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INFLUENCE OF THE COMPLEX TREATMENT OF HYPOTHYROIDISM ON THE LEPTIN LEVEL IN PATIENTS WITH PRIMARY HYPOTHYROIDISM

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The total of 188 patients with primary hypothyroidism and 30 people without an impaired function of thyroid gland were examined and compared according to sex and age. While evaluating leptin level in blood serum of patients with hypothyroidism, we noticed that an increase of the body mass in these patients is accompanied by the growth of its concentration. We revealed a more expressed hyperleptinemia in patients with postsurgical hypothyroidism. Basic treatment with levothyroxine and especially its comorbidity with atorvastatin contributed to the improvement of the clinical state of the patients, to the decrease of hypothyroidism manifestations, to the decrease of body mass. Addition of atorvastatin to the complex treatment had a significant impact on the leptin level in patients with hypothyroidism and obesity independently from hypothyroidism etiology.

Key words. Hypothyroidism, hyperleptinemia, obesity, treatment.

The work is a fragment of the scientific research project "Development of New Approaches to Complex Treatment of Hypothyroidism", state registration number 0113U005376.

Lately pathogenetic significance of leptin in metabolic syndrome and obesity pathogenesis, their influence on the glucose and lipids metabolism, development of arterial hypertension, abdominal obesity by a decreased function of the thyroid gland have been intensively studied [13, 11, 6, 10, 7, 2, 1].

Free fatty acids peroxidation is activated due to leptin resistance that may stimulate the development of lipotoxic disorders: development of insulin resistance (IR), endothelial dysfunction, oxidative stress [10, 2, 1, 14]. In some researchers' opinion, thyroid hormones and thyroid-stimulating hormone (TSH) volumes do not have any effect on synthesis and secretion of adipose tissue hormone: leptin. Other studies show that there is a positive correlation between leptin and TSH levels in patients with obesity that reflects a positive correlation between TSH and body mass index (BMI) [7, 15]. Besides, a number of works shows an increase of leptin level in blood serum in patients with hypothyroidism even after correction of BMI [6]. Leptin regulates an energetic homeostasis physiologically informing the central nervous system about fatty tissue deposits, influences neuroendocrine and behavioral responses to overeating, and TSH, in its turn, stimulates leptin secretion in the fatty tissue, the increase of leptin induces stimulation of thyroliberin secretion [6].

Trials of latest years are aimed to study influence of thyroid hormones on insulin behavior, relationship between thyroid function and IR, as well the role of adiponectin, resistin and leptin in regulation of the main metabolism in patients by decreased thyroid function, however these relations are enough complicated [2, 9, 12, 4]. Some works describe the true relationship between leptin level in blood serum and anthropometric data, including IR indices in patients alongside subclinical hypothyroidism (SCH) [6]. Also, a fact was noted that replacement therapy with levothyroxine sodium of patients with SCH did not, however, cause significant results in the decrease of body mass, but showed a significant decrease of leptin level in blood serum in patients with SCH without cardiovascular diseases. Other researchers suppose that hormone replacement therapy not always normalizes cytokines volume [1].

Latest studies have shown that the patients with hypothyroidism present significantly increased cytokines volume causing distorted tissue microcirculation and hypoxia that provokes activation and accumulation of free radicals, damage of the heart, endothelial vascular dysfunction with further increase of tissue hypoxia and distorted oxygenation processes. By hypothyroidism, leptin levels in plasma increase, while adiponectin levels decrease [6].

The purpose of the research was to study the influence of complex treatment of hypothyroidism on the level of leptin in patients with primary hypothyroidism.

Materials and methods. Clinical and functional biochemical tests in patients were performed at the Department of Endocrinology, the Dispensary Department of Endocrinology of Ivano-Frankivsk Regional Clinical Hospital. The study included 188 patients with primary hypothyroidism. Inclusion criteria were: patients' age from 36 to 60 years, newly detected or decompensated hypothyroidism. The diagnosis was made on the basis of complaints, anamnesis, and characteristic clinical picture of manifesting hypothyroidism and was confirmed with the results of hormonal tests. The group for comparison included 30 people without impaired thyroid function, compared according to the sex and

age. All patients underwent a complex clinical examination, measurement of waist circumference (WC) (cm), BMI, estimation of urea, creatinine, total protein levels. Total cholesterol and TSH were estimated with the fermentative method with the help of *Human* reagents, HDL with the help of *Diakon* reagents, respiratory system on an *Accept-200* analyzer. Very-low-density lipoprotein cholesterol (VLDL-C) level in blood was evaluated using a mathematical formula: VLDL = TSH/2,2 mmol/L, and low-density lipoprotein cholesterol (LDL-C) level using a mathematical formula: LDL = total cholesterol – (HDL + TSH/2,2) mmol/L. Additionally, the atherogenic coefficient (CA) was calculated by the formula: CA = (HDL-C)/HDL. Leptin level in blood serum was evaluated with the *DRG Leptin Elisa* reagent set (Germany), norm 3.7–11.1 ng/ml, immunoreactive insulin (IRI) level with the *DRG Diagnostics* ones (Germany). Thyroid hormones (free T_4 and free T_3) levels, as well TSH were evaluated with the *DRG* reagent set (USA). Evaluation of thyroid functional indices (TSH, free T_3, free T_4), leptin and IRI levels was performed with the method of enzyme-linked immunosorbent assay on the *Stat Fax 303 Plus* analyzer (USA) in an accredited intradepartmental science immunoferment laboratory based on the Ye. M. Neyko Chair of Internal Medicine №1, Clinical Immunology and Allergology of IFNMU. Obligatory instrumental examination included measurement of blood pressure, ultrasound imaging of urinary organs. Statistical analysis was performed with the variational statistical method. During analysis of the materials, we calculated medial magnitudes (M), their standard measurement errors (m) and confidence interval. The probability of differences was evaluated according to a Student's *t*-test for dependent and independent samples; by uneven distributions, we used a nonparametric test Mann-Whitney test (U), Wilcoxon test (W). Differences were considered as probable by $p<0.05$. Dependence of indices was evaluated with the Spearman's rank correlation coefficient. Statistical processing of the material was performed with the help of variational and descriptive statistics using standard analytics software packages *Statistica 6.0, Foxbase, Exel 6.0* on the personal computer *Pentium III*.

Results of the study and their discussion: Among the examined 188 patients with hypothyroidism, 152 patients presented with android-type obesity. A pathogenetic link to the metabolic syndrome development is IR that forms alongside abdominal obesity. It is known that abdominal obesity more correlates with insulin resistance index (HOMA IR), than the increase of BMI. Visceral obesity according to WC turned out characteristic for all patients of groups II and IV among men, as well as women. Moreover, the biggest WC indices were noted in patients of the group II with hypothyroidism alongside Hashimoto's thyroiditis.

It was established that IRI level was significantly higher in all examined groups than in the control group ($10/30 \pm 0/34$ mIU/L), $p < 0.05$ (table 1) that testifies expressed hyperinsulinemia in all examined patients with hypothyroidism. However, it was the highest in patients with postsurgical hypothyroidism, and obesity and made up 38.34 ± 2.33 mIU/L, i. e. 3.7 times higher, than in healthy people and 1.9 times exceeded this index in patients with hypothyroidism alongside Hashimoto's thyroiditis without obesity ($p < 0.05$).

HOMA IR index was significantly higher in all groups ($p < 0.05$), but while comparing this index between groups, we revealed that average levels of values in group II were higher in 3.5 times than in control group and in 1.7 times ($p < 0.05$), than in patients of the group I ($p < 0.05$). This index was highest in the group IV among all groups.

In patients of all groups, Caro index was in 1.72–2.9 times lower compared to healthy people ($p < 0.05$) that proves the presence of IR in examined patients with, as well as without obesity.

Correlation analysis showed presence of a direct correlational relationship between HOMA IR index and TSH level: it was direct of medium strength in the group I ($r = 0.485$, $p < 0.05$), the group II ($r = 0.475$, $p < 0.05$) and the group III ($r = 0.621$, $p < 0.05$). The correlational relationship was most expressed in patients with postsurgical hypothyroidism with obesity ($r = 0.741$, $p < 0.05$). A similar dynamics was revealed during the study of relation between Caro index and TSH level: a reversed relationship of medium strength was established in all groups ($r = –0.376$, $p < 0.05$ – in the group I; $r = –0.589$, $p < 0.05$ – in the group II; $r = –0.534$, $p < 0.05$ – in the group III; $r = –0.654$, $p < 0.05$ – in the group IV). A direct relationship of medium strength was revealed also between HOMA IR and WC as in men ($r = 0.376$, $p < 0.05$; $r = 0.589$, $p < 0.05$; $r = 0.534$, $p < 0.05$; $r = 0.654$, $p < 0.05$), as well as in women ($r = 0.376$, $p < 0.05$; $r = 0.589$, $p < 0.05$; $r = 0.332$, $p < 0.05$; $r = 0.654$, $p < 0.05$) respectively.

So, revealed relationships indicate IR presence in all patients with manifested hypothyroidism, with higher expression grade in patients with abdominal obesity.

While evaluating of leptin level in blood serum in patients with hypothyroidism, we noted that increase of body mass in these patients is accompanied by the growth of its concentration. So, the patients with hypothyroidism alongside Hashimoto's thyroiditis presented median leptin level in 4 times

higher in a group with BMI > 24.9 kg/m^2 ($p < 0.05$), than in the group with BMI < 24.9 kg/m^2 ($p < 0.05$) and compared to the index in the control group ($p < 0.001$).

Table 1

Anthropometric and Carbohydrate Metabolism Indices in Patients with Primary Hypothyreosis

Index	Control group, n = 30	Group I patients with Hashimoto's thyroiditis, hypothyroidism, without obesity, n = 45	Group II patients with Hashimoto's thyroiditis, hypothyroidism and obesity, n = 46	Group III patients with manifested hypothyroidism without obesity, n = 47	Group IV patients with manifested hypothyroidism with obesity, n = 50
Fasting lycemia, mmol/L	4.14±0.07	4.73±0.1*	5.13±0.08*	4.41±0.21	5.39±0.10*
BMI, kg/m^2	23.73±0.15	23.80±0.29	32.52±0.37*	23.73±0.20	33.03±0.31*
WC (cm), f	75.75±1.58	77.38±1.10	109.56±1.25*	87.03±0.87*	102.70±1.48*
WC (cm), m	88.40±1.00	89.67±0.79	119.64±1.61*	96.75±0.80*	117.07±2.30*
IRI, mIU/L	10.30±0.34	19.99±0.98*	31.59±1.99*	29.82±1.79*	38.96±2.54*
HOMA IR	2.02±0.14	4.26±0.29*	7.22±0.51*	6.83±0.51*	8.80±0.63*
Car	0.43±0.02	0.25±0.01*	0.17±0.01*	0.18±0.01*	0.15±0.01*

Note. * – difference is probable comparatively to indices in practically healthy people ($P < 0.05$).

The patients with hypothyroidism alongside Hashimoto's thyroiditis without obesity (group I) presented an average leptin value 9.98 ± 0.34 ng/ml that did not significantly differed from an average value in healthy people (10.02 ± 0.87 ng/ml). The patients with hypothyroidism alongside Hashimoto's thyroiditis with obesity that had BMI > 24,9 kg/m^2, showed a significant increase in leptin value compared to the patients with hypothyroidism alongside Hashimoto's thyroiditis without obesity ($p < 0.05$) and the value in the control group ($p < 0.05$) – 39.2 ± 1.41 ng/ml.

In patients with postsurgical hypothyroidism, average leptin levels were higher in all examined groups than in the healthy people. In group III (patients with postsurgical hypothyroidism without obesity) this value was 14.37 ± 0.49 ng/ml significantly higher compared to the value in the control group ($p < 0.05$).

In patients of group IV (patients with postsurgical hypothyroidism with obesity) a significant increase of leptin level-up to 60.36 ± 4.37 ng/ml was established compared to as the control group ($p < 0.05$), as well as the group III ($p < 0.05$).While comparing leptin levels in blood serum in patients with hypothyroidism alongside Hashimoto's thyroiditis and postsurgical hypothyroidism we revealed significantly higher values in patients with postsurgical hypothyroidism as in groups without obesity (groups I and III), $p < 0.05$, as well as groups with obesity (groups II and IV), $p < 0.05$ that indicates more expressed hyperleptinemia in patients with postsurgical hypothyroidism. Hyperleptinemia can be observed as a marker of hypothyroidism with components of metabolic syndrome and can be an independent factor in the development of IR by hypothyroidism. So, development of leptin resistance occurs in an undividable relationship with forming of insulin resistance that proves one more time a principle about systematic, codependent character of development. A golden standard for treatment of hypothyroidism of any etiology is replacement therapy with levothyroxine medication (LT_4). Administration of hormone replacement therapy optimizes lipid-lowering effects of statins but is not an alternative to lipid-lowering therapy [4]. Results of last years studies showed that statins have additional, so-called pleiotropic effects influencing apoptosis, endothelial cell function, anti-inflammatory, antithrombotic action and suppress proliferation of smooth muscle cells, oxidative processes [4]. A further research included 133 patients. All patients were divided into groups dependently on an administered treatment (table 2).

Table 2

Division of Patients Dependently on a Treatment Scheme

Group I (n=32) patients with Hashimoto's thyroiditis, hypothyroidism without obesity	Group I A (n=16)	Group I B (n=16)
	basic treatment with LT_4	LT_4 + atorvastatin 20 mg/day
Group II (n=34) patients with Hashimoto's thyroiditis, hypothyroidism and obesity	Group II A (n=17)	Group II B (n=17)
	basic treatment with LT_4	LT_4 + atorvastatin 20 mg/day
Group III (n=34) patients with manifested hypothyroidism without obesity	Group III A (n=17)	Group III B (n=17)
	basic treatment with LT_4	LT_4 + atorvastatin 20 mg/day
Group IV (n=33) patients with manifested hypothyroidism with obesity	Group IV A (n=15)	Group IV B (n=18)
	basic treatment with LT_4	LT_4 + atorvastatin 20 mg/day

The treatment included 2 stages. The first stage was titration of LT_4 dose. The second treatment stage: atorvastatin 20 mg/day was added to the adjusted LT_4 doses. No patient had any contraindications to administration of atorvastatin. To evaluate the safety of atorvastatin, according to the product label, we

checked in 4 weeks blood glucose, creatine phosphokinase (CPK), liver transaminases (ALT, AST) and uric acid levels in all patients. Any significant abnormalities were not revealed in tested indices.

Using of LT_4 and especially its combination with atorvastatin contributed to the improvement of the clinical state of the patients, the decrease of hypothyroidism manifestations, the decrease of weight and improvement of lipid panel indices. Results of some studies presented a pleiotropic effect of statins in females with Hashimoto's thyroiditis manifested in the decrease of leptin level and positive influence on the cellular link of the immune response.

Table 3

Influence of the Basic and Complex Treatment of Hypothyroidism on Leptin Levels M ± m

Group of Patients		Before treatment	After treatment	Δ, %
Group I	I A	9.73±0.53	9.55±0.35	–1.85
	I B	10.26±0.41	9.81±0.29	–4.4
Group II	II A	38.62±2.48	30.6±1.21*	–20.8
	II B	40.62±1.49	25.22±1.32*#	–37.91
Group III	III A	15.91±0.56	11.19±0.51*	–29.67
	III B	15.83±0.44	10.09±0.57*	–36.26
Group IV	IV A	56.9±3.41	45.4±1.77*	–20.2
	IV B	57.12±3.84	39.34±1.03*#	–31.1

Notes**:** 1. Δ, % is a relation between final and initial index values in percents; 2. Probability between indices before and after treatment * – $p < 0.05$; # – $p < 0.05$ comparing groups A and B.

In our research dynamics of leptin levels in patients with hypothyroidism alongside Hashimoto's thyroiditis without obesity was insignificant independently from used treatment (table 3), whilst in all other groups of patients independently from treatment scheme leptin level decreased significantly alongside compensated hypothyroidism in 6 months. So, in group II A an average value of leptin decreased in 20.8% ($p < 0.05$), in group II B in 37.91% ($p < 0.05$). While comparing results between groups we received significantly better changes in group II B ($p < 0.05$).

In group III A the average leptin level decreased during basic therapy in 29.67% ($p < 0.05$), and in group III B the complex treatment caused a decrease of average leptin value in 36.26% ($p < 0.05$), but the data gotten in subgroups did not significantly differ.

In group IV A that included patients with postsurgical hypothyroidism and obesity the average leptin level decreased in 21.3% ($p < 0.05$) alongside compensated hypothyroidism, and in the group IV B in 31.1% that was significantly lower than before treatment and in the group IV A ($p < 0.05$).

Conclusion

The results obtained show that compensation of hypothyroidism causes a significant decrease of leptin level in patients with obesity independently from hypothyroidism etiology, and the inclusion of atorvastatin to complex treatment had a significant influence on leptin level in patients with hypothyroidism independently from hypothyroidism and BMI etiology.

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Реферати

ВПЛИВ КОМПЛЕКСНОГО ЛІКУВАННЯ ГІПОТИРЕОЗУ НА РІВЕНЬ ЛЕПТИНУ У ХВОРИХ ІЗ ПЕРВИННИМ ГІПОТИРЕОЗОМ

Дідушко О.М., Герич П.Р., Чернявська І.В., Яцишин Р.І., Паньків В.І.

Обстежено 188 хворих на первинний гіпотиреоз та 30 людей без порушення функції щитоподібної залози, порівнянних за статтю і віком. При оцінці рівня лептину в сироватці крові хворих на гіпотиреоз відзначено, що збільшення маси тіла у даних пацієнтів супроводжується наростанням його концентрації. Виявлено більш виражену гіперлептинемію у хворих на післяопераційний гіпотиреоз. Базове лікування левотироксином і особливо його поєднання з аторвастатином сприяло покращенню клінічного стану хворих, зменшенню проявів гіпотиреозу, зниженню ваги тіла. Включення до комплексного лікування аторвастатину мало достовірний вплив на рівень лептину у хворих на гіпотиреоз із ожирінням незалежно від етіології гіпотиреозу.

Ключові слова. Гіпотиреоз, гіперлептинемія, ожиріння, лікування.

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ВЛИЯНИЕ КОМПЛЕКСНОГО ЛЕЧЕНИЯ ГИПОТИРЕОЗА НА УРОВЕНЬ ЛЕПТИНА У БОЛЬНЫХ С ПЕРВИЧНЫМ ГИПОТИРЕОЗОМ

Дидушко О.Н., Герич П.Р., Чернявская И.В., Яцишин Р.И., Панкив В.И.

Обследовано 188 больных первичным гипотиреозом и 30 человек без нарушения функции щитовидной железы, сопоставимых по полу и возрасту. При оценке уровня лептина в сыворотке крови больных гипотиреозом отмечено, что увеличение массы тела у данных пациентов сопровождается нарастанием его концентрации. Выявлено более выраженную гиперлептинемию у больных послеоперационным гипотиреозом. Базовое лечение левотироксином и особенно его сочетание с аторвастатином способствовало улучшению клинического состояния больных, уменьшению проявлений гипотиреоза, снижению веса тела. Включение в комплексное лечение аторвастатина имело достоверное влияние на уровень лептина у больных гипотиреозом с ожирением независимо от этиологии гипотиреоза.

Ключевые слова. Гипотиреоз, гиперлептинэмия, ожирение, лечение.

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HOLDAWAY`S SOFT-TISSUE CEPHALOMETRIC ANALYSIS NORMS FOR THE UKRAINIAN POPULATION

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Numerous studies prove the opposite viewpoint and conclusions about the influence of cephalometric parameters of hard and soft tissues on the aesthetic result that the physician gets at the end of orthodontic treatment. Therefore, there is a need to continue research on the accumulation, analysis and modeling of the patterns of the structure of the craniofacial complex, taking into account ethnic, age and sexual characteristics. The purpose of the work is to study the features of cephalometric parameters in Ukrainian boys and girls with orthognathic bite using the Holdaway method compared to the results established for other races and ethnic groups. With the Veraviewepocs 3D device, Morita (Japan) in 38 boys (in age from 17 to 21 years) and 55 girls (aged from 16 to 20 years) with physiological bite maximally close to the orthognathic side teleroentgenograms were obtained. Measurements were carried out in accordance with the recommendations of R. A. Holdaway (1983, 1984), and cephalometric points were determined according to A. E. Athanasiou (1997) and S. I. Doroshenko, Ye. A. Kulgynskiy (2007). The article presents the cephalometric parameters of soft facial tissues by the Holdaway method for the Ukrainian population of juvenile age with orthognathic bite and evaluates the discrepancies of these parameters with the results obtained by researchers in the study of other populations according to this technique. Among the Ukrainian boys or girls with orthognathic bite and gender-specific indicators of the Saudi, Turkish, North American, Palestinian and Persia populations, as well as with the Japanese (regardless of sex), there are numerous differences in teleroentgenogram indices by the Holdaway method. The largest number of discrepancies in these indicators is set with the Japanese, and the smallest - with the Palestinians.

Keywords: Holdaway`s analysis, cephalometry, Ukrainian boys and girls, orthognathic bite.

The paper is a fragment of the research project "Clinical and experimental justification of the application of new methods for prevention, diagnosis, treatment of children and adolescents with anomalies in the dento-jaw system and caries complications" (state registration No. 0115U007010).

When studying the possibilities of correction of tooth-jaw deformations and the profile of soft facial tissues for the further conduct of orthodontic or surgical treatment or contouring facial plastic surgery, in addition to his subjective vision and wishes of the patient, it is very important for doctor to have more precise meanings of metric indices and their individual variations. After all, the nature of the correlation of the anatomical structures of the head itself creates a sense of harmony and aesthetic perception of its own face [10].