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PHOTOPERIODIC VARIATION OF THYROID HORMONES AND AUTOANTIBODIES IN MALES OF THE EUROPEAN NORTH

Aim: to study the circannual dynamics of the concentrations of TSH, thyroglobulin, total and free fractions of iodothyronines, and thyroid autoantibodies in 20 healthy men (average age 33.8 ± 1.1 years), who are permanently resident in Arkhangelsk (64°32'N), and examine the relationship between these measurements and the climatic factors, such as daylight hours, ambient temperature, pressure, and humidity.

Materials and methods. An analytical, prospective, uncontrolled study was conducted with voluntary informed consent. Blood samplings for the assay of the above hormones were collected quarterly during one calendar year. The serum concentration of hormones and antibodies was determined using enzyme-linked immunoassay.

Results. Significant intra-annual rhythms of total iodothyronine concentration were found with lower values in the autumn-winter period. The annual variation in serum thyroid peroxidase antibodies showed a slight, but statistically significant increase in antibody levels in the autumn-winter period compared to the spring one. The levels of thyroglobulin, a marker of thyroid activity, were statistically significantly higher in the spring compared to the autumn period. There were no significant seasonal rhythms in TSH, free iodothyronines and thyroglobulin antibodies.

Conclusion. A study of the circannual rhythms in the level of thyroid hormones in the adult male population of the European North showed year-round variation in total iodothyronines. Only the differences in thyroxine level can be explained by the climatic factors such as air pressure and daylight hours. At the same time, the seasonal variation of total iodothyronine, thyroglobulin and thyroid peroxidase antibody was characterized by small amplitude of the year-round rhythm.

Keywords: thyroglobulin antibodies, thyroid peroxidase antibodies, thyroid stimulating hormone, thyroglobulin, thyroxine, triiodothyronine, photoperiodicity.

Introduction. Seasonal changes in TSH and iodothyronine levels are known both in euthyroid individuals living in extreme Arctic and subarctic environmental and in individuals with a long stay in the Antarctic [8, 9, 16]. Most studies showed an increase in TSH in the winter or through prolonged exposure to cold temperatures [8, 16], in several studies an increase in T3 was observed [8], however, a decrease in iodothyronine levels was also observed [6, 16]. Previous research of seasonal and photoperiodic changes in thyroid hormones in adult residents of the European North showed an increase in the T4 content during the minimum daylight hours, while the T3 content was significantly higher during the maximum daylight hours [5]. Yakut men and women both displayed significant declines of free fractions of iodothyronines, and significant increase in TSH from summer to winter, which indicates a strict relationship between the hormones involved in the axis of the hypothalamus-pituitary-thyroid gland [13]. The results of a study of the circumannual variations of thyroid hormones levels in the adult population of Western Siberia revealed the maximum TSH in February-March in men and in January-February in women, with minimal TSH in September-October and August-September in men and women, respectively. Moreover, the maximum T3 levels accrue to April-May in both men and women, and T4 − September-October [1]. On the other hand, only a few studies revealed seasonal variations in the levels of free fractions of iodothyronines [13]. Since thyroglobulin values were affected by small changes in the thyroid gland volume, some authors consider thyroglobulin as a sensitive indicator of thyroid activity [10]. At the same time, the seasonal variability of thyroglobulin has been poorly studied [8].

Thyroid antibodies can be detected not only in patients with autoimmune diseases, but also in people without severe thyroid dysfunction [2]. Intra-annual dynamics of autoantibody levels can be mediated by seasonal changes in thyroid function associated with daylight hours and temperature. At the same time, seasonal variation of thyroid autoantibodies in the available literature is represented by singular works. So, in the study by Lutfalieva G.T. it was shown an increased level of thyroglobulin antibodies (Anti-Tg) in the winter [3].

Most of the studies lacked reliability as they were conducted before the development of new and efficient assays methods of statistical analysis [5], or it was a retrospective study [7], based on extensive databases which were got from different people in different year seasons. So it remains poorly known the question of seasonal and photoperiodic dynamics of hormones in the same representatives of the population.

The aim of the study was to study the circannual dynamics of the concentrations of TSH, thyroglobulin, total and free fractions of iodothyronines, and thyroid autoantibodies in healthy men and examine the relationship between these measurements and the climatic factors, such as daylight hours, ambient temperature, pressure, and humidity.

Material and methods. 20 euthyroid men (mean age 33.8 ± 1.1 years) residing in Arkhangelsk (64°32'N) took part in a prospective, analytical, uncontrolled

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study on the basis of Voluntary Informed Consent. The study was conducted in accordance with the ethical principles stated in Declaration of Helsinki of 1964 (revised in Seoul in 2008). Criteria for inclusion in the study were: age from 25 to 44 years, passing regular (at least once a year) preventive or medical examination, absence of cardiovascular complaints, systemic diseases and endocrine pathology. Blood for the study was obtained on an empty stomach in the morning. The survey of the same men was carried out quarterly in the period from March to December. With the help of fully automated ELISA analyzer Elisys Uno (Germany) the serum levels of thyroid-stimulating hormone - TSH, total triiodothyronine - T3, total thyroxine - T4, free triiodothyronine - fT3, free thyroxine - fT4, thyroglobulin, thyroid peroxidase antibody – Anti-TPO, thyroglobulin antibodies – Anti-Tg (using test kits from Alkor-Bio, Russia) were determined by enzyme immunoassay. Statistical analysis was performed using the statistical software STATISTICA 10. The normality of distribution of continuous variables was tested by Shapiro-Wilk's W test. In accordance with the obtained results, a nonparametric repeated measures analysis of variance for dependent factorial measures (Friedman test) was used, followed by pairwise comparison using the Wilcoxon test to assess the significance of differences between the two related samples. Spearman's rank correlation coefficient was calculated to measure the strength and direction of the relationship between two variables. A probability value of $p<0.05$ was considered statistically significant.

Results. In the present study, the annual dynamics of the total iodothyronines (T3 and T4) was noted, at the same time, there were no significant seasonal rhythms of the free iodothyronines, which was also shown in the studies by D. Santi et al. [15] (Table). Minimum T3 levels were observed in autumn and winter, and maximum - in the spring and summer, while the examined group of men was characterized by moving of T3 values to the lower limit of normal in spring and summer, and in autumn and winter the median of T3 was below the lower limit of normal. The proportion of individuals with decreased serum T3 was statistically significantly lower in the fall and winter than in the summer, which was 65% versus 35% ($p = 0.03$). The level of T4 was statistically significantly reduced in winter compared to other periods of the year.

Serum TSH levels were highest in winter and lowest in autumn, however, there were no statistically significant differences between the four periods of the year. At the moment many authors identify the value of 2.5 μMU / L as the upper control limit of TSH level due to the fact that its higher values may be associated with impaired thyroid function in the future. So in the present study the prevalence of its increased values were defined [12]. Thus, the proportion of individuals with TSH levels of more than 2.5 μMU/L was statistically significantly higher in the winter than in the autumn and corresponds to 60% versus 25% ($p = 0.01$). In addition, it was found that the annual maximum of serum TSH level (winter) corresponds to the annual minimum of T4, which indicates that the annual spread of T4 partially determines the level of TSH.

The study of the annual variation of thyroid autoantibody levels revealed statistically significantly lower Anti-TPO levels in spring compared to the autumn-winter period with a maximum in December, while there was no seasonal dynamics of Anti-Tg levels. In the study group of men, there were no individuals with positive antibodies whose concentrations exceed the physiological limits, and the median values of autoantibody levels were so low that they did not exceed one unit of measurement, and their spread within one season of the year was also insignificant, which may indicate a low autosensitization in the examined group of healthy men and their ability to maintain body balance and health in the North.

An analysis of the correlation relationships, carried out on the entire database without separation by photoperiods, showed that only the serum T4 level significantly correlated with climatic factors, that is, with daylight hours expressed in minutes ($r = 0.31$; $p = 0.005$), and with atmospheric pressure ($r = -0.32$; $p = 0.004$).

Discussion. The study of Variability in Hormone Concentrations in men of the European North suggests that periods of increasing daylight hours and maximum daylight hours (spring and summer) are characterized by increased levels of hormones that activate metabolic processes (T3 and T4). The absence of seasonal dynamics of the free iodothyronines may indicate the preservation of a sufficient serum level of biologically active thyroid hormone fractions throughout the year, which are necessary for adaptation to changing environmental conditions, while the functional activity of the thyroid gland decreases during the minimum duration of daylight hours, as indicated by significantly lower levels of T4 in the winter. A higher TSH level in winter compared to other periods corresponds to a similar prospective study of healthy men in Finland [16]. Elevated TSH levels in winter may be associated with a decrease in iodothyronine levels in the pituitary gland or with a decrease in the release of somatostatin or dopamine from the hypothalamus. The data presented in this study on a decrease in total iodothyronines levels in the winter period as well as data from studies of subjects wintering on Antarctic bases, which showed a decrease in serum T3 and T4 and an increase in TSH levels, confirm this conclusion [14].

The seasonal dynamics of thyroid hormones can be caused not by a change in the clearance of hormones by thyroid cells, but by a change in the intrinsic

Quantitative data of blood parameters in men of the city of Arkhangelsk depending on the photoperiod of the year (the results are presented as a median and 10/90 percentiles)

Variable	March	June	September	December	p-value
TSH 0,23-3,4 μIU/l	2.43 (1.12; 3.81)	2.17 (1.22; 4.24)	1.81 (0.95; 4.69)	2.64 (1.14; 4.16)	p>0.05
T3 1,0-2,8 nmol/l	1.04 (0.86; 1.37)	1.09 (0.82; 1.38)	0.92 (0.73; 1.21)	0.94 (0.75; 2.26)	p_{1-3}=0.004 p_{2-3}=0.004 p_{2-4}=0.003
T4 53-158 nmol/l	111.91 (95.96; 134.31)	113.45 (101.41; 126.49)	111.07 (87.22; 128.79)	99.03 (90.59; 117.13)	p_{1-4}=0.002 p_{2-4}=0.0002 p_{3-4}=0.014
св. T3 2,5-7,5 pmol/l	5.09 (4.16; 5.59)	5.21 (4.69; 6.68)	5.35 (4.39; 5.85)	5.23 (4.30; 6.07)	p>0.05
св. T4 10,0-23,2 pmol/l	12.55 (11.20; 14.90)	13.05 (11.70; 14.90)	12.90 (10.30; 15.20)	12.90 (11.70; 15.10)	p>0.05
Thyroglobulin 2-50 ng/ml	28.5 (10.58; 54.2)	22.75 (8.55; 52.2)	20.64 (7.91; 49.45)	21.16 (9.69; 62.2)	p_{1-3}=0.036
Anti-Tg <65 U/ml	0.0 (0.0; 0.58)	0.0 (0.0; 0.29)	0.0 (0.0; 0.87)	0.0 (0.0; 0.58)	p>0.05
Anti-TPO <30 Ед/мл	0.08 (0.0; 2.59)	0.24 (0.0; 5.99)	0.49 (0.08; 8.25)	0.65 (0.0; 6.39)	p_{1-3}=0.0005 p_{1-4}=0.008

thyroidal synthetic activity, independent marker of which can be thyroglobulin secretion [8]. So, in our study, the minimum values of thyroglobulin in the autumn-winter period correspond to minimum values of T3 and T4, and the maximum levels of thyroglobulin in the spring period correspond to those for TSH. Thus, we could assume that our study demonstrated a decrease in the thyroidal synthetic activity in the autumn-winter period, followed by a TSH-mediated compensatory increase in the levels of total iodothyronines in the spring.

According to Lutfalieva G.T. and Churkina T.S. the annual dynamics of autoantibodies was associated with changes in natural and climatic factors [3], and therefore, the point of interest was studying the intra-annual fluctuation of autoantibody levels in the same people living in the same climatic conditions. Although there were no representatives with positive antibodies in the studied sampling of healthy men, the dynamics of the absolute values of Anti-TPO showed significant intra-annual changes. The seasonal fluctuations of Anti-TPO with the maximum values in December correspond to the ideas of Nelson R.J. and Demas G.E. that many types of immune reactions are usually enhanced during the minimum duration of daylight hours [11].

The duration of daylight hours and air pressure turned out to be the determining factors affecting the annual dynamics of thyroxine, according to the data of the correlation analysis. At the same time, the correlation relationships of the studied hormones and antibodies with air temperature and humidity were not shown. Since the seasonal variation in levels of total iodothyronines, thyroglobulin and thyroid peroxidase antibodies was characterized by a small amplitude of the year-round rhythm, it can be assumed that healthy young men aged 25 to 44 years old, living permanently in the European North environmental, are successfully adapted and experience slight impact of environmental factors. In this connection, the question of seasonal dynamics of indicators of the hypothalamic-pituitary-thyroid system in men older than 45 years and in the representatives of the female population of the European North remains open.

Conclusion. The main results of this study are that the serum concentrations of T3 and T4 in healthy young men affected by seasonal fluctuations, with higher levels in the spring and summer compared to the fall and winter, while the levels of free iodothyronines and TSH are independent of year season. The study showed a significant decrease in thyroglobulin levels from spring to autumn. Seasonal dynamics are also noted in relation to Anti-TPO levels.

The results of the correlation analysis showed that only differences in T4 levels can be explained by climatic indicators, such as air pressure, and daylight hours.

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