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Serum concentrations of leptin, adiponectin, and interleukin-6 in postmenopausal women with Hashimoto's thyroiditis

Stężenie leptyny, adiponektyny i interleukiny-6 w surowicy krwi u kobiet po menopauzie z chorobą Hashimoto

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Abstract

Introduction: Leptin and adiponectin are involved in the pathogenesis of several autoimmune diseases. Very little is known about adipocytokine production in autoimmune thyroid diseases. Interleukin-6 (IL-6) plays an important role in the inflammatory and autoimmune processes.

Material and methods: The aim of this study was to assess the serum levels of leptin, adiponectin, and IL-6 in postmenopausal euthyroid women with Hashimoto's thyroiditis and compared them with concentrations in control women.

Ninety-eight euthyroid women with Hashimoto's thyroiditis were enrolled in the study. The diagnosis was confirmed with elevated thyroid peroxidise autoantibody (TPOAb) levels in serum and typical hypoechogenic pattern on thyroid ultrasound. The control group, matched for body mass index (BMI), consisted of 105 healthy postmenopausal euthyroid women. Serum levels of leptin, adiponectin, IL-6, thyroid-stimulating hormone (TSH), free thyroxine (fT_4), and TPOAbs were determined.

Results: When compared with controls, the women with Hashimoto's thyroiditis were characterized by significantly elevated serum concentrations of IL-6, whereas concentrations of leptin and adiponectin were not different. Hashimoto's thyroiditis patients had significantly higher serum levels of TSH than the controls.

The simple linear regression analyses of the Hashimoto's thyroiditis group and all of the studied women indicated that serum leptin levels correlated positively with BMI, waist to hip ratio (WHR), TSH, and IL-6 and negatively with adiponectin. No correlation was observed between serum adiponectin and TSH, fT_4, or TPOAbs. There were no associations between serum IL-6 levels, TPOAbs, and TSH levels; however, positive correlations between IL-6 and BMI, WHR, and leptin were observed. TSH correlated positively with leptin, age, and TPOAbs.

Conclusions: Hashimoto's thyroiditis is characterized by an increased production of IL-6 but does not have a direct influence on leptin or adiponectin serum levels. The correlations between TSH and leptin demonstrated in this study highlight the need for future investigations. **(Pol J Endocrinol 2010; 61 (1): 112–116)**

Key words: *Hashimoto's thyroiditis, leptin, adiponectin, interleukin-6*

Streszczenie

Wstęp: Leptyna i adiponektyna odgrywają rolę w patogenezie wielu chorób o podłożu autoimmunologicznym. Niewiele wiadomo na temat produkcji adipocytokin w autoimmunologicznych schorzeniach tarczycy. Udowodniony jest udział interleukiny-6 (IL-6, *interleukin 6*) w procesach zapalnych i autoimmunologicznych.

Celem pracy była ocena stężenia leptyny, adiponektyny i IL-6 u kobiet po menopauzie z chorobą Hashimoto i porównanie ze stężeniami u kobiet z grupy kontrolnej.

Materiał i metody: Dziewięćdziesiąt osiem kobiet z chorobą Hashimoto, będących w stadium eutyreozy, tworzyło grupę badaną. Rozpoznanie stawiano na podstawie podwyższonego miana przeciwciał antyperoksydazowych (TPOAb, *thyroid peroxidise autoantibodies*) i typowego obrazu ultrasonograficznego gruczołu tarczycowego. Grupę kontrolną, dobraną pod względem wskaźnika masy ciała (BMI, *body mass index*), stanowiło 105 zdrowych kobiet po menopauzie. Oceniano stężenia leptyny, adiponektyny, IL-6, hormonu tyreotropowego (TSH, *thyroid-stimulating hormone*), wolnej tyroksyny (fT_4, *free thyroxine*) oraz TPOAb.

Wyniki: Średnie stężenie IL-6 u kobiet z chorobą Hashimoto było wyższe niż u kobiet z grupy kontrolnej, natomiast nie stwierdzono różnic w stężeniach leptyny i adiponektyny. W grupie badanej średnie stężenie TSH było wyższe niż w grupie kontrolnej. Stężenie leptyny, zarówno w grupie badanej, jak i wśród wszystkich kobiet razem, dodatnio korelowało z BMI, wskaźnikiem talia–biodro (WHR, *waist to hip ratio*), TSH, IL-6 oraz ujemnie z adiponektyną. Nie stwierdzono zależności pomiędzy adiponektyną, TSH, fT_4 oraz TPOAb. Dodatnią korelację wykryto między stężeniami IL-6 oraz BMI, WHR i leptyną, natomiast nie wykazano powiązań ze stężeniami TPOAb. Stężenie TSH dodatnio korelowało z wiekiem oraz stężeniem TPOAb i leptyny.

Wnioski: Choroba Hashimoto sprzyja zwiększonemu wydzielaniu IL-6, natomiast nie wiąże się ze zmienioną produkcją leptyny i adiponektyny. Wykazana zależność pomiędzy wydzielaniem TSH i leptyny wymaga potwierdzenia w dalszych badaniach.
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Słowa kluczowe: *choroba Hashimoto, leptyna, adiponektyna, interleukina-6*

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Introduction

Autoimmune diseases affect 5–10% of the population and are characterized by an overactive immune response of the body related directly against its own tissues, causing prolonged inflammation. Endocrine autoimmune diseases include Hashimoto's thyroiditis, Graves' disease, and type 1 diabetes mellitus. Hashimoto's thyroiditis is the most common autoimmune thyroid disorder, with a higher prevalence in postmenopausal women. Different genetic and environmental factors are involved in the pathogenesis, including iodine and selenium intake, bacterial and viral infections, cytokine therapy, stress, female sex, and age.

There is evidence for crosstalk between adipose tissue and the immune system. Proper production of adipocytokines is needed to keep optimal immune responses. Over-nutrition has been found to increase the risk of autoimmune diseases and, conversely, undernutrition has been associated with impairment of cell-mediated immunity [1]. Leptin and adiponectin, adipocyte-derived proteins, have immunoregulatory properties and they control immune responses and inflammation. These adipocytokines play an important role in the pathogenesis of several autoimmune diseases such as rheumatoid arthritis, type 1 autoimmune hepatitis, lupus erythematosus, type 1 diabetes mellitus, and autoimmune encephalomyelitis [2–6]. However, very little is known about adipocytokines production in autoimmune thyroid diseases. We have previously found elevated levels of adiponectin in Graves' disease, and hyperadiponectinemia was related to hyperthyroidism and to TSH-R antibodies [7]. To the best of our knowledge, the problem regarding relationships between adipocytokines and Hashimoto's thyroiditis has not been discussed in literature.

Interleukin-6 (IL-6) has been proposed as a marker of inflammatory status. There is evidence of overproduction of IL-6 in obesity [8] and autoimmune diseases such as rheumatoid arthritis [9], systemic lupus erythematosus [10], allergic uticaria [11], and Crohn's disease [12]. Among thyroid autoimmune diseases, increased IL-6 levels have been observed in Graves' disease [13], in subacute thyroiditis, and in amiodarone-induced thyrotoxicosis [14]. The role of this cytokine in Hashimoto's thyroiditis remains unclear. IL-6 regulates growth and differentiation of thyroid cells and its expression in thyreocytes correlates positively with the degree of lymphocyte infiltration [15].

The aim of the present study was to assess the serum levels of adiponectin, leptin, and IL-6 in postmenopausal women with Hashimoto's thyroiditis and to compare them with healthy postmenopausal women in the control group. To eliminate the influence of hypothyroidism on serum concentrations of adipocytokines and IL-6 we selected only euthyroid women for the study.

Material and methods

Ninety-eight euthyroid women with Hashimoto's thyroiditis were enrolled in the study. They were recruited from patients visiting endocrinological clinics for routine check-ups. The diagnosis was confirmed with elevated thyroid peroxidise autoantibody (TPOAb) levels in serum and typical hypoechogenic pattern on thyroid ultrasound. Thyroid function was assessed by measuring serum thyroid-stimulating hormone (TSH). Only women with TSH greater than 0.4 and less than 4.5 mIU/L were enrolled into the study. Smokers and women with diabetes mellitus or coronary artery disease were excluded from the study. The control group, matched for BMI, consisted of 105 healthy postmenopausal euthyroid women, with TPOAbs in normal range, with normal physical and ultrasonographic thyroid examination and with no familiar predisposition to autoimmune thyroiditis. Subjects were accepted for participation in the study after completing a medical evaluation (medical history, physical examination). BMI was calculated as the ratio of weight to the square of height, and WHR was calculated by dividing the circumferences of the waist and hip. Venous fasting blood samples were obtained. Sera were frozen at –70°C for later determination. The study was approved by the Ethics Committee of the Silesian Medical University (Katowice, Poland).

Serum levels of leptin and adiponectin were determined by RIA method using commercial assays (Linco Research). Serum concentrations of IL-6 were assessed by ELISA method (R & D Systems). TSH and free thyroxine (fT_4) were measured by RIA method (ZenTech SA) and normal ranges were from 0.8 to 1.8 ng/ml for fT_4, and from 0.4 to 4.5 uIU/ml for TSH. TPOAbs were determined by RIA kit (Immunotech); the test was positive for values > 20 IU/ml. Measurements were made at the endocrinology clinic immunology laboratory. The intra- and interassay coefficients of variation (CVs) were less than 10%. Results are given as mean ± SD for normally distributed data or median plus (25^{th}; 75^{th}) percentiles for non normal distribution in W Shapiro-Wilka test. For comparisons between groups, t test or Mann-Whitney U test were used. It was assumed that the difference was significant at $p<0.05$. Spearman's correlation coefficients were used to estimate linear relationships between variables. Statistical analysis was performed using Statistica 7.1 package, StatSoft Inc., Tulsa, USA.

Table I. *Clinical and biochemical characteristic of postmenopausal women with Hashimoto's thyroiditis and of the control women*

Tabela I. *Porównanie parametrów klinicznych i biochemicznych w grupie kobiet po menopauzie z chorobą Hashimoto i w grupie kontrolnej*

	Hashimoto's thyroiditis women n = 98	Control group n = 105	p
Age (years)	58.41 ± 6.20	57.35 ± 6.81	NS
BMI [kg/m^2]	28.38 ± 10.86	28.02 ± 9.45	NS
WHR	0.84 ± 0.05	0.84 ± 0.06	NS
Adiponectin [μg/ml]	18.71± 8.73	19.03 ± 7.94	NS
Leptin [ng/ml]	23.39± 13.42	24.05 ± 10.82	NS
IL-6 [pg/ml]	5.51 [3.34; 6.72]	3.26 [2.58; 4.81]	<0.01
TSH [mIU/ml]	3.12 ± 1.27	2.26 ± 1.16	<0.01
fT_4 [ng/dl]	1.2 ± 0.53	1.3 ± 0.46	NS
TPOAb [mIU/ml]	210 [63; 315]	10.35 [6.76; 17.42]	<0.001

Normally distributed data are given as mean ± SD. Skewed data are given as median plus [25th; 75th] percentiles. The significance tests used are the Mann-Whitney U test for not normally distributed variables and unpaired *t* test for normally distributed variables

Results

The characteristics of the study groups are shown in Table I. When compared with controls, the women with Hashimoto's thyroiditis were characterized by significantly elevated serum concentrations of IL-6, whereas concentrations of leptin and adiponectin were not different. Hashimoto's thyroiditis patients had significantly higher serum levels of TSH than controls, but no difference in fT_4 was found.

The simple linear regression analyses of Hashimoto's thyroiditis group and all of the studied women indicated that serum leptin levels correlated positively with BMI, WHR, TSH, and IL-6 and negatively with adiponectin. No correlation was observed between serum adiponectin and TSH, fT_4, or TPOAbs. There were no associations between serum IL-6 levels, TPOAbs, and TSH levels; however, positive correlations between IL-6 and BMI, WHR, and leptin were observed. TSH correlated positively with age, TPOAbs, and leptin (Fig.1). The results of regression analyses for the Hashimoto's thyroiditis group are presented in Table II.

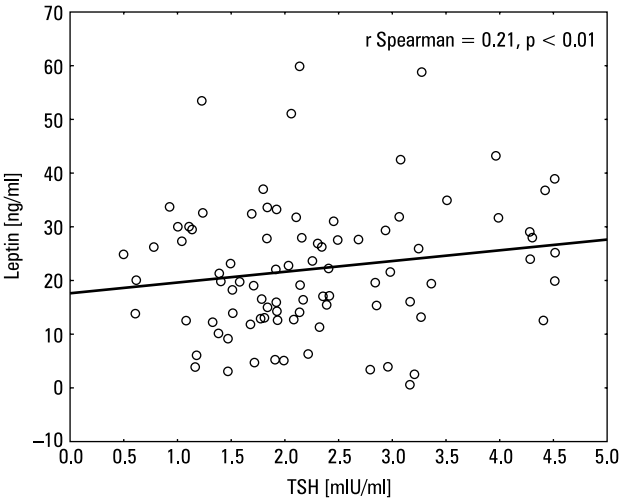

Figure 1. *Relationship between serum TSH and leptin in the Hashimoto's thyroiditis group*

Rycina 1. *Korelacje między stężeniem TSH i leptyny u kobiet z chorobą Hashimoto*

Discussion

Hashimoto's thyroiditis is a localized autoimmune disease which is characterized by the production of the antibodies against thyroid auto-antigens and infiltration of cytotoxic T cells in the thyroid gland leading to the destruction of follicles. Different cytokines released by immune cells cause thyroid cell damage and are involved in inflammatory processes. Diseased thyroids exhibit enhanced expression of IL-6 [16], which induces monocyte chemoattractant protein-1 (MCP-1) production in follicular cells [17] and enhances lymphocyte infiltration in goitrous [15]. IL-6 is produced by B and T lymphocytes (mainly Th-2 cells) as well as by different cells including macrophages and fibroblasts. IL-6 is involved in B-cell activation into antibody-producing cells, proliferation, maturation and in the cytotoxic differentiation of T-cells. In Hashimoto's thyroiditis, deficient functioning of T cells and an imbalance of Th-1/Th-2 cells predominantly expressing Th-1 have been reported [16]. A number of studies have demonstrated that IL-6 concentrations are elevated in the peripheral circulation of patients with autoimmune diseases such

Table II. *Spearman«s coefficients of the relationships between clinical and biochemical parameters in the Hashimoto's thyroiditis group*

Tabela II. *Współczynniki korelacji r Spearmana pomiędzy ocenianymi parametrami klinicznymi i biochemicznymi w grupie badanej*

	r Spearman	p
Leptin & BMI	0.71	< 0.001
Leptin & WHR	0.32	< 0.001
Leptin & TSH	0.21	< 0.01
Leptin & IL-6	0.24	< 0.01
Leptin & adiponectin	–0.30	< 0.001
IL-6 & BMI	0.22	< 0.001
IL-6 & WHR	0.28	< 0.001
TSH & age	0.17	< 0.05
TSH & TPOAbs	0.28	< 0.001

as rheumatoid arthritis [9], systemic lupus erythematosus [10], and allergic uticaria [11]. To date there have been only a few studies regarding connections between IL-6 and Hashimoto's thyroiditis, and the results are not clear. In animal experiments, IL-6 plays a minor role in the development of thyroglobulin-induced autoimmune thyroiditis; however, this cytokine is not involved in iodine-induced thyroiditis [18]. In a recent study, Rugerri et al. found increased levels of IL-6 in Hashimoto's thyroiditis patients [19].

The main finding of our study is that serum IL-6 levels are increased in women with Hashimoto's thyroiditis when compared with a control group, suggesting that IL-6 is involved in the development of the disease. It may be that the elevated concentration is a systematic manifestation of immune activation; however, the clinical significance of our observation is uncertain. The chronic activation of the immune system due to Hashimoto's thyroiditis can lead to impaired endothelium-dependent vasodilation and may cause endothelial dysfunction in humans [20]. It has been shown that IL-6 promotes atherogenesis directly by endothelial-dependent mechanisms and indirectly by stimulating hepatic production of C reactive protein [21].

Although TSH levels in our Hashimoto's females were kept within the normal range, the studied group was characterized by significantly higher TSH concentrations than the controls. It is worth noting that more severe coronary atherosclerosis has been reported in patients with low but clinically normal thyroid function [22]. In the HUNT Study of more than 25 000 people, TSH levels within the reference range were positively associated with coronary heart disease in women [23]. The authors stated that the connections might be the result of the inflammation associated with autoimmune thyroiditis [24]. In our study, TSH correlated positively with leptin, and this adipocytokine promotes atherosclerosis [2].

The second question of our study asked whether there were any associations between IL-6 and other analyzed parameters. Although in *in vitro* studies TSH has been shown to stimulate IL-6 release from differentiated adipocytes [25], in our observations there were no correlations between IL-6 and thyroid function or antithyroid antibodies. However, this cytokine positively correlated with BMI, WHR, and serum concentration of leptin. The results suggest the increased occurrence of Hashimoto's thyroiditis in obesity; however, in our study, the study group had a similar BMI range as in the control group.

In the next step, we examined the serum concentrations of adiponectin and leptin dependent on the presence of Hashimoto's thyroiditis. It is well known that adipocytokines have immunoregulatory functions and their concentrations are elevated in the peripheral circulation of patients with many autoimmune diseases such as type 1 autoimmune hepatitis [4], rheumatoid arthritis [6], and systemic lupus erythematosus [5]. Detailed mechanisms of adiponectin actions remain unknown. The adipokine possesses anti-inflammatory properties although recent studies have documented pro-inflammatory and immunomodulatory effects. Adiponectin activates proinflammatory transcription factor NF-κB and ERK1/2MAPK [26], and influences immune responses by regulating T cell activation and suppressing B cell development. It has been reported that the interplay between adiponectin and immune cells plays a role in the development of autoimmune diseases, and in these states, adiponectin correlates with increased serum levels of leptin and IL-6 [27]. Leptin, another adipocytokine, also influences immune cell function. This protein promotes the proliferation and activation of thymic T cells, and induces a switch towards Th-1 cell immune responses and the suppression of Th-2 cell responses [28]. Leptin is probably a link between nutritional status and immune function. On one hand, leptin-deficient *ob/ob* mice display obesity, thymic atrophy, and defects in immune reactions (innate and adaptive) [29]. In starvation, it has been documented that low serum leptin levels are associated with impaired inflammatory T cell responses, and administration of leptin reverses the immunosuppressive effects [30]. On the other hand, in obesity, decreased immunological tolerance might be a consequence of changed secretion of adipocytokines by adipose tissue. Although overproduction of adiponectin and leptin is pathologically involved in collagen-induced inflammatory autoimmune diseases, in the present study no difference of

serum adiponectin or leptin levels was observed with regard to the presence of Hashimoto's thyroiditis. This finding suggests that the pathogenesis of autoimmune thyroiditis is different and independent of connections with adipose tissue.

In our study, we observed a strong positive correlation between leptin and BMI and WHR, as well as positive connections with TSH and IL-6. The exact mechanism mediating the relationship between leptin and TSH remains unknown. TSH receptors have been found on several fat depots [31]. In animal experiments, TSH directly influences adipose tissue and stimulates adipogenesis through these receptors on the surface of adipocytes [32]. In our study, higher levels of TSH were detected in the studied group and they correlated positively with TPOAbs. The exact role of antibodies against thyroid peroxidase is unclear but it is likely that they promote the release of a variety cytokines including IL-6, TNF-α, and IFN-γ [33]. Nevertheless, we did not find any significant correlation between concentrations of IL-6 and TPOAbs in the peripheral circulation of women with Hashimoto's thyroiditis. This suggests that the two phenomena may not be directly related to each other. Considering the fact that high TPOAbs concentrations correlate with increased frequencies of Th-1 responsible for thyroid damage and the loss of thyroid function, it can be speculated that antibodies influence the level of TSH. Indeed, the presence of TPOAbs is associated with increased risk of the development of hypothyroidism in the future [34].

Conclusions

The findings presented here suggest the possible involvement of IL-6 in the pathogenesis of Hashimoto's thyroiditis. In contrast, the results suggest that autoimmune thyroiditis does not have a direct influence on adiponectin and leptin serum levels. The correlations between TSH and leptin demonstrated in this study highlight the need for future investigations.

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