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Review Article

HORMONAL CHANGES IN THE HYPOTHALAMUS-PITUITARY-ADRENAL- GONADS SYSTEM IN YOUNG MEN WITH HYPOTHALAMIC OBESITY

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Abstract.
Purpose of the study - to analyze the frequency and severity of hormonal changes in the hypothalamus-pituitary-adrenal-gonads system in young men with hypothalamic syndrome and alimentary-constitutional obesity. Materials and methods. We examined 340 males (mean age 21.27±2.44 years). Examined patients were divided into the following groups: Group I – hypothalamic syndrome of the late puberty (n=84); Group II – constitutional-exogenous obesity of the late puberty (n=20); Group III – hypothalamic syndrome of mature age (n=158); Group IV – constitutional-exogenous obesity of mature age (n=78). Results. In groups of patients with hypothalamic syndrome, a higher level of morning cortisol ($p<0.05$), evening cortisol ($p<0.05$), prolactin ($p<0.05$), luteinizing hormone ($p<0.05$), follicle-stimulating hormone ($p<0.05$) than in patients with constitutionally-exogenous obesity. In groups of patients with hypothalamic syndrome, lower testosterone levels were recorded than in patients with constitutionally-exogenous obesity ($p<0.05$). Violation of the daily rhythm of cortisol production was more common in patients with hypothalamic syndrome than in constitutionally-exogenous obesity ($p<0.05$). In groups of patients with hypothalamic syndrome, the incidence of high prolactin was higher than in groups of patients with constitutionally-exogenous obesity ($p<0.05$). In groups of patients with signs of hypothalamic syndrome, low testosterone levels were more common than with constitutionally exogenous obesity ($p<0.05$). Conclusion. The data obtained indicate a higher functional activity of the hypothalamus-pituitary-adrenal axis and lower functional activity of the hypothalamus-pituitary-gonads axis in patients with hypothalamic syndrome in comparison with patients with constitutionally-exogenous obesity.

Keywords: hypothalamus dysfunction, hypothalamic obesity, obesity in adolescents, hormonal disorders in adolescents, hormonal disorders in young men

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INTRODUCTION

The protection of youth health is one of the urgent problems of public health and society as a whole (Avdeeva et al. 2011; Evseev 2019). Over the past 30 years, the prevalence of obesity in the world has doubled (GBD 2015), and the problem of obesity in children and adolescents has become one of the most important public health problems in many developed countries (Mattsson et al. 2019). In recent years, there has been a growth trend in obesity among children and adolescents (Telnova and Petunina 2017; GBD 2015; Skinner et al. 2018). In Russia, as in other regions of Russia, there is also an increase in the primary and general incidence of obesity among children and adolescents (Gabbasova et al. 2017; Kruk 2019). Childhood and adolescent obesity subsequently becomes the source of the development of most endocrine and cardiovascular diseases in adulthood (Friedemann et al. 2012; Genovesi et al. 2010; Valerio et al. 2018). Adolescent obesity is associated with morbidity and mortality higher than expected in adulthood (Poluboyarinova 2010). The metabolic phenotyping of obese people is crucial in understanding the pathophysiology of metabolic disorders and is important for identifying high-risk groups and optimizing the prevention strategy for cardiometabolic diseases in the pubertal period (Filatova et al. 2018). Obesity with pink striae is the leading symptom of the hypothalamic syndrome of puberty it is associated with dysfunction of the hypothalamus and emerging hormonal-metabolic disorders (Nikonova et al. 2019; Stroyev et al. 2019). Hypothalamic syndrome is a consequence of primary immaturity of hypothalamic structures (Borovska-Stryuk 2018) or secondary dysfunction caused by structural and functional damage to the hypothalamus (Bereket et al. 2012; Bereket et al. 2015). Manifestations of the hypothalamic syndrome in the form of pink striae, tall, vegetative dysfunction can occur in 46–80% of obese children and adolescents (Ershevskaya et al. 2018; Otto et al. 2018). Over the past 20 years, the prevalence of hypothalamic syndrome of puberty has doubled (Tochilina 2018). However, hypothalamic obesity is not well understood, as evidenced by the small number of studies and publications on this subject (Bereket et al. 2012). In this regard, the study of the problem of hypothalamic syndrome of puberty appears to be very relevant.

PURPOSE OF THE STUDY

To analyze the frequency and severity of hormonal changes in the hypothalamus-pituitary-adrenal-gonads system in young men with hypothalamic syndrome and constitutionally-exogenous obesity.

MATERIALS AND METHODS OF THE STUDY

The study included 340 males of military age (18–27 years old; average age 21.27±2.44 years) examined in the endocrinology department of the St. Petersburg «Mariinsky City Hospital». The study design is shown in Figure 1.

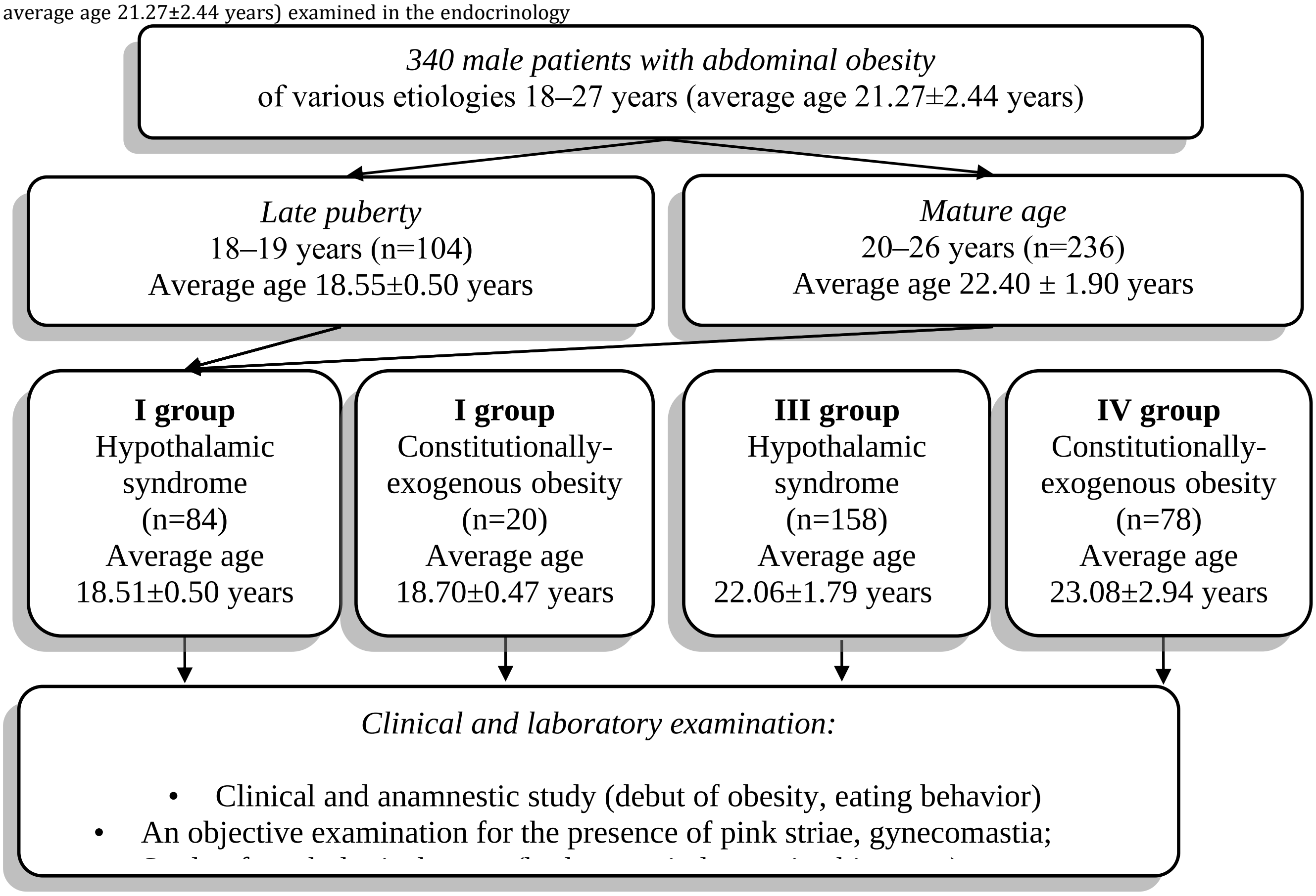

Figure 1. Study design

Criteria for inclusion in the study: age 18–27 years; signs of abdominal obesity; availability of voluntary informed consent to participate in the study. Criteria for not inclusion in the study: patients with diabetes mellitus (fasting venous blood plasma glucose ≥7 mmol/L and / or 2 hours after an oral glucose tolerance test ≥11,1 mmol/L); lack of signs of abdominal obesity; pituitary adenoma; Cushing's syndrome; lack of voluntary informed consent to participate in the study.

In all patients who had pink striae on their skin, the onset of obesity was in childhood. All patients were divided into 4 groups: Group I – patients of the late puberty with hypothalamic syndrome (n=84); Group II – patients of the late puberty with constitutionally-exogenous obesity (n=20); Group III – patients of puberty with obesity associated with hypothalamic syndrome (n=158); Group IV – patients of puberty with constitutionally-exogenous obesity (n=78). Hypothalamic syndrome (hypothalamic obesity, obesity with pink striae) was verified in the presence of a symptom complex, including obesity and pink striae (Stroyev et al. 2019).

Patients of I and II groups were comparable in age (18.51±0.5 and 18.7±0.47 years; p>0.05). Patients of III and IV groups were also comparable in age (22.06±1.79 and 23.08±2.94 years; p>0.05). There were significant age differences between patients of late puberty and patients of puberty (18.55±0.5 and 22.4±1.9 years; p<0.01).

Statistical analysis was carried out in the application package «Statistica 10.0». Quantitative variables are presented as arithmetic mean ± standard deviation (M±σ). Categorical variables are presented in %. Hypotheses on the equality of two averages for parametric data were tested using the Student t-test. The differences were considered statistically significant at p<0.05. To identify intergroup differences in ≥3 groups, the Kruskal-Wallis test (H) was used.

RESULTS AND DISCUSSION

An analysis of laboratory parameters, characterizing the state of the hypothalamus-pituitary-adrenal-gonads system, revealed differences between groups of patients with hypothalamic syndrome and constitutionally-exogenous obesity. This concerned the level of cortisol, both in the morning (361.86±49.0 and 305.18±32.75 nmol/L; p<0.01), and in the evening (245.59±11.44 and 193.48±10.26 nmol/L; p<0.01) (Figure 2).

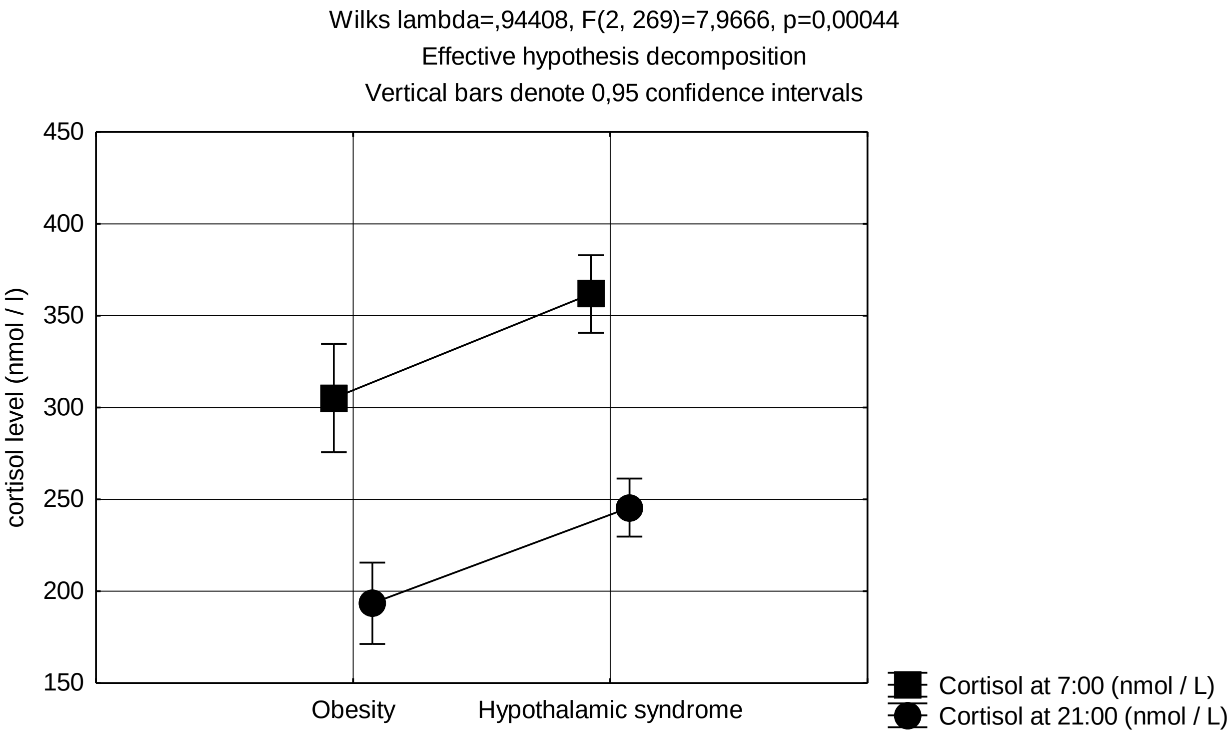

Figure 2. Cortisol levels at 7[00] and 21[00] in patients with hypothalamic syndrome and constitutionally-exogenous obesity

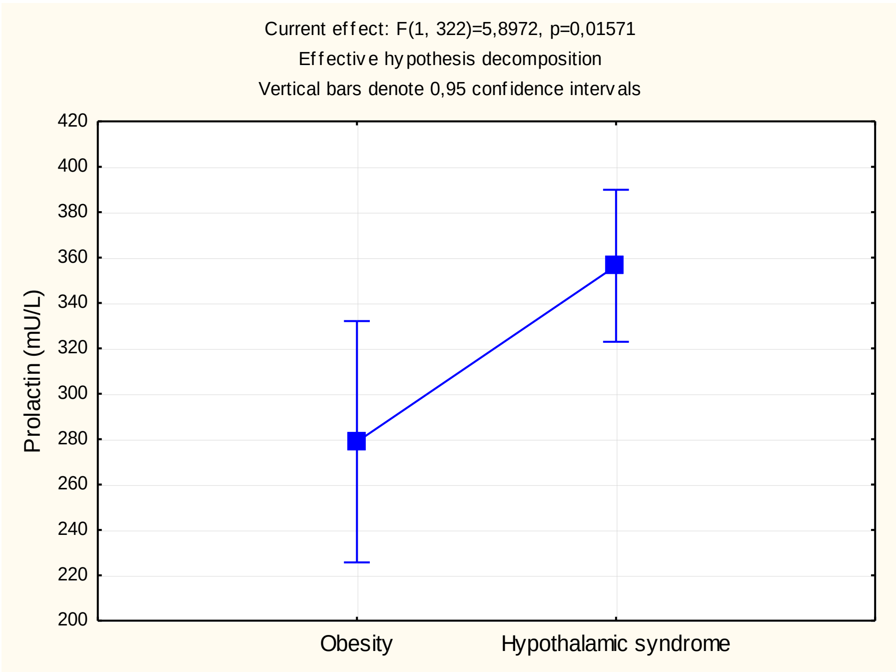

Figure 3. Blood levels of prolactin in patients with hypothalamic syndrome and constitutionally-exogenous obesity

Patients with hypothalamic syndrome differed from patients with constitutionally-exogenous obesity with a higher prolactin level (356.39±29.07 and 278.85 ± 26.65 mU/L; p<0.015 (Figure 3) and lower testosterone (15.50±5.59 and 16.75±6.53 nmol/L; p<0.05) (Figure 4).

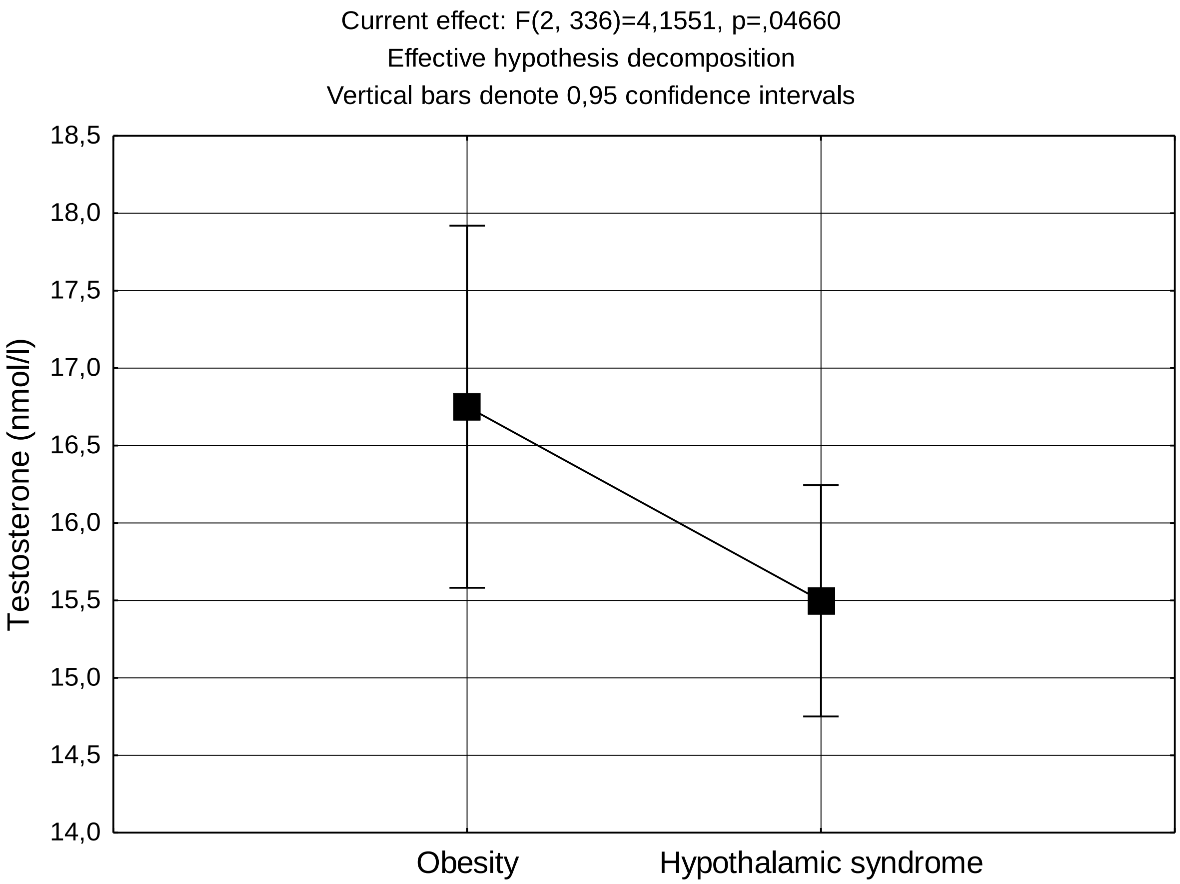

Figure 4. Blood levels of testosterone in patients with hypothalamic syndrome and constitutionally-exogenous obesity

The synthesis and secretion of testosterone are regulated by luteinizing and follicle-stimulating hormones produced by the pituitary gland. Inverse relationship was found between the levels of luteinizing hormone and testosterone ($r=-0.37$; $p<0.05$). The study showed that patients with hypothalamic syndrome have a higher level of luteinizing hormone than patients with constitutionally-exogenous obesity (7.43±4.40 and 5.68±2.65 IU/ ml; $p<0.05$). The average level of luteinizing hormone in the blood, both in hypothalamic syndrome and in constitutionally-exogenous obesity, was normal. The average level of follicle-stimulating hormone did not exceed the norm and did not depend on the etiology of obesity (4.16±2.90 and 4.13±2.59 IU/ml; $p>0.05$) (Figure 5).

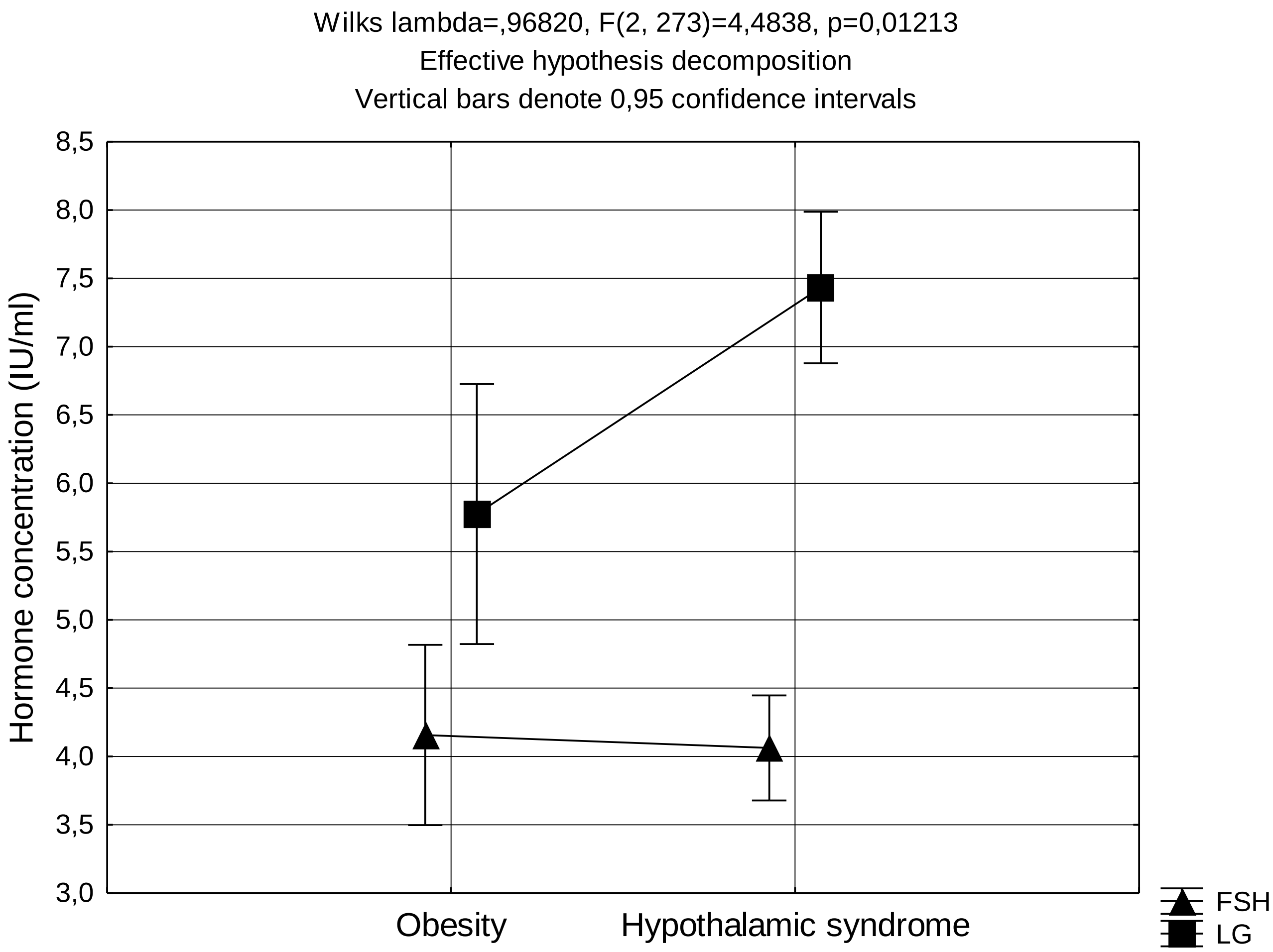

Figure 5 - Blood levels of follicle-stimulating hormone and luteinizing hormone in patients with hypothalamic syndromes and constitutionally-exogenous obesity

Violation of the daily rhythm of cortisol production was more common in patients with hypothalamic syndrome than in constitutionally-exogenous obesity (15.2 and 10.4%; p <0.05). In 7.3% of patients with hypothalamic syndrome, high cortisol values were determined in the morning and 9.6% of patients had high cortisol values in the evening, but this was not observed with constitutionally-exogenous obesity (Figure 6).

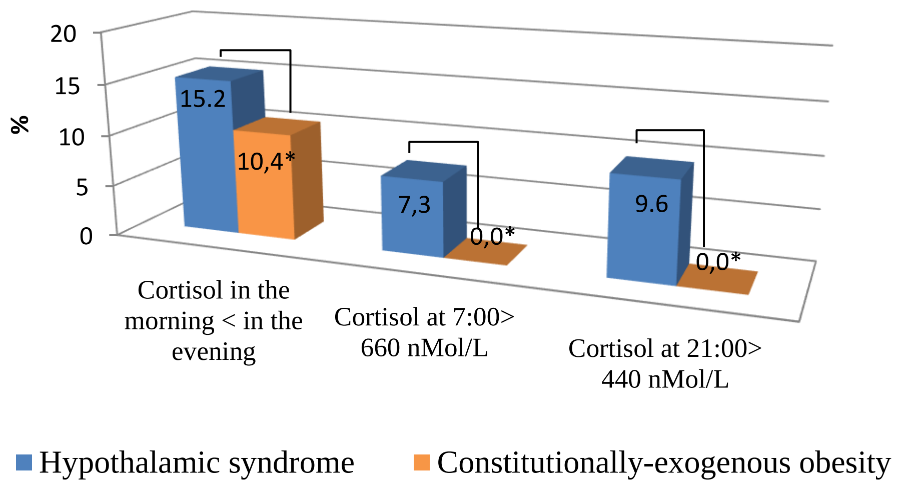

Figure 6. The frequency of violations of the daily rhythm of cortisol production depending on the etiology of obesity (* – p<0.05)

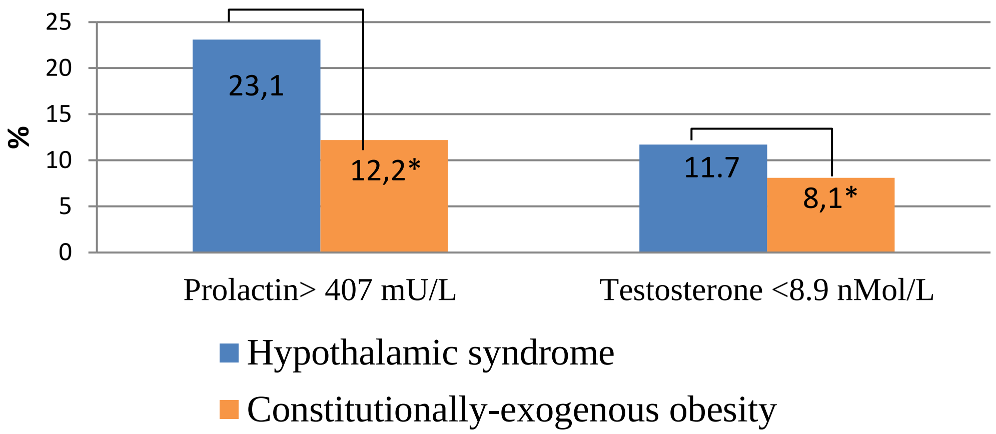

Figure 7. The frequency of abnormalities of prolactin, testosterone and anabolism index depending on the etiology of obesity (* – p<0.05)

Figure 7 shows the frequency of prolactin deviation of more than 407 mU/L, testosterone below 8.9 nMol/L in patients with various etiology of obesity. In hypothalamic syndrome, an increase in prolactin (23.1 and 12.2%; p<0.05) were more common than in constitutionally exogenous obesity. Cases of increased prolactin in patients with constitutionally-exogenous obesity are due to the metabolic effects of the hormone and its secretion by adipose tissue.

The features of hormonal changes in the hypothalamus-pituitary-adrenal gonads system were studied depending on the cause of obesity and the degree of maturity of the body. According to the Kruskal-Wallis test, differences were found in the blood levels of morning cortisol (H=12.07; p<0.01), evening cortisol (H=12.4; p<0.01), testosterone (H=12, 6; p<0.05), anabolism index (H=10.8; p<0.01), prolactin (H=16.1; p<0.05) and luteinizing hormone (H=9.9; p<0.01) between the compared groups of patients (table 1).

Table 1. Hormonal changes depending on the etiology of obesity and the degree of maturity of the body

Indicators	*Late puberty*		*Mature age*		H	p
	I group (M ± σ) n = 84	II group (M ± σ) n = 20	III group (M ± σ) n = 158	IV group (M ± σ) n = 78		
Cortisol at 7:00 (nmol/L)	347,58±17,77	249,78±16,92	363,40±26,47	320,57±33,50	12,07	<0,01
Cortisol at 21:00 (nmol/L)	232,28±13,72	192,16±15,66	261,12±10,41	214,56±12,68	12,4	<0,01
Total testosterone (nmol/L)	15,07±1,55	16,19±0,69	15,14±0,41	17,18±0,73	12,6	<0,05
Prolactin (mU/L)	326,18±15,03	260,00±11,39	372,91±28,98	283,44±14,85	16,1	<0,05
FSH (IU/ml)	3,74±0,25	2,83±0,30	4,54±0,35	4,36±0,26	13,0	<0,01
LH (IU/ml)	7,21±0,45	6,90±0,31	7,63±0,40	5,44±0,31	9,9	<0,05
Estradiol (pmol/L)	105,74±51,72	103,67±81,70	108,83±58,72	101,28±43,72	5,15	>0,05

The highest values of morning cortisol, evening cortisol and prolactin were obtained in patients with hypothalamic syndrome, regardless of the degree of maturity of the body. So, in group I, morning cortisol is higher than in group II (347.58 ±17.77 and 249.78±16.92 nmol/L; p<0.01), and in III group it is higher than in IV (363.4±26.47 and 320.57±33.50 nmol/L; p<0.01). There were also significant differences between groups I and III (347.58±17.77 and 363.40±26.47 nmol/L; p<0.01). A similar situation was observed with regard to evening cortisol levels. So, in group I, the evening level of cortisol was higher than in group II (232.28±13.72 and 192.16±15.66 nmol/L; p<0.01), and in group III higher, than in IV (261.12±10.41 and 214.56±12.68 nmol/L; p<0.01). Significant differences were established between groups I and III (232.28±13.72 and 261.12±10.41 nmol/L; p<0.01), which may indicate an increase in cortisol production as patients with hypothalamic syndrome. In groups of patients with hypothalamic syndrome, lower testosterone levels were recorded than in patients with constitutionally-exogenous obesity (15.07±1.55 and 16.19±0.69 nmol/L; p<0.05; 15.14±0.41 and 17.18±0.73 nmol/L; p<0.05).

An analysis of intergroup differences showed that the highest level of prolactin was in patients with hypothalamic syndrome, regardless of the degree of maturity of the body. In particular, significant differences were obtained between groups I and II (326.18±15.03 and 260.00±11.39 mU/L; p<0.01), as well as between groups III and IV (372.91±28.98 and 283.44±14.85 mU/L; p<0.01). Intergroup differences between groups I and III were also revealed (326.18±15.03 and 372.91±28.98 mU/L; p<0.01), which may indicate an increase in prolactin production as patients with hypothalamic syndrome mature.

A similar situation was observed with respect to luteinizing hormone, since the level of this hormone in group I was higher than in group II (7.21±0.45 and 6.90±0.31 IU/ml; p<0.01), and in group III higher than in IV (respectively: 7.63±0.40 and 5.44±0.31 IU/ml; p<0.01). There were also differences in the level of luteinizing hormone between groups I and III (7.21±0.45 and 7.63±0.40 IU/ml; p<0.05). This may explain the increased production of luteinizing hormone as patients with hypothalamic syndrome mature.

It should be noted that the content of follicle-stimulating hormone in group I exceeded that in group II (3.74±0.25 and 2.83±0.30 IU/ml; p<0.01), and in group III it exceeded that in group IV (4.44±0.35 and 4.36±0.26 IU/ml; p<0.05). Intergroup differences in the content of follicle-stimulating hormone between groups I and III were revealed (3.74±0.25 and 4.54±0.35 IU/ml; p<0.01). This is most likely due to increased production of follicle-stimulating hormone as patients with hypothalamic syndrome mature.

We studied the frequency of violations of the circadian rhythm of cortisol production in patients with a different cause of obesity and maturity of the body (Figure 8).

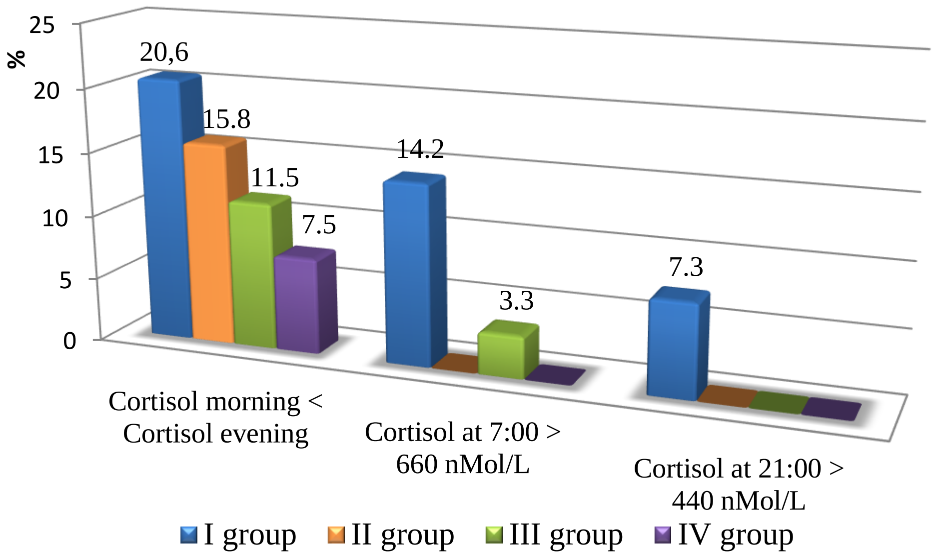

Figure 8. The frequency of violations of the daily rhythm of cortisol production in patients with a different cause of obesity and the degree of maturity of the body

It was found that in patients with hypothalamic syndrome (group I and III), more often than in patients with constitutionally- exogenous obesity (group II and IV), the circadian rhythm of cortisol production was disturbed. So the percentage of patients with dysfunction of the daily rhythm of cortisol in group I was higher than in group II (20.6 and 15.8%; p<0.05), and in group III higher than in group IV (11.5% and 7.5%; p<0.05). In patients of group I with hypothalamic syndrome, high cortisol in the morning was determined in 14.2% of cases, and in group II with constitutionally-exogenous obesity, such cases were not detected (14.2% and 0.0%; p<0.05). In patients of group III with hypothalamic syndrome, high cortisol in the morning was determined in 3.3% of cases, and in group IV with constitutionally-exogenous obesity, such cases were not recorded (3.3% and 0.0%; p<0.05). Identify cases of high values of cortisol in the evening were found only in group III patients of mature age with hypothalamic syndrome (7.3%).

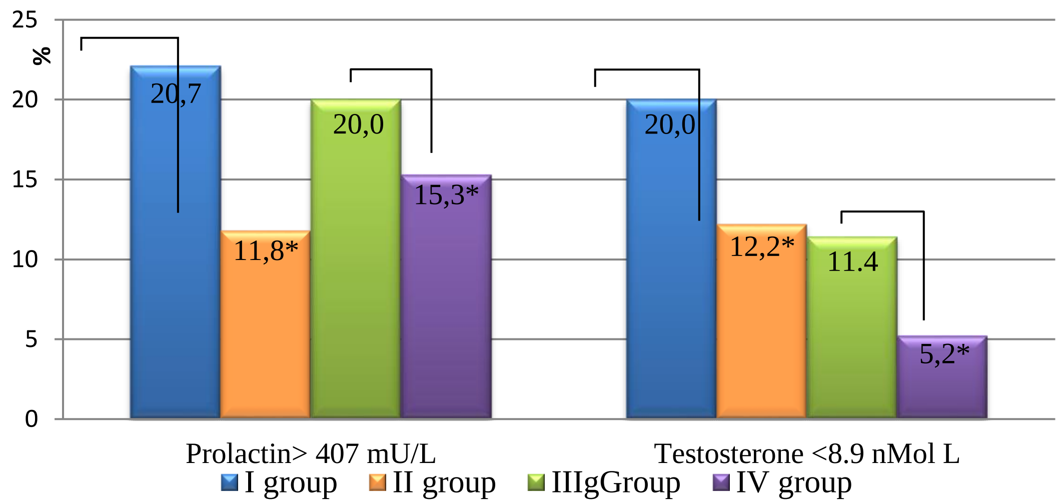

Figure 9. The frequency of abnormalities of prolactin, testosterone and anabolism index in patients with a different cause of obesity and the degree of maturity of the body (* – p <0.05)

In groups of patients with hypothalamic syndrome, the incidence of high prolactin was higher than in groups of patients with constitutionally-exogenous obesity. So, in group I, the frequency of high prolactin levels was 20.7%, and in group II –11.8% (p<0.05). In group III, increased prolactin levels were more common than in group IV (20.0% versus 15.3%; p<0.05). In groups of patients with signs of hypothalamic syndrome, low testosterone levels were more common than with constitutionally exogenous obesity. In group I, the frequency of low testosterone levels was 20.0%, and in group II – 12.2% (p<0.05). In group III patients, decreased testosterone levels were more common than in group IV (11.4% versus 5.2%; p<0.05) (Figure 9).

CONCLUSION

1. In patients with hypothalamic syndrome, there is a higher functional activity of the axis of the hypothalamus-pituitary-adrenal-glands than in constitutionally-

exogenous obesity with a violation of the daily rhythm of cortisol production.

2. Patients with hypothalamic syndrome differ from patients with constitutionally-exogenous obesity have a higher level of prolactin, follicle-stimulating hormone and luteinizing hormone.
3. Patients with hypothalamic syndrome are characterized by lower functional activity of the hypothalamus-pituitary-gonads axis than in constitutionally-exogenous obesity with a decrease in testosterone production. In hypothalamic syndrome, in contrast to constitutionally-exogenous obesity, anabolic activity predominates over androgenic.

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