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Original Article

Serum Levels of Leptin and Adiponectin in Patients with Autoimmune Hashimoto's Thyroiditis

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Abstract

Introduction: Adipose tissue is immunologically and hormonally active, and these effects are mediated largely by adipocytokines. Thyroid hormones regulate metabolism and organ function, and Hashimoto's thyroiditis (HT) is the most common autoimmune disease affecting thyroid function.

Aim: To evaluate the levels of the adipocytokines leptin and adiponectin in patients with autoimmune HT, and to perform a comparative intragroup analysis in patients with different stages of gland functional activity, and in a control group.

Materials and methods: Ninety-five patients with HT and 21 healthy controls were enrolled in the study. Venous blood was taken without anticoagulants after at least 12 hours of fasting, and serum samples were frozen at −70°C until analysis. Serum levels of leptin and adiponectin were determined by an enzyme-linked immunosorbent assay (ELISA).

Results: Serum levels of leptin in HT patients were higher than those in the control group (4.5±5.2 ng/mL vs. 1.9±1.3 ng/mL). The hypothyroid patient's group showed significantly higher levels of leptin than those of the healthy controls (5.1±5.2 ng/mL vs. 1.9±1.3 ng/mL), (p=0.031). Leptin levels correlated positively with body mass index (r=0.533, p<0.001), triglycerides (r=0.223, p=0.033), and immunoreactive insulin (r=0.488, p<0.001) levels. Serum adiponectin concentrations were higher in euthyroid HT patients than in the other groups, but the difference was not statistically significant (p=0.68). We found a positive correlation between adiponectin and HDL cholesterol levels (r=0.442, p<0.001), and negative with body mass index (r=−0.217, p=0.03), and immunoreactive insulin (r=−0.341, p=0.002).

Conclusions: The results of this study suggest that leptin has a stronger effect than adiponectin in Hashimoto's thyroiditis, which can be used to develop new therapeutic agents that modify its effect in the organism.

Keywords

adipocytokines, Hashimoto's thyroiditis

INTRODUCTION

Adipose tissue has long been accepted not only as an energy storage but also as an immunologically and hormonally active tissue.[1] There are two main types of adipose tissue in the body – brown adipose tissue, which is more typical for early childhood, and white adipose tissue, which is more typical of adults. These two main types have radically different structures and functions. The cells of the brown adipose tissue are rich in mitochondria and small lipid droplets, and they mainly burn lipids to produce heat, while the cells of the white adipose tissue have much less mitochondria and are filled with stored lipids. The uncoupling protein 1 (UCP1), which is activated in brown adipose tissue cells, interrupts the pathway to ATP synthesis and redirects it to heat production.[2] Hormonal activity is the main characteristic of visceral white adipose tissue. The released adipocytokines have a key effect on energy metabolism, immunity, and inflammation.[3]

Adiponectin is a protein secreted exclusively from adipose tissue, with a relatively high serum concentration in healthy individuals with normal weight (>5-10 μg/mL). It decreases with obesity.[4] It has a considerable anti-inflammatory effect, increases insulin sensitivity and tissue glucose utilization, and inhibits the hepatic gluconeogenesis.[5]

Leptin is a peptide hormone produced mainly by adipocytes, but also by some other cells in the human body, such as enterocytes, T cells, and others. It is one of the main energy balance regulators in the body that acts through appetite control.[6] Unlike adiponectin, its serum level increases with the increases of body's energy reserves in adipose tissue. Thus, leptin levels directly correlate with BMI.[7]

Thyroid hormones regulate the function of many organs and systems in the body by controlling the metabolism of carbohydrates and fats, and the transport of many protein molecules. Changes in their concentrations can decrease glucose utilization or promote insulin resistance in tissues. [8] Thyroid hormones also affect lipid metabolism by regulation of lipolysis, endogenous cholesterol synthesis, activity of lipoprotein lipase and liver lipase, and serum triglyceride levels.[9] The most common autoimmune disease that affects thyroid function is Hashimoto's thyroiditis (HT).[10]

AIM

The purpose of the study was to evaluate the levels of the adipocytokines leptin and adiponectin in patients with autoimmune HT, and to perform a comparative intragroup analysis in patients with different stages of gland functional activity, and in a control group.

MATERIALS AND METHODS

The diagnosis of Hashimoto's thyroiditis was confirmed by the medical history, physical examination, and ultrasound examination of the patients, as well as by the positive anti-thyroid peroxidase antibody (TPO Ab) and anti-thyroglobulin antibody (TG Ab) levels.

Patients

This cross-sectional study was conducted in the Clinic of Endocrinology and Metabolic Diseases of St George University Hospital in Plovdiv between September 2019 and August 2021 among the adult patients who attended the Clinic and were examined there. A total of 106 patients with HT were enrolled in the study, 11 of whom were excluded due to lipid-lowering medications. The diagnosis of Hashimoto's thyroiditis was confirmed by the medical history, physical examination, and ultrasound examination of the patients, as well as by the positive anti-thyroid peroxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-TG Ab) levels. The inclusion criteria were established diagnosis of HT, age >18 years, and a signed informed consent form. The exclusion criteria included acute infections within the previous two months, drug or alcohol abuse, other chronic autoimmune diseases, and lipid lowering medication. The control group included 21 healthy autoimmune disease-free subjects.

The study was approved by the Institutional Ethics Committee of the Medical University of Plovdiv and was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from all participants prior to their enrollment in the study.

Laboratory tests

Venous blood was taken from all patients between 7:30 a.m. and 9:00 a.m. after at least 12 hours of fasting. Blood samples were collected without anticoagulants. Serum samples were obtained by centrifugation after approximately 30 minutes, which was required for full coagulation, and were subsequently frozen at −70°C until analysis.

Serum levels of leptin and adiponectin were determined by the ELISA method using commercially available kits (Sigma Aldrich, Cat Nos RAB0333 and RAB0005), in which monoclonal antibodies against respective adipocytokines were used. The method sensitivity was lower than 2 pg/mL for leptin and 25 pg/mL for adiponectin. Declared inter- and intra- assay reproducibility was lower than 12%, and recovery was in the range of 83% to 104% for both tests. Measurements were made using TECAN Sunrise ELISA reader at 450 nm.

Statistical analysis

Body mass index (BMI) was calculated using the formula: BMI = weight (kg)/height (m^2). Data analysis was performed using the IBM SPSS, version 19.0, for Windows (SPSS Inc., Chicago, Il, USA) with methods of descriptive statistics and statistical inference. Normally distributed data were expressed as mean and standard deviation (SD),

and non-normal distributed data were expressed as median (IQR). For comparisons between groups, Student *t*-test, Mann-Whitney U-test, or Kruskal-Wallis test were used. Correlation was assessed with the Pearson and Spearman's correlation tests. Box plot diagrams were used to visualize the distribution of adiponectin and leptin values among the three subgroups of patients and the control group, and between men and women.

RESULTS

All studied HT patients were allocated into three groups depending on the functional activity of the gland: 40 (42.1%) patients with hypothyroidism, 50 (52.6%) patients with euthyroid status, and 5 (5.3%) patients with hyperthyroidism. Most of the participants (55.8%) were under 42 years old, with more than 59% of them having euthyroid status. Patients with hypothyroid status were predominant in the age group ≥50 years (57.1%). The characteristics of the study groups are shown in **Tables 1, 2**.

The mean BMI was 28.0±6.9 for HT patients and 21.6±2.8 for the control group.

Figs 1, 2 show the serum levels of adiponectin and leptin in the HT groups and the control group.

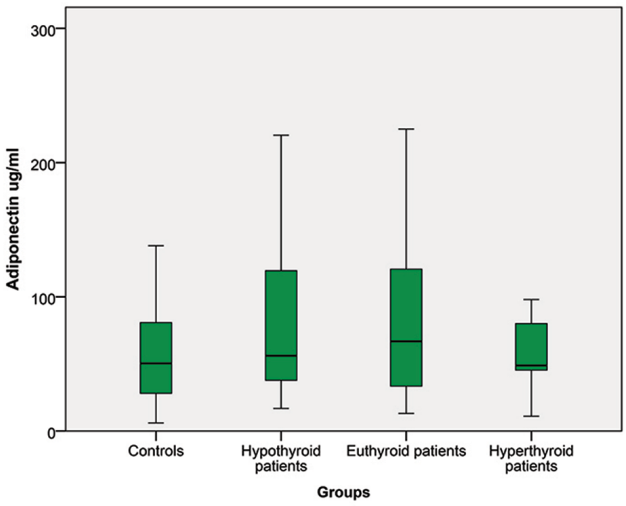

Figure 1. Serum levels of adiponectin in the studied groups.

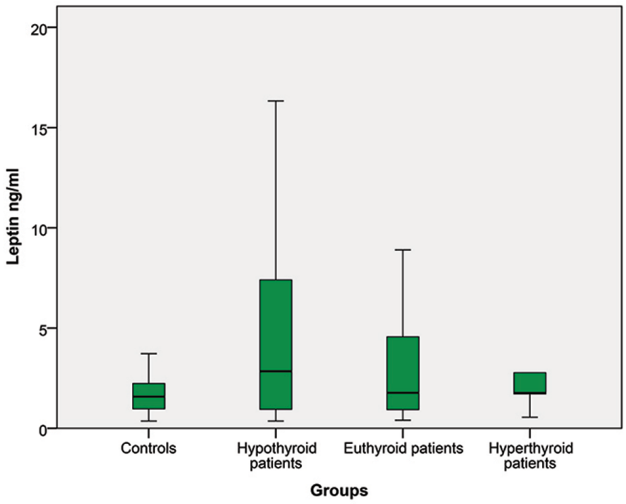

Figure 2. Serum levels of leptin in studied groups.

Table 1. Distribution of participants by gender

	Female	Male	Total
	N (%)		
Control group	17 (81.0%)	4 (19.0%)	21 (100%)
HT group	78 (82.1%)	17 (17.9%)	95 (100%)
Hypothyroid	33 (82.5%)	7 (17.5%)	40 (42.1%)
Euthyroid	43 (86.0%)	7 (14.0%)	50 (52.6%)
Hyperthyroid	2 (40.0%)	3 (60.0%)	5 (5.3%)

Table 2. Demographic and laboratory characteristics of the studied HT groups

Characteristics	Minimum	Maximum	Mean ± SD	Median (IQR)
Age, years	18	73	39.8±13.7	37 (19)
Disease duration, years	< 1	21	3.5±5.1	1 (6)
Height, m	1.5	1.96	1.68±0.1	1.67 (0.08)
Weight, kg	43	140	80.5±21.1	72.0 (33.6)
BMI, kg/m^2	17.7	54.7	28.5±7.1	25.5 (10.5)
TPO Ab, IU/mL, (0-9)	0.3	1192.8	233.8±342.0	13.5 (343.6)
Tg Ab, IU/mL, (0-4)	0.9	2500	74.3±330.0	0.9 (3.2)
TSH, mIU/L, (0.34-5.60)	0.005	100	5.1±13.6	2.4 (2.1)
FT4, pmol/L, (7.84-14.41)	0.7	27.8	11.1±3.3	11.0 (2.8)
FT3, pmol/L, (3.8-6.0)	2.6	12.7	4.9±1.4	4.9 (1.4)
Adiponectin, μg/mL	11	253.8	83.1±61.8	61.5 (83.8)
Leptin, ng/mL	0.4	20.3	4.2±5.2	1.7 (4.5)

BMI: body mass index; TSH: thyrotropin; FT3: free triiodothyronine; FT4: free thyroxine; Tg Ab: thyroglobulin antibodies; TPO Ab: thyroid peroxidase antibody

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Serum adiponectin concentrations ranged from 6 μg/mL to 253.8 μg/mL in all participants. The mean concentration was 77.6 μg/mL and median 57.2 μg/mL. We found that patients with euthyroid status had higher serum adiponectin concentration than the patients in hypothyroid, hyperthyroid, and control groups (83.0±61.3 μg/mL, 78.6±56.3 μg/mL, 56.6±33.6 μg/mL, and 67.6±54.2 μg/mL, respectively) but the difference was not statistically significant (p=0.68).

Serum leptin concentrations were between 0.36 and 25.8 ng/mL in the HT patients, and between 0.36 and 5.0 ng/mL in the control group. The mean leptin value (±SD) was 5.1±5.2 ng/mL for hypothyroid, 3.8±5.1 ng/mL for euthyroid, 5.4±8.3 ng/mL for hyperthyroid patients, and 1.9±1.3 ng/mL for the control group. There are statistically significant differences between the control group and the hypothyroid (p=0.031) patient group.

In the HT patients group, we found significant difference between the serum leptin (p=0.003) and adiponectin (p=0.047) in men and women **(Figs 3, 4)**. We did not find significant difference in the men and women in the control group (leptin p=0.097, adiponectin p=0.395).

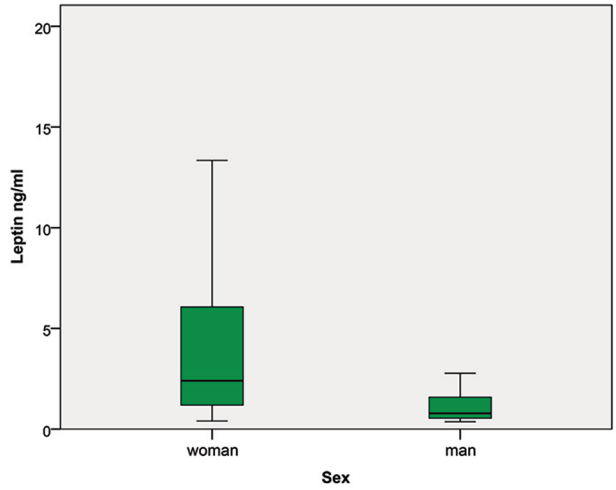

Figure 3. Serum leptin concentration distributed by gender.

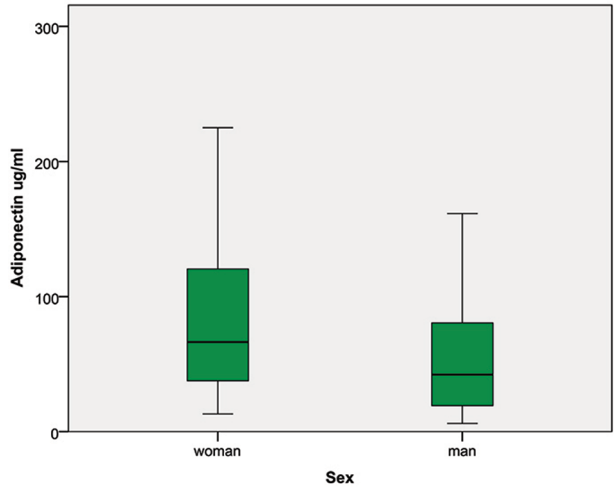

Figure 4. Serum adiponectin concentration distributed by gender.

Correlation analysis showed a positive correlation between adiponectin and HDL-cholesterol (r=0.442, p<0.001) and total cholesterol (r=0.245, p=0.019), and negative correlation with BMI (r=−0.202, p=0.02), and IRI (r=−0.388, p=0.002) in the group of patients with HT. No significant correlation was found between adiponectin levels and age and triglycerides levels.

Leptin levels correlated positively with age (r=0.223, p=0.033), BMI (r=0.533, p<0.001), TG (r=0.223, p=0.033) and IRI (r=0.488, p<0.001). No significant correlation was detected between leptin levels and HDL-cholesterol and liver enzymes.

We found a significant correlation between duration of the disease and antithyroid antibodies (r=0.317, p=0.005 for anti-TG Ab; r=0.294, p=0.0.007 for anti-TPO Ab).

For both adipocytokines, we found no correlation between their serum concentrations and those of thyrotropin, thyroid hormones, thyroid autoantibodies, as well as with the duration of autoimmune disease. We did not find a correlation between thyroid hormones and total cholesterol, HDL-cholesterol, and triglycerides. All correlation data are presented in **Table 3**. All characteristics of HT patients are presented in **Table 4**.

DISCUSSION

Hashimoto disease is the most common cause of hypothyroidism in iodine-sufficient areas of the world.[11] The disease is characterized by diffuse T-cell infiltration of the thyroid gland with lymphoid follicles formation, changes in the thyroid epithelial cells, and development of connective tissue fibers.[12] There is a disturbed Th1/Th2 ratio, with a predominance of Th1 and increased IL-6 levels.[13] The etiology of the disease is not fully understood, but numerous causes have been proposed, including genetic predisposition, stress, vitamin D deficiency, various infection agents, pesticides, polyaromatic hydrocarbons, polyhalogenated bisphenols, and other environmental toxins.[10] Some immunity modulating factors, such as iodine intake, which affect Treg and Th17 differentiation and functions, are also discussed as causes.[14]

HT can occur in various forms - latent or overt hypothyroid type, and euthyroid or, less commonly, hyperthyroid form. The change in the serum thyroid hormone concentration affects the carbohydrate and lipid metabolism. In a previous study, Tagami et al. found a positive correlation between lipid metabolism and TSH levels, and inverse correlation with T4 levels in patients with HT.[15] In the present study, we did not find such correlation.

Under normal conditions, the sympathetic nervous system regulates the functional activity of both types of adipose tissue. This regulation is carried out both directly, through the rich innervation of the brown adipose tissue, and via the synthesis of norepinephrine, thyrotropin, and T4, which increase the lipolysis, the fatty acid release in the circulation, and in the same time their utilization in brown

Table 3. Established correlations in patients with HT

Characteristics	Adiponectin		Leptin		Duration of disease		TSH		FT3		FT4	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	−0.017	0.871	0.223	**0.033**	0.323	**0.002**	0.58	0.586	−0.451	**<0.001**	−0.068	0.528
BMI	−0.217	**0.034**	0.533	**<0.001**	0.110	0.288	0.149	0.157	−0.041	0.717	−0.105	0.32
Cholesterol	0.245	**0.019**	0.175	0.097	0.087	0.411	0.052	0.629	−0.196	0.083	−0.043	0.687
HDL-cholesterol	0.442	**<0.001**	0.034	0.747	−0.097	0.361	0.014	0.901	−0.185	0.102	−0.041	0.707
Triglycerides	−0.184	0.081	0.223	**0.033**	0.167	0.113	0.122	0.257	−0.154	0.177	−0.088	0.414
AST	0.099	0.381	−0.078	0.493	−0.117	0.302	0.134	0.247	−0.014	0.911	0.073	0.529
ALT	−0.156	0.167	0.026	0.826	−0.094	0.407	0.163	0.157	0.071	0.564	−0.045	0.700
TSH	−0.015	0.889	−0.004	0.970	0.115	0.274	1	–	−0.178	0.115	−0.199	0.060
FT3	−0.165	0.140	−0.128	0.254	−0.218	0.051	−0.178	0.115	1	–	0.303	**0.006**
FT4	0.106	0.315	−0.126	0.234	0.183	0.083	−0.199	0.06	0.303	**0.006**	1	–
IRI	−0.341	**0.002**	0.488	**<0.001**	0.061	0.588	−0.088	0.437	−0.065	0.586	−0.098	0.391
Anti TG Ab	0.056	0.628	0.064	0.586	0.317	**0.005**	0.185	0.111	−0.045	0.707	0.008	0.947
Anti-TPO Ab	0.006	0.956	0.047	0.674	0.294	**0.007**	0.211	0.057	−0.173	0.137	0.11	0.924
Duration of disease	−0.095	0.361	0.147	0.156	1	–	0.115	0.274	−0.218	0.051	0.183	0.083

BMI: body mass index; HDL: high-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotrasferase; TSH: thyrotropin; FT3: free triiodothyronine; FT4: free thyroxine; IRI: immunoreactive insulin; anti TG Ab: anti-thyroglobulin antibodies; anti-TPO Ab: anti thyroid peroxidase antibodies. The bold numbers indicate a statistically significant correlation.

Table 4. Laboratory results for HT patients

Test	HT patients by status		
	Hypothyroid	Euthyroid	Hyperthyroid
	Mean (SD)	Mean (SD)	Mean (SD)
Cholesterol, mmol/L	5.53±1.9	5.10±1.0	5.49±1.4
HDL-cholesterol, mmol/L	1.56±0.4	1.43±0.4	1.28±0.5
Triglycerides, mmol/L	1.16±0.7	22511.07±0.7	1.28±1.1
AST, U/L	21.3±5.1	21.4±7.5	21.1±7.0
ALT, U/L	18.7±6.9	20.4±12.6	18.7±9.5
TSH, mU/L	9.66±21.1	2.41±1.3	0.51±0.9
FT3, pmol/L	4.55±1.1	4.98±0.9	7.10±4.8
FT4, pmol/L	10.5±3.4	11.2±1.9	17.1±9.8
HOMA index	1.63±1.2	1.63±1.3	2.82±2.7
Anti-TG Ab, IU/mL	148.7±491.6	10.4±20.0	3.00±3.6
Anti-TPO Ab, IU/mL	370.0±395.6	155.6±332.2	217.51±365.9
Leptin, ng/mL	5.1±5.2	3.8±5.1	5.4±8.3
Adiponectin, µg/mL	78.6±56.3	83.0±61.3	56.6±33.6

TSH: thyrotropin; FT3: free triiodothyronine; FT4: free thyroxine; Tg Ab: thyroglobulin antibodies; TPO Ab: thyroid peroxidase antibody

adipose tissue for heat production. The synergistic effect of norepinephrine and T4 enhances UCP1 expression in brown adipose tissue mitochondria more than 20 times.[16]

The impaired regulation of adipose tissue is also connected with its hormonal activities and blood levels of adipocytokines. The adipocytokines secreted by the adipose tissue are involved in its regulation. Leptin, whose secretion is directly associated with the amount of adipose tissue in the body, exerts its effect by suppressing hunger in the hypothalamus. Leptin levels have been shown to be strongly correlated with BMI.[7] In the present study, we also found a significant correlation of leptin levels with BMI (r=0.533,

p<0.001). Elevated leptin levels are associated with compensatory activation of the hypothalamic-pituitary axis, increased TSH secretion, and connected thyroid hormones, to increase energy expenditure by the body.[1,17] Sieminska et al. reported a correlation between the levels of TSH and leptin.[13] In the central nervous system, leptin has an effect similar to that of insulin on glucose metabolism, but opposite to the effect of body weight. In animal models, elevated leptin concentration is associated with increased insulin sensitivity compared to controls.[18] Also, we found that serum leptin concentrations in HT patients were higher than those in controls. According to Wang et al., this can be accounted for by the higher leptin secretion from CD4+ T cells.[19]

Adiponectin stimulates the transport of glucose in the muscles, while increasing fatty acid utilization by activation of 5'-AMP-activated protein kinase. It also inhibits liver gluconeogenesis and lipogenesis. Therefore, a higher serum adiponectin concentration is associated with increased insulin sensitivity and a low risk for diabetes type II.[20] In healthy people, adiponectin concentration is inversely dependent on the amount of adipose tissue in the body and, in particular, on visceral adipose tissue. In the present study, we found differences between HT and the control group, but they were not statistically significant (p=0.33). In another study, Santini et al. found no statistically significant difference in adiponectin levels between the different groups.[21] Seifi et al. in their study with experimental animals showed that adiponectin gene expression was directly controlled by thyroid hormones.[22]

However, it seems that thyroid status is not the only factor that affects adipocytokine levels in blood - for example, Iglesias et al. looked at serum adiponectin and leptin levels in patient with hyper-, eu- and hypothyroidism and did not find any significant differences between the groups.[23]

Thyroid hormones and adipocytokines have a number of regulatory functions not only in the body metabolism but also in immunity. The effects of leptin on immunity are multilateral – it activates monocytes proliferation, NK and Th1 cell proliferation and differentiation, enhances macrophages phagocytic capacity, stimulates the proinflammatory cytokines TNFα, IL-2, IL-6, IL-12, IFNγ secretion, and inhibits Treg proliferation.[24] Also, leptin is associated with TH17 proliferation. Adiponectin, in contrast to leptin, has anti-inflammatory activities inhibiting monocytes and macrophages proliferation, NK-cells cytotoxicity, and proliferation and activation of T- and B-cells. It also stimulates Treg proliferation, and suppresses VCAM-1, ICAM-1, and selectin expression in vascular endothelium.[24] In experiments with laboratory animals, adiponectin was shown to inhibit IL-6 and stimulate IL-10 production, even in lipopolysaccharide-activated macrophages.[25] Another autoimmune disease such as rheumatoid arthritis responds very well to administration of adiponectin. Experiments with animals have shown a significant reduction in disease activity, a suppression reduction of inflammation, decline of proinflammatory cytokines TNFα and IL-6, stimulation of IL-10 secretion, but without significant depletion of serum autoantibodies.[26]

Although obesity itself is actually related to the promotion of pro-inflammatory processes and increased Th1 and Th17 cells and reduced Treg cells, it is a suitable environment for the occurrence of an autoimmune process.

Limitations of the study

Some limitations of the study need to be recognized. The group of patients with hyperthyroid status includes only 5 individuals, due to the generally low incidence of such status in patients with Hashimoto's thyroiditis. Participants in the control group had a lower BMI than participants with Hashimoto's thyroiditis.

CONCLUSIONS

Regardless of the thyroid status of HT patients, we found higher BMI values in their group compared to the control group. This may be due to the stronger effect of leptin than that of adiponectin in HT. Taking into account other organ-specific autoimmune diseases, as well as the changed Treg/Th17 ratio that characterizes them, as well as the effect of adiponectin on the proliferation and function of these cells, a new direction in the treatment of these diseases should be discussed. For greater objectivity of results, especially for patients with HT patients in hyperthyroid status, more studies are needed to cover a longer period of time for recruitment of a greater number of patients with that status.

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Сывороточные уровни лептина и адипонектина у пациентов с аутоиммунным тиреоидитом Хашимото

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Резюме

Введение: Жировая ткань иммунологически и гормонально активна, и эти эффекты в значительной степени опосредованы адипоцитокинами. Гормоны щитовидной железы регулируют метаболизм и функцию органов, а тиреоидит Хашимото (ТХ) является наиболее распространённым аутоиммунным заболеванием, влияющим на функцию щитовидной железы.

Цель: Оценить уровни адипоцитокинов лептина и адипонектина у больных аутоиммунной ТХ и провести сравнительный внутригрупповой анализ у больных с разной стадией функциональной активности железы и в контрольной группе.

Материалы и методы: В исследование были включены 95 пациентов с ТХ и 21 здоровое лицо в качестве контрольной группы. Венозную кровь брали без антикоагулянтов не менее, чем через 12 часов после последнего приёма пищи, а образцы сыворотки замораживали при -70°C до проведения анализа. Уровни лептина и адипонектина в сыворотке определяли с помощью твёрдофазного иммуноферментного анализа (ELISA).

Результаты: Уровни лептина в сыворотке у пациентов с ТХ были выше, чем в контрольной группе (4.5±5.2 ng/mL против 1.9±1.3 ng/mL). Группа пациентов с гипотиреозом показала значительно более высокие уровни лептина, чем у здоровых людей (5.1 ± 5.2 ng/mL против 1.9 ± 1.3 ng/mL) (p=0.031). Уровни лептина положительно коррелировали с индексом массы тела (r=0.533, p<0.001), уровнями триглицеридов (r=0.223, p=0.033) и иммунореактивного инсулина (r=0.488, p<0.001). Концентрация адипонектина в сыворотке была выше у эутиреоидных пациентов с ТХ, чем в других группах, но разница не была статистически значимой (p=0.68). Мы обнаружили положительную корреляцию между уровнями адипонектина и холестерина HDL (r=0.442, p<0.001) и отрицательную с индексом массы тела (r=–0.217, p=0.03) и иммунореактивным инсулином (r= –0.341, p=0.002).

Заключение: Результаты этого исследования позволяют предположить, что лептин оказывает более сильное действие, чем адипонектин, при тиреоидите Хашимото, что может быть использовано для разработки новых терапевтических средств, модифицирующих его действие на организм.

Ключевые сова

адипоцитокины, тиреоидит Хашимото