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Original Article

Effect of Daily Rhythms of Cortisol Secretion on the Rate of Aging in Men

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Abstract

The phenomenon of human aging is the result of a complex interaction among several factors in which the immune system plays a key role. Cortisol is a glucocorticoid secreted by the adrenal gland and has a specific secretion pattern. The current study aimed at identifying the cause and pathogenesis of premature aging using biological markers. This study was performed based on the results of clinical and instrumental examinations on 91 middle-aged men aged 45-59 years. VaseraVS-1500 sphygmomanometer based on standard methods was used to measure biological age. The relationship between biological age and circadian rhythms of cortisol secretion was calculated to elucidate the pathophysiological mechanisms of aging development. The recorded data showed that the violation of the circadian rhythms of cortisol secretion characterized by a consistently high level of the hormone throughout the day was typical among individuals with accelerated types of aging. Based on the obtained data, a formula for determining the biological age of the studied groups of patients was prepared by considering the circadian rhythm of cortisol secretion, which can be an additional tool for early detection of aging in men.

Keywords: Aging markers, Biological age, Cortisol, Premature aging

1. Introduction

The phenomenon of human aging is the result of a complex interaction among several factors in which the immune system plays a key role. As humans get older, their body's defense mechanisms start to become weaker. The compatible immune system that each human has acquired throughout their lives protects them against the pathogens they come in contact with, gradually declines with age (1). However, a human's innate or non-specific immune system, which is the first line of defense against a wide range of pathogens, becomes overactive, resulting in chronic inflammation (2). Persistent inflammation can cause serious damage to the body. Chronic inflammatory diseases consequently lead to several disorders, such as atherosclerosis or arthritis, which are far more common in elderly patients. Nonetheless, the cause of these inflammatory reactions is still unclear (3). The inflammatory process is related to the individual's age, and the amount of cortisol produced in the body increased with aging (4).

One of the priorities of our government policy is to improve the population conditions, which is primarily related to a reduction in mortality (5, 6). The average life expectancy of the Russian population, especially men, is lower than the average life expectancy in economically developed countries. The main reason is the high mortality rate of the working-age population.

For every four Russian feet, one death occurs at the working age. In this regard, the demographic policy predicts that measures can be taken to improve the socio-economic status of the population, increasing the average life expectancy to 75 years by 2025 (7).

Aging is a complex biological process that reflects the development of the living organism in time. Currently, the terms "physiological" and "premature" or "accelerated" aging are widely used. Accelerated aging is a partial or general acceleration of age-related changes, leading an individual to outstrip the general population level (8). Therefore, accelerated aging is a deviation from the natural course of the process, mediated by a variety of factors, leading to a decrease in life expectancy (9).

According to one of the scientific hypotheses, the realization of accelerated aging is not associated with diseases or exogenous causes, rather it is mediated by certain endocrine metabolic disorders. In this regard, more and more attention is paid to the neuroendocrinological (elevation) theory of aging by Dilman (10), which attaches the key importance in the aging process to the age-related increase in the threshold of sensitivity of the hypothalamus to homeostatic signals. Disruption in the incretion of cortisol, which exhibits antagonistic interactions with melatonin, a hormone that regulates the biological rhythms of the body, leads to an acceleration in the rate of body aging (11). Changes in secretion can be characterized by an increased level or a change in circadian rhythms of hormone incretion, which is described in the concept of “anabolic balance” (12).

The hypothalamus is damaged by a variety of factors, one of the most important of which is an increase in the concentration of the hormone cortisol. Cortisol is secreted by the adrenal glands. The secretion of this hormone is controlled by the hypothalamus. Cortisol is a hormone used by the body to deal with stress (13). Whenever the body is under stress, more cortisol is secreted. This hormone is released more with age and its blood concentration increases. Excess cortisol damages the hypothalamus and disrupts the regulation of hormone secretion. On the other hand, the regulation of cortisol secretion is disrupted and it is secreted more and more, and a vicious cycle occurs, which causes more damage to the hypothalamus (14). Accordingly, one method of treating aging is to modify the irritability of the hypothalamus to hormones. Some doctors believe that taking medications, such as metformin, increases the irritability of the hypothalamus and delays aging (15).

Cortisol is a glucocorticoid that is secreted from the fascicular area of the adrenal gland, which is the most extensive area and controls more than 95% of the glucocorticoid activity of adrenal secretions. Cortisol is one of the physiological variables indicating the rhythmic circadian system, which has the lowest value in the first half of the night (silent period), and during the second half, it experiences a sudden increase and after waking up, it reaches its maximum level. The concentration of cortisol, known as the wake-up hormone, decreases steadily throughout the day, and this process continues until the end of the day, except in stressful situations where its level rises (16). The internal precursor causes changes in the daily rhythm of the hormone cortisol located in the supraspinatus nucleus of the hypothalamus. In recent years, the obtained data show a change in the rhythm of cortisol circadian rhythms during shift work, especially at night (17). One of the main causes of cortisol secretion is the disruption of the sleep cycle and the problem of inappropriate phases. Researchers studying nurses reported that after the fifth night of work, the nurses' evening cortisol levels were higher than their morning cortisol levels (18, 19). Cortisol and its inactive form, cortisone, commonly referred to as stress hormones, are released by the adrenal glands. The hormone cortisol acts as a biochemical signaling molecule and is involved in several metabolic processes in the body (20). The lack of cortisol in the body leads to an inflammatory reaction. It has been reported that serum cortisol levels are low in the elderly (21). In addition, macrophages, an important type of immune cell, can convert inactive cortisone into active cortisol. Macrophages are also important cells in the immune system that use signaling molecules to control other immune cells. They play a considerable role in

determining the extent of the body's inflammatory response. However, macrophage function deteriorates with age (22). This can lead to an increase in the amount of anti-inflammatory signaling molecules, which in turn direct the activity of other inflammatory cells in the immune system.

The diagnosis of aging rates is based on the study of biological age (BA) (23). Biological age is an indicator of the level of development, change, or wear of the structure or function of an element of an organism, a functional system, an organism as a whole, expressed in time units (24). Despite the complexity of identifying the accelerated aging syndrome, the significance of its study is determined by clinical practice and the need to identify the etiology and pathogenesis of premature aging, its main biological markers, and the ways of a possible correction.

2. Materials and Methods

2.1. Study Design

This study was based on the results of the clinical and instrumental examinations on 91 middle-aged men (45-59 years) with a mean chronological age of 51.61±0.57 years. Biological age was determined using the VaseraVS-1500 barometer (Fukuda Denshi, Japan) according to standard methods. Chronological age refers to the actual amount of time a person has been alive, and BA is a measurement of age based on various biomarkers. If the BA is 3-7.9 years less than the calendar age, the person is in functional class II aging, and if the difference is 8 years or more, he/she is in the age group with a slow aging rate.

Cortisol is a steroid hormone with a clear circadian rhythm with maximum values in the early morning hours after a person wakes up. Reference values in the morning and evening hours are 138-635 nmol/l and 55-327 nmol/l, respectively, and the sensitivity of the method is 0.5 nmol/l. The difference between morning and evening concentrations should normally be at least 100 nmol/l. Blood sampling for the study of hormonal status was carried out twice with an interval of 12 h. The study was conducted on an automatic chemiluminescent immune analyzer (Immulite 2000, Siemens, USA). The specificity of the method for cortisol is 100%.

2.2. Statistical Analysis

In this study, the relationship between BA and the circadian rhythms of cortisol secretion was calculated to elucidate the pathophysiological mechanisms of aging development. In the first step, Pearson and Spearman pair correlation coefficients were calculated in separate and combined groups of patients, and subsequently, multiple linear regression models were used. Biological age was considered a dependent variable (or response variable) and the combinations of circadian rhythms of cortisol secretion were considered independent explanatory variables. Different methods were used to build the models.

The collected data were analyzed in SPSS 21 software. Tukey test and Kruskal-Wallis analysis were used to compare the groups. Student's t-test and Mann-Whitney and Wilcoxon tests were employed to compare the two groups. Arithmetic mean and standard error were used as descriptive statistics determinants, and frequency analysis and χ^2 criteria were used to analyze qualitative or nominal data.

3. Results

Heterogeneity in the male population was identified when determining the BA of patients. The subjects in this study were classified into three groups, including the control group (I) who had normal physiological aging (n=30), the accelerated aging group (II) (n=30), and the group with severe accelerated aging (III) (n=31). The results are presented in table 1.

Analysis of morning serum cortisol secretion in patients of all intervention groups is summarized in table 2, which showed significant differences, compared to the control group (P<0.001). The highest rate was obtained in group III patients at 538.48±16.26 nmol/l, which was 189.51 nmol/l more than that in the control group (I) (P<0.001) and 98.08 nmol/l higher than that in the second group (II) (P=0.012). Therefore, morning cortisol secretion was at the highest level in patients with severely accelerated aging.

Table 1. Indicators of biological age of the surveyed

Indicator (year)	Group I (n=30)	Group II (n=30)	Group III (n=31)	Significance of differences
CA	50.03±0.66	51.37±0.82	52.61±0.60	*P*1-2=0.511 *P*1-3=0.089 *P*2-3=0.561
BA	47.30±0.91	54.83±1.12	63.94±0.55	*P*1-2<0.001 *P*1-3<0.001 *P*2-3<0.001
BA-CA	-2.73±0.43	3.46±0.73	11.33±0.41	*P*1-2<0.001 *P*1-3<0.001 *P*2-3<0.001

CA: Chronological age; BA: Biological age

Table 2. Indicators of circadian rhythms of cortisol secretion

CST	Group I (n=30)	Group II (n=30)	Group III (n=31)	Significance of differences
Morning (nmol/L)	348.97±10.57	440.40±15.42	538.48±16.26	*P*1-2<0.001 *P*1-3<0.001 *P*2-3=0.012
Evening (nmol/L)	168.57±19.00	353.43±19.52	492.94±16.59	*P*1-2<0.001 *P*1-3<0.001 *P*2-3=0.036
Reduction (%)	51.69	19.75	8.46	

CST: Cortisol secretion time

Analysis of data related to overnight serum cortisol secretion showed that there was a significant difference between the studied groups (P<0.001). The highest secretion of cortisol was related to group III, which was higher than the control group and group II (324.34 nmol/l, P<0.001; and 139.51 nmol/l, P=0.036, respectively).

The circadian rhythm of stress hormone secretion in the control group was calculated at 180.4nmol/l. It was important to note the characteristics of the circadian rhythm of stress hormone secretion in patients with accelerated aging (groups II and III). In the second group, physiological indicators of hormone concentration in the morning indicated a slight decrease (86.97±16.07 nmol/l). In group III, a uniform secretion of stress hormone was observed during the day. Therefore, the difference between morning and evening secretion was 45.74±12.87 nmol/l.

To search for the new biological markers of aging, a correlational relationship was determined between the indicators of biological aging and studied parameters of daily cortisol secretion. The analysis of the relationships was carried out by determining Spearman's rank correlation coefficients. A moderate correlation was found between the indicators of BA and the values of morning and evening cortisol secretion in the group of persons with a physiological rate of aging. The indicators of morning cortisol secretion were moderately correlated with BA (r=0.584, P<0.001), while a higher correlation was recorded for the values of evening secretion (r=0.612, P<0.001).

Similarly, for men with accelerated aging, correlations of BA with morning and evening cortisol secretion were determined (r=0.459, P<0.001; and r=0.595, P<0.001, respectively). However, in contrast to patients with physiological aging, individuals with FC IV and V of aging showed an inverse correlation of biological aging with the difference between morning and evening cortisol secretion (r=-0.667, P<0.001).

Based on the performed mathematical modeling, a formula was drawn up to determine the BA of the examined groups of patients, taking into account the circadian rhythms of cortisol secretion.

BA = 41 + (0.05 × evening cortisol secretion)

BA = 68.94 - (0.143 × daily dynamics of cortisol secretion)

4. Discussion

A violation of the "biological clock" of cortisol secretion, consisting of a change in the amplitude of fluctuations in the "day-night" period (the difference between morning and evening secretion is less than 100 nmol/l), was recorded for patients with an accelerated rate of aging. The obtained data were consistent with the results of the studies conducted by the domestic and foreign scientists on the antagonism of cortisol and melatonin, which is a hormone of longevity (25, 26). It is also associated with a simultaneous decrease in the secretion of dehydroepiandrosterone (DHEA), which has a protective role in excess cortisol concentrations. It has been noted that even if the indicators of cortisol secretion do not go beyond the reference values, this does not exclude its toxic effects due to a decrease in DHEA incretion. In this regard, at present, impaired secretions of cortisol and DHEA are considered markers of accelerated aging in individuals (27).

As can be seen from the results of table 2, the rates of morning discharge in groups II and III were 1.26 and 1.54 times that of the control group, respectively; however, the rate of decrease in the evening did not follow the trend of the control group, so that the rate of evening discharge declined 51.69% in the control group and 19.75 and 8.46% in the groups II and III, respectively. Consequently, patients with accelerated types of aging are characterized by a violation of the circadian rhythms of cortisol secretion, distinguished by a consistently high level of the hormone throughout the day.

Concentrated cortisol concentrations naturally decrease with sleep at night; however, this amount was found to be increased as twice the amount of cortisol stabilizers in night shift workers due to disturbed sleep cycles and inappropriate phases. These results are in line with those studies conducted by Chatterton and Dooley (28). On a working day with adequate sleep at night, the maximum plasma cortisol level is at the time of waking up in the morning, which decreases in the evening. This pattern can be seen to some extent in the cortisol secretion profile of fixed-sleepers in this study. Consequently, the formulas obtained in the current study for determining the BA of an organism can be an additional tool for the timely diagnosis of the aging rate of men and the formation of the correct trajectory in the management of accelerated aging to prevent premature mortality among this contingent of persons.

Authors' Contribution

Study concept and design: O. N. B. and E. V. T.
Acquisition of data: S. G. G. and S. V. B.
Analysis and interpretation of data: N. O. Z.
Drafting of the manuscript: S. A. N.
Critical revision of the manuscript for important intellectual content: S. G. G.
Statistical analysis: O. N. B.
Administrative, technical, and material support: S. G. G.

Ethics

The study protocol was approved by the Belgorod State University, Belgorod, Russia. The study included only adults and written informed consents were provided by all the subjects participated in the study

Conflict of Interest

The authors declare that they have no conflict of interest.

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