk were also correlated with increased cortisol levels.	parameters, no such association was noted in the parameters analyzed in this study. However, higher serum cortisol concentrations were found to be associated with increased frailty burden, supporting the hypothesis that age-related HPA axis dysregulation may be associated with frailty status in the elderly.
Hollanda et al. (2021) [11]	Brazil	Cross-sectional	A cross-sectional study was conducted with 70 elderly people. Sarcopenia was assessed using the EWGSOP2 algorithm and cortisol by saliva collection. The statistical analysis used was the T test, Chi-square test and ANOVA ($p<0.05$).	A total of 17.1% of the older adults evaluated were considered sarcopenic. The associated variables were older age ($p = 0.001$); lower body mass index ($p = 0.008$); lower brachial circumference measurements ($p < 0.001$), waist ($p = 0.011$) and hip ($p = 0.001$). Cortisol levels were higher among sarcopenic older adults for all three measurements	The higher salivary cortisol levels found in sarcopenic elderly nursing home residents help to understand the underlying mechanisms of sarcopenia and health services in this population.

				throughout the day (p = 0.02), as well as for the derived measurement.	
Barca et al. (2018) [12]	Norway	Cross-sectional	Cross-sectional study of a sample of 650 elderly people, from community (nursing homes and nursing homes) and special care (memory clinic and geriatric psychiatric ward), mean age 76.8 (SD = 10.3) (dementia n = 319, depression, n = 154, dementia plus depression n = 53, and reference group n = 124)Assessments included the Mini Mental State Examination (MMSE), the Cornell scale for depression in dementia, the activities of daily living scale, and salivary cortisol.	The highest cortisol ratio was among patients with dementia and comorbid depression compared to patients with depression or dementia and the reference group. Characteristics significantly associated with cortisol levels were higher MMSE scores (in patients with dementia and comorbid depression), male gender (in those with dementia), and number of medications (in the reference group).	the highest cortisol ratio among patients with dementia and comorbid depression compared with patients with depression or dementia and the reference group. The relationship between cortisol levels and MMSE scores in patients with dementia and depression may further indicate that increased stress is associated with cognitive function.
Orihashi et al. (2022) [13]	Japan	Cohort	A longitudinal study was conducted in Kurokawa-cho, Imari, Saga Prefecture, Japan, in people aged 65 years and older, as previously reported. The first survey was	There was no significant difference in serum cortisol levels between men (72.32 ± 17.30 ng/ml) and women (76.60 ± 21.12 ng/ml) at baseline. Additionally, no	Serum cortisol levels may serve as a peripheral biomarker of age-related volume changes involving the hippocampus in adults aged 65 years and older.

			conducted from October 2009 to March 2011 (Timepoint 1) and the second survey was conducted from November 2016 to September 2017 (Timepoint 2). Blood samples for serum cortisol level analysis were collected from participants at Timepoint 1. Serum cortisol levels were measured using enzyme-linked immunosorbent assay. Participants underwent brain MRI examination, and Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) for assessment of cognitive function at Timepoint 1 and Timepoint 2. We recruited 70 participants (16 males, mean age 72.69 ± 3.18 years; 54 women, mean age 72.69 ± 4.60 years, at Timepoint 1) for analysis. Correlation analysis was performed between baseline serum cortisol levels (Timepoint 1) and	influence of the time of blood collection on cortisol levels was observed in the participants. Small volume correction analysis at the cluster level by applying multiple comparisons correction (family-wise error; $P < 0.05$) showed a negative correlation between serum cortisol levels (Timepoint 1) and brain volume (Timepoint 2) in the region containing the left hippocampus.	

			brain volume (difference of Timepoint 1, Timepoint 2, and Timepoint 1–Timepoint 2) using voxel-based morphometry methods.		
Weller et al. (2014) [14]	USA	Cross-sectional	In a cross-sectional study of a sample of healthy older adults (55–85 years), we examined the extent to which variations in diurnal cortisol rhythms, an index of hypothalamic-adrenal-pituitary axis dynamics, are associated with differences in risky decision making.	Diurnal cortisol declines predicted performance on a daily task , a risky decision-making task that independently examines risk taking to achieve gains and risk taking to avoid losses. As for potential benefits, we found that greater risk-taking was associated with lower diurnal cortisol declines, independent of participant age or sex. Compared with men who experienced more general diurnal declines, those who exhibited lower diurnal declines made more risky choices and showed lower sensitivity to the	Decreased diurnal cortisol was associated with increased risk taking in decisions involving potential gains.

				expected value of those risky choices.	
Karlamangla et al. (2018)	American	Cross-sectional	In adults aged 35 to 86 years, cortisol testing from 16 saliva samples over 4 consecutive days was used to calculate diurnal dynamic range and area under the curve (AUC). Childhood economic hardship was measured based on memories of parental education, dependence on family welfare, and perceptions of financial status; and childhood social difficulties due to parental separation, death, and abuse.	Age, race/ethnicity, and education also had significant independent associations with diurnal cortisol dynamic range in the expected direction (in the final model with total childhood adversity): Dynamic range decreased with age ($p < 0.0001$), was greater in non-Hispanic whites compared to others ($p < 0.0001$), smaller in those with progressively lower education, and also smaller in those reporting more social conflict in adulthood and gender had a significant association with diurnal cortisol AUC, with greater AUC in older individuals and in men, compared to younger individuals and	Adjusted for age, sex, and race/ethnicity, both childhood adversities were significantly associated with smaller adult cortisol diurnal dynamic range, but not AUC. The relationship with cortisol dynamic range was explained by adult social and economic variables.

				women. Race/ethnicity, adult SES, and social conflict had no association with diurnal AUC.	
Huo et al (2020) [15]	USA	Cross-sectional	Cross-sectional study of adults aged 60 years and older (N = 435) from the National Study of Daily Experiences, part of the Midlife in the United States Study. They completed an initial interview regarding functional limitations and background characteristics, demonstrated voluntary activity in a daily interview, and also provided saliva samples over 4 days.	Multilevel models showed that older adults with greater functional limitations exhibited irregular cortisol dynamic responses and diurnal cortisol declines across the day, compared to older adults with less functional limitations.	There are functional limitations and responses to cortisol stress with increasing age with irregular cortisol dynamics and diurnal cortisol declines throughout the day.

4. Discussion

Cortisol is a major stress hormone implicated in the pathogenesis of many age-related diseases and the development of aging phenotypes. Literature studies have shown that blood cortisol levels are maintained or slightly increased with age with a diurnal decline in cortisol throughout the day. 16 One study has suggested that lower cortisol levels may be adaptive for memory as we age, and that cortisol has the potential to be a sensitive marker of risk for cognitive decline. 20 The ability of human physiological systems to respond and adapt to a variety of challenges and stressors is critical to the maintenance of health and function. In fact, adaptability is a prerequisite for the thriving of almost every organizational structure in a challenging or changing environment, including biological species, ecosystems, human communities, and business firms. 17 The body's adaptation to its physiological environment in response to demands is called allostasis and the adaptive capacity of a system is called its allostatic reserve. The adaptive capacity of a system depends on its dynamic range—the spread between the maximum levels that can be achieved when there is a challenge

and minimum resting levels. Dynamic range reduction is seen in aging and occurs in almost every physiological system and organ in the human body. Dynamic range compression is also the price the system pays for frequent allostasis in the face of repeated or intense challenges. When adaptation is excessive, due to increased frequency, duration, or severity of challenges, it leads to dysregulation of the system and the stress response. 17

Cortisol, a stress hormone produced by the hypothalamic-pituitary-adrenal (HPA) axis, has been linked to an individual's response to both daily and chronic life stress. Cortisol follows a diurnal rhythm. Each day, this response increases and peaks approximately 30–45 minutes after awakening (cortisol awakening response [CAR]), which is part of healthy circadian physiology that prepares the individual for the day ahead. The hormone then declines throughout the day until bedtime (diurnal cortisol slope [DCS]). Flat CAR and DCS reflect an aberrant HPA axis response, which is often observed in individuals experiencing chronic stress. 15 Regarding the endocrine system, the role of cortisol deserves attention as a possible modulator in the genesis of sarcopenia. This hormone is a glucocorticoid produced by the hypothalamic-pituitary-adrenal (HPA) axis in response to challenging or threatening situations. Circulating diurnal cortisol concentrations in the body provide information about the activity of the HPA axis and also serve as negative feedback for the system itself to maintain its concentration at physiological levels.18

The Strengths and Vulnerability Integration (SAVI) model posits that older adults are more susceptible to the physiological effects of stress than younger adults. SAVI bases this prediction on research findings and biological theories of aging that attempt to explain cellular aging and the higher prevalence and incidence of disease with age. For example, researchers have found that cells accumulate damage over time, leading to decreased adaptability, structural defects, and cellular instability. In the case of cortisol, research based on the glucocorticoid cascade hypothesis of aging suggests that chronic exposure to high levels of cortisol disrupts cellular function, making neurons in older adults, compared with younger adults, more susceptible to insults, which can lead to adverse health outcomes. For this reason, irregular cortisol effects (ie, diurnal patterns that deviate from the typical daily rise and fall) may have greater physical health consequences later in life. 19 Cortisol dysregulation appears to manifest as hyperactive or hypoactive patterns. To identify individual diurnal patterns, recent studies have used mixture modeling, such as group-based trajectory modeling or growth mixture modeling. These approaches parsimoniously assess how multiple components of the diurnal pattern (eg, overall output, cortisol awakening response (CAR), diurnal slope, evening levels) co-occur within a single day, and distinguish different diurnal level patterns within the same person.19

Cortisol is involved in several physiological systems, including metabolism, the immune system, and the body's response to stress. Dysregulation of the HPA axis occurs in pathological situations such as Cushing's syndrome or even in chronic physical or psychiatric stress. Excessive and persistent cortisol secretion causes muscle breakdown, which can lead to sarcopenia. However, there is little research involving the relationship between sarcopenia and changes in circulating cortisol levels in the body. It has also been reported that higher cortisol levels in older adults decrease overall cognitive performance. In addition, high cortisol levels are associated with

smaller hippocampal volumes. Hippocampal volume has been closely associated with memory performance and increased risk of dementia and is considered a reliable MRI biomarker for disease progression. Furthermore, to the best of our knowledge, no similar long-term follow-up studies have been conducted in older adults. Therefore, it is clinically important to know the relationship between serum cortisol levels and brain volume, especially in the hippocampus.8,13

5. Conclusion

Based on the systematic review conducted in this study, it was concluded that there were changes in the dynamics of cortisol secretion in the elderly with a significant increase in secretion in certain elderly groups related to the level of stress and comorbidities they had. However, further research is needed to clarify the dynamics of cortisol in the elderly with a more in-depth approach.

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