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Association of GDF 15 and Telomere Length of Circulating Leukocytes in Patients with Sleep Apnea

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Abstract

Background: According to the modern paradigm of scientific research in gerontology, preventing and correcting early involutional processes in the sleep-wake pattern requires a multidisciplinary approach. The aim of this study was to evaluate the relationship between circulating GDF 15 protein levels, relative telomere length (RTL), and functional outcomes in patients with obstructive sleep apnea (OSA).

Methods and Results: The study involved 60 men with an average age of 50.1±3.3 years. The main group (n=36) included OSA patients with snoring, apnea, and excessive daytime sleepiness. The control group consisted of 24 men without complaints of sleep disorders, selected according to the "copy-pair" type. The groups were comparable in age and the presence of chronic diseases. The following methods were used: questionnaires, respiratory monitoring, determination of GDF15 content in blood serum by quantitative sandwich enzyme immunoassay, and RTL using PCR, according to Richard M. Cawthon (2009). A significant negative correlation was found between the blood level of GDF 15 and RTL (r=-0.552, *P*=0.000), and a direct correlation between GDF15 and the apnea/hypopnea index (AHI) (r=0.253, *P*=0.033).

Conclusion: Our results allow us to expand the possibilities of preventing and correcting premature aging by influencing the trigger factors of the pathological process that lead to a cascade of metabolic disorders and early aging of the cell and, subsequently, to age-related structural and functional disorders in the body.(**International Journal of Biomedicine. 2025;15(1):167-170.)**

Keywords: growth differentiation factor 15 • apnea-hypopnea index • telomere length obstructive sleep apnea • aging

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Abbreviations

AHI, apnea-hypopnea index; **ESS**, Epworth sleepiness scale; **GDF15**, growth differentiation factor 15; **NC**, neck circumference; **RLT**, relative telomere length; **WC**, waist circumference

Introduction

Obstructive sleep apnea (OSA) is a serious and life-threatening respiratory disorder for patients. Obstructive sleep apnea is characterized by recurring episodes of respiratory arrest during sleep due to the collapse of the upper respiratory tract. Episodes of apnea contribute to the appearance of nocturnal intermittent hypoxia, sleep fragmentation, and a characteristic complaint of patients with OSA - increased daytime sleepiness.[1-4] Previously, it was believed that this pathology is the "prerogative" of elderly and senile people. However, recent epidemiological studies show a steady increase in the incidence of OSA among the working-age population population.[5,6]

According to the paradigm of scientific research in the field of aging, the need for prevention and correction of early involution in the sleep-wake pattern requires a multidisciplinary approach. Therefore, searching for biomarkers of early pathological aging in respiratory disorders during sleep is an urgent task of modern somnology and geriatric neurobiology. We have previously described telomeric-telomerase relationships in OSA and their changes against the background of elimination of nocturnal intermittent hypoxia.[7-9] Telomere length is known to shorten with age, and

progressive telomere shortening can lead to somatic cell aging, apoptosis, or oncogenic transformation, all of which can affect a person's health and life expectancy.[10-12]

Further search for biomarkers of aging in patients with obstructive breathing disorders during sleep was associated with a change in the content of circulating growth differentiation factor 15 (GDF15), a potential biomarker of aging.[13] The levels of GDF15 dramatically increase in age-related diseases, such as cardiovascular diseases, type 2 diabetes, neurodegeneration, renal chronic disease, and cancer, as well as with aging independently from the health state; thus, GDF15 has been proposed as a novel biomarker of biological aging in humans. [14-17]

We did not find the role of GDF 15 in the pathogenesis of various sleep disorders in the available literature. For the first time in Russia, we described the results of a comparative analysis of the level of circulating GDF 15 in patients with OSA before and after therapy. Our previous data allowed us to conclude that OSA is a pathological condition leading to early cellular aging in average working-age people.[18,19]

This study aimed to evaluate the relationship between circulating GDF 15 protein levels and relative telomere length and functional outcomes in patients with OSA.

Materials and Methods

The study involved 60 men with an average age of 50.1±3.3 years. The main group (MG) consisted of 36 OSA patients who presented to the Irkutsk Somnological Center complaining of snoring, respiratory arrest during sleep, increased daytime drowsiness, morning headaches, and "weak" sleep. The average duration of these complaints was 3.1±0.8 years. The control group consisted of 24 men without complaints of sleep disorders, selected according to the "copy-pair" type. The groups were comparable in age and the presence of chronic diseases.

Anthropometric indicators (BMI, neck and waist circumferences) were measured for all patients. Smokers were defined as those who smoked at least one cigarette per day. Diagnoses established before inclusion in the study were studied by reviewing data from outpatient records. The Epworth sleepiness scale (ESS), a self-administered questionnaire with 8 questions, was used to assess increased daytime sleepiness. [20] In general, ESS scores can be interpreted as follows:

0 to 8: Low daytime sleepiness (normal)
9 to 12: Mild excessive daytime sleepiness
13 to16: Moderate excessive daytime sleepiness
≥17: Severe excessive daytime sleepiness

The sleep data were collected utilizing a MediByte device (Braebon Medical Corporation; Carp, ON, Canada). This method allows us to record the snoring sound and extract the frequency signal while analyzing the airflow during breathing. We can also identify respiratory efforts using inductive plethysmography and register apnea with a thermal sensor and nasal cannula (nasal pressure sensor). The raw data can be displayed for both manual editing and automatic counting.

AHI was calculated during a sleep study. The AHI (the average number of apneas and hypopneas per hour of sleep) was categorized according to the American Academy of Sleep Medicine (AASM): mild (5-15 events/hour), moderate (15-30 events/hr), and severe (> 30 events/hr).[21]

Oxygen desaturation index ODI was defined from the PSG test.[22] ODI refers to the average number of desaturation episodes occurring per hour, where desaturation episodes are defined as a decrease in the mean oxygen saturation of ≥3% (over the last 120 seconds) that lasts for at least 10 seconds.

Determination of Serum GDF15 Level

We collected blood samples in the morning after an overnight fast of more than 8 hours. The fasting serum GDF15 level was measured by quantitative sandwich enzyme immunoassay technique using the SEC113 RA kit from Cloud-Clone Corp. on a Chem Well device (USA) with preliminary application of a specific antibody for GDF 15 followed by protein binding to immobilized antibodies, the detection range is 7.8 pg/mL-500 pg/mL.

Method of Measuring Telomere Length

Genomic DNA was extracted directly from blood samples using standard procedures. RTL was measured using PCR, according to Richard M. Cawthon.[23] The values of the RTL were obtained by evaluating the difference between the values of threshold cycles for telomeric DNA and the reference albumin gene (ΔCt).[23]

Statistical analysis was performed using the STATISTICA 10 software package (Stat-Soft Inc., USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. The normality of the distribution of continuous variables was tested by the Kolmogorov-Smirnov test with the Lilliefors correction and Shapiro-Wilk test. For data with normal distribution, inter-group comparisons were performed using Student's t-test. The frequencies of categorical variables were compared using the chi-square test. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

The BMI, NC, WC, ESS score, AHI, and ODI levels were significantly greater in the main group than in the control group (Table 1).

Table 1

Clinical characteristics and study parameters in individuals who participated in the study.

Characteristics	OSA (n=36)	Control (n=24)	*P*-value
Age, yrs	53.6±2.9	52.2±2.6	0.0614
BMI , kg/м^2	31.2±1.8	28.3±1.9	<0.0001
Smoking, n (%)	10 (27.8%)	6 (25%)	0.8117
NC, cm	42.6±1.9	33.3±1.85	<0.0001
WC, cm	109.9±8.3	82.2±5.6	<0.0001
ESS, score	10.1±0. 9	4.3±0.8	<0.0001
AHI, events/hr	18.1±1.9	4.1±0.5	<0.0001
ODI, events/hr	10.5±2.3	6.5±0.5	<0.0001

An earlier pilot study showed changes in GDF 15 content and relative telomere length in patients with OSA before and after therapy.[7,18,24] In our study, a significant negative correlation was found between the blood GDF 15 and RTL (r=-0.552, *P*=0.000) and a direct correlation between GDF15 and AHI (r=0.253, *P*=0.033). However, there was no statistically significant correlation between GDF15 and ODI (r=0.125, *P*=0.291).

Recent studies have shown that cellular aging plays a significant role in many age-related changes and the development of age-associated diseases. The existing markers of cellular aging are strongly linked to pathological changes in different organs and systems of the body. Additionally, clinical studies have found a strong association between poor sleep quality and increased risk of age-related conditions.[25-28]This suggests that there may be a link between cellular aging and poor sleep quality.

The results of our study support this idea, as they show a negative correlation between GDF 15 and RLT and a positive correlation with the severity of OSA. These findings suggest that cellular changes may be one of the biological mechanisms through which poor sleep can increase the risk of age-related illnesses. Our results align with those of Ortolá et al.[29] At the same time, GDF15 can act as a mediator in processes that protect against inflammatory damage and other stressors. However, under unfavorable conditions in the body's vital functions and increasing age, it can have the opposite effect - GDF-15 becoming a biomarker for chronic diseases in older adults.

In a study by Sari et al.,[30] no significant correlation was found between the level of GDF-15 in the group of patients with OSA and in healthy individuals, which contradicts the results we obtained. In their conclusion, the authors suggested that further studies using a combination of GDF-15 with other OSA biomarkers are needed, which we showed in our study.

In 2019, a group of researchers suggested that the activity of GDF 15 increases in response to telomere dysfunction.[31] We have shown a significant negative correlation between GDF 15 and RLT in OSA. At the same time, there was a close positive relationship between the level of GDF 15 and AHI, but no relationship was found with the ODI. It should be noted that the existing technologies for treating certain diseases that cause systemic accumulation of aging cells make it possible to control the aging process. Our results allow us to expand the therapeutic "windows of opportunity" for the prevention and correction of premature aging by influencing the trigger factors of the pathological process, leading to a cascade of metabolic disorders and early cell aging and, subsequently, to age-related structural and functional disorders at the organizational level.

In conclusion, elimination of intermittent nocturnal hypoxia will reduce the activity of key proteins and markers of aging, and a set of correction methods that take into account the heterogeneity of the pathogenetic mechanisms of sleep disorders will enhance the therapeutic effect on the aging body.[7,9,13]

Ethical Considerations

The study was conducted in accordance with ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Ethics Committee at the Scientific Centre for Family Health and Human Reproduction Problems (Irkutsk, Russia). Written informed consent was obtained from all participants.

Competing Interests

The author declares that there are no competing interests.

This work was carried out using the equipment of the Center for the Development of Advanced Personalized Health Technologies, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

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