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Original Scientific Paper

THE ASSOCIATION OF SUBCLINICAL INSULIN RESISTANCE WITH THYROID AUTOIMMUNITY IN EUTHYROID INDIVIDUALS

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SUMMARY – Hashimoto thyroiditis is characterized by anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies that gradually lead to thyroid cell destruction. As hypothyroidism has been associated with insulin resistance (IR), we aimed to investigate whether IR is associated with thyroid antibody presence and whether the degree of IR correlates with their concentration in euthyroid individuals. A total of 164 non-diabetic, euthyroid individuals, average age 34 years, were included in the study, divided into two groups according to Hashimoto thyroiditis and underwent 5-hour oral glucose tolerance test. The degree of IR was evaluated by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). The Hashimoto thyroiditis group had higher HOMA-IR ($p=0.003$) and lower glucose levels ($p=0.04$). HOMA-IR correlated positively with anti-TPO ($p<0.001$). Linear logistic regression revealed that anti-TPO concentration increased by 18.13 ($p=0.001$) with each HOMA-IR unit. IR might trigger thyroid antibody production and Hashimoto thyroiditis development, which needs to be evaluated in further larger scale follow up studies.

Key words: *Insulin resistance; 5-hour oral glucose tolerance test; Hashimoto thyroiditis*

Introduction

Thyroid disorders are present in a great proportion of general population worldwide[1], with hypothyroidism that affects up to 10% of adult population as the most common one[2]. Although there is a spectrum of pathophysiologic factors that precipitate this condition, autoimmune hypothyroidism, i.e. Hashimoto thyroiditis is the most common one in the areas of adequate iodine intake[3]. Hashimoto thyroiditis is part of the spectrum of autoimmune thyroid diseases and is characterized by various cell- and autoantibody-mediated destruction of thyroid cells[4]. The presence of typically anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies (Abs) delineates the cause of hypothyroidism as Hashimoto thyroiditis or its variant, although 10%-15% of patients with Hashimoto thyroiditis may be antibody negative[4,5].

It is well established that hypothyroidism contributes to insulin resistance (IR)[5,6] and related disorders including central obesity, dyslipidemia, impaired cardiac contractility, endothelial dysfunction, atheroscle-

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rosis and increased carotid intima-media thickness[7,8]. In addition, several studies demonstrated overt and subclinical hypothyroidism due to Hashimoto to be more prevalent in individuals with diabetes mellitus as compared with general population[9], and women with subclinical hypothyroidism are believed to be at a higher risk to develop gestational diabetes[10]. Thyroid hormones are known to have a stimulating effect on maturation of the insulin secreting beta cells, and thyroid hormone receptors have been detected in these cells[11]. They also enhance gluconeogenesis and glycogenolysis in an opposing effect to insulin[12], while being known to facilitate the cellular glucose uptake by expressing the glucose transporter-4 isozyme[13].

Knowing that overt hypothyroidism and even subclinical hypothyroidism have been associated with disorders of glucose and insulin metabolism[14] and that thyroid replacement therapy is unable to restore insulin mediated glucose uptake[15], while IR-index is simultaneously showing association with anti-TPO[16], we hypothesized that IR might contribute to Hashimoto disease development. Thus, the primary aim of this study was to investigate whether IR is associated with thyroid autoantibody presence and whether the degree of IR correlates with their concentration in euthyroid individuals.

Subjects and Methods

This cross-sectional study was conducted at Day Hospital of the Mladen Sekso Department of Endocrinology, Diabetology and Metabolic Diseases, Sestre milosrdnice University Hospital Centre in Zagreb, Croatia, and included 164 non-diabetic, euthyroid individuals with clinical signs of IR, i.e. obesity or history of excessive body weight, history of biochemical abnormalities such as dyslipidemia detected during routine screening or workup for a cardiovascular disease, history of hypertension, symptoms of coronary artery disease, symptoms related to other macrovascular disease (e.g., stroke, peripheral vascular disease), microvascular angina, young women with obesity and features of hyperandrogenism (frontal baldness and hirsutism, but rarely features of virilization), women with polycystic ovary syndrome, infertile individuals without evident endocrine disorder, and individuals with the history of hypoglycemia[17].

Body weight was measured with light clothing on a balance scale and height to the nearest 0.5 cm using a meter that was stabilized on the wall. Body mass index (BMI) was calculated as weight (kilograms) divided by height (square meters). All laboratory tests were performed after a 12-h overnight fast. Biochemical parameters including glucose and lipid levels (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG)) and liver enzymes (alanine transaminase (ALT), aspartate transaminase (AST), high-sensitivity C-reactive protein (hsCRP) and creatinine) were evaluated on an Olympus analyzer (Olympus AU600, Olympus Optical Co., Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula[18]. Each individual underwent 5-hour oral glucose tolerance test (5h-OGTT). They were instructed about adequate carbohydrate consumption prior to testing. The test was performed after an overnight fast, between 7 AM and 8 AM. An intravenous catheter was placed in the forearm. After obtaining the baseline blood samples, the participants ingested 75 g of glucose at 0 min, and additional blood samples were obtained every 30 min thereafter for 5 hours.

Insulin resistance was assessed by the homeostasis model assessment index (HOMA-IR): fasting glucose (mmol/L) × fasting insulin (uIU/mL)/22.5). Thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxin (T4) concentrations were measured by immunochemiluminescense assay. Anti-TPO and anti-Tg were determined by radioimmunoassay. The threshold for anti-TPO was <34 kIU/L and for anti-Tg <115 kIU/L.

Diagnosis of hypothyroidism was established if serum TSH concentration was more than 4 mIU/L (reference range 0.4-4 nmol/L) and serum T4 concentration less than 58 nmol/L (reference range 58-161 nmol/L). Individuals with serum TSH level more than 4 mIU/L accompanied by normal T4 and T3 levels were considered as subclinical hypothyroid cases. All patients with enlarged rubbery thyroid and positive serum anti-TPO and/or anti-Tg antibody concentration were categorized as Hashimoto thyroiditis.

Patients with diabetes mellitus, overt hypothyroidism, history of thyroid surgery or radioiodine ablation, cardiovascular disease, cerebral vascular disease, corticosteroid consumption, pregnancy, chronic liver disease, thyroid cancer, renal dysfunction and any autoim-

Table 1. Differences in anthropometric and laboratory findings between euthyroid patients with and without Hashimoto disease

Variable	Patients without Hashimoto thyroiditis (N=53)	Patients with Hashimoto thyroiditis (N=111)	p
Age (years)	35.9±1.9	32.3±1.2	0.103
Gender, female, n (%)	3 (5.6)	9(8.1)	0.159
Body mass index (kg/m^2)	25.5±3.1	26.0±2.9	0.605
Total serum cholesterol (mmol/L)	4.56±0.71	4.91±0.66	0.124
HDL cholesterol (mmol/L)	1.89±0.56	1.45±0.61	0.213
LDL cholesterol (mmol/L)	3.12±0.64	3.18±0.60	0.841
Triglycerides (mmol/L)	0.98±0.41	1.01±0.33	0.935
Fasting plasma glucose (mmol/L)	4.71±0.55	4.69±0.48	0.452
5h-OGTT glucose (mmol/L)	6.27±0.20	5.11±0.16	0.04
Fasting plasma insulin (mIU/L)	11.41±1.59	13.93±1.79	0.07
5h-OGTT insulin (mIU/L)	52.44±1.4	46.71±1.2	0.004
HOMA-IR	3.21±2.8	4.35±2.1	0.003
TSH (mIU/L)	1.50±0.6	3.20±0.3	<0.001
T3 (nmol/L)	1.30 ± 0.21	1.22± 0. 03	0.09
T4 (nmol/L)	98.87±2.55	101.01±1.19	0.902
Anti-TPO (kIU/L)	5.45±0.95	165.61±4.25	<0.001
Anti-Tg (kIU/L)	85.15±5.78	171.15±2.71	<0.001

HDL = high-density lipoprotein; LDL = low-density lipoprotein; 5h-OGTT = 5-hour oral glucose tolerance test; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; anti-TPO = anti-thyroid peroxidase antibodies; anti-Tg = anti-thyroglobulin antibodies

mune disease such as lupus erythematous and rheumatoid arthritis were not included in the study. None of the study individuals was under medication known to affect glucose or lipid metabolism.

The study protocol was approved by the Ethics Committee of the Sestre milosrdnice University Hospital Centre, Zagreb, Croatia, and was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. A written informed consent was obtained from all study participants prior to entering the study.

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) version 23. The normality of distribution was accessed by Shapiro-Wilk test. All variables were log-transformed to correct for their skewed distribution. Baseline characteristics of the groups were compared using t-test or χ^2-test. Correlations were tested by Pearson's coefficient of correlation. The HOMA-IR was adjusted for the possible confounders in linear logistic regression analyzing its association with TSH, anti-TPO and anti-Tg, and in binary logistic regression with Hashimoto thyroiditis as an independent variable. The level of statistical significance was set at $p<0.05$.

Results

A total of 164 non-diabetic, euthyroid individuals, average age 34 years, 92.69% (n=152) of females, were included in the study. They were divided into two groups according to the presence or absence of Hashimoto thyroiditis. Their anthropometric and laboratory characteristics, as well as differences between them are shown in Table 1. Briefly, patients with Hashimoto thyroiditis were younger, had higher BMI, total and LDL cholesterol, as well as triglycerides, fasting and 5h-OGTT insulin concentration and HOMA-IR but lower both fasting and 5h-OGTT glucose levels. Anti-Tg and anti-TPO were positive in 50 (45.05%), anti-Tg in 8 (7.2%) and anti-TPO in 53 (47.74%) patients. In the Hashimoto group, 73 (65.77%) patients had HOMA-IR >2.5, significantly

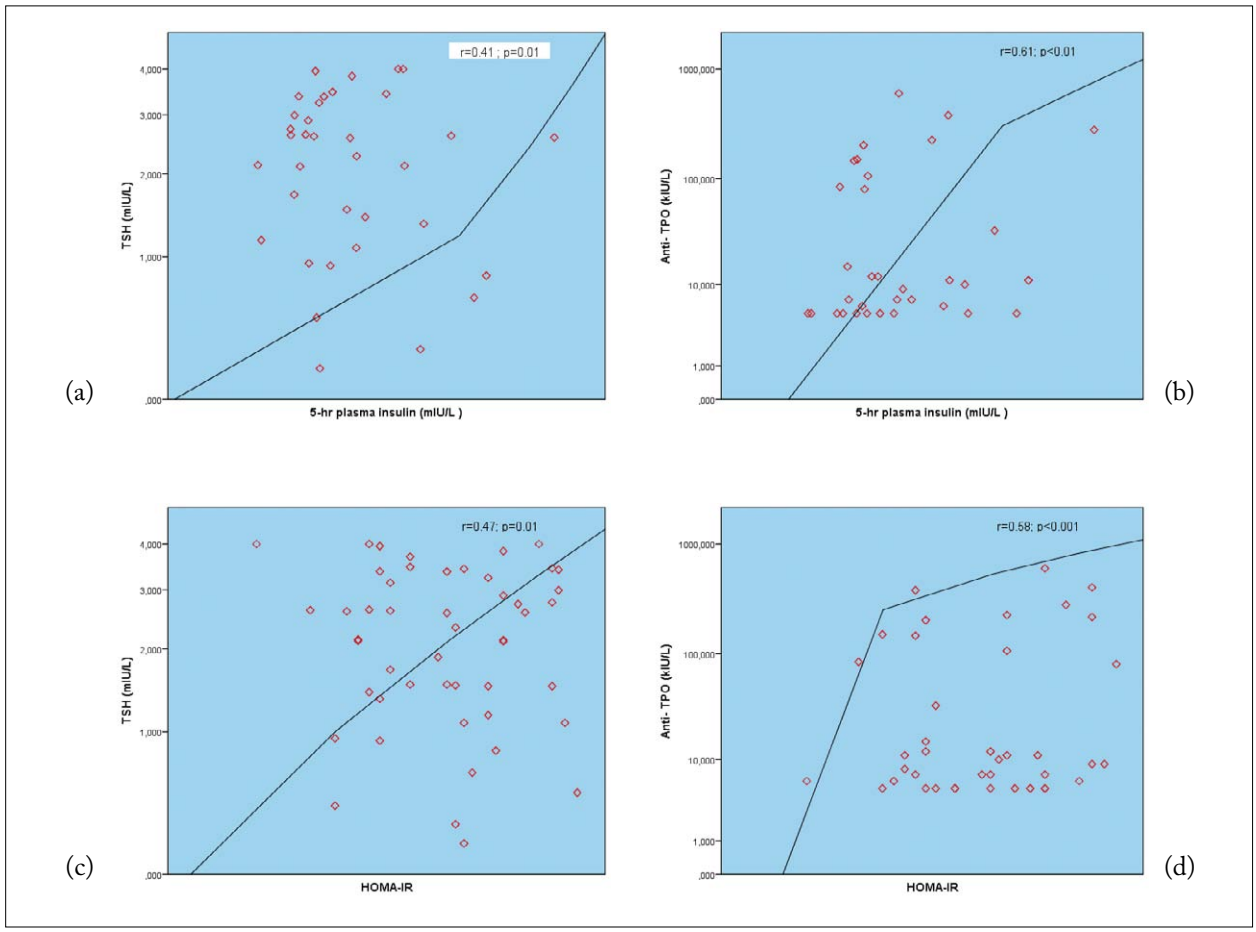

Fig. 1. (a) Correlation between 5-h insulin concentration and TSH; (b) correlation between 5-h insulin concentration and anti-TPO; (c) correlation between HOMA-IR and TSH; (d) correlation between HOMA-IR and anti-TPO.

TSH = thyroid-stimulating hormone; anti-TPO = anti-thyroid peroxidase antibodies; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance

higher compared to the Hashimoto free group (n=18; 33.96%; p=0.001).

The 5h-OGTT plasma insulin correlated positively with TSH (r=0.41, p=0.01) and anti-TPO (r=0.61, p<0.001) but negatively with T3 (r=-0.25, p=0.05) and T4 (r=-0.24, p=0.05). Similarly, HOMA-IR correlated positively with TSH (r=0.47, p=0.01) and anti-TPO (r=0.58, p<0.001) but negatively with T3 (r=-0.25, p=0.05) and T4 (r=-0.31, p=0.02) (Fig. 1a-d).

Linear logistic regression revealed that with each 1 mIU/L increase in 5h-OGTT plasma insulin, TSH concentration raised by 0.22 nmol/L (0.13-0.31; p<0.001) and anti-TPO by 1.56 (1.39-3.28; p=0.018) after age, gender and BMI adjustment. In addition, with each HOMA-IR unit increase, TSH concentration raised by 1.16 nmol/L (0.24-2.07; p=0.015) and TPO by 18.13 (11.43-28.75; p=0.001), whereas T4 dropped by 1.44 nmol/L (-2.69-(-0.303; p=0.016). Other study variables showed no statistical significance (data not shown).

Finally, on binary logistic regression HOMA-IR remained an independent predictor of Hashimoto thyroiditis with a prevalence of 1.755 (95% CI 1.773-1.899; p<0.001).

Discussion

Our study results showed a high prevalence of IR in euthyroid patients with Hashimoto disease and

strong positive correlation between HOMA-IR degree and anti-TPO. In addition, we clearly demonstrated that 5h-OGTT plasma insulin and HOMA-IR correlated not only with TSH but also with anti-TPO, i.e. that an increase in 5h-OGTT plasma insulin, as well as HOMA-IR increased TSH and anti-TPO concentrations in otherwise metabolically healthy individuals. These results are partially in accordance with Iacobellis *et al.*[19], who clearly demonstrated a significant relationship between thyroid function and insulin resistance parameters such as M index from euglycemic clamp, fasting insulin and HOMA-IR index. However, as indicated by these authors, their findings should be interpreted with caution since they might be influenced by BMI because their study included obese women with BMI >40 kg/m^2. The participants in our study did not have BMI >30 kg/m^2 and thus the weight itself could not influence the results. Furthermore, it confirms the data that IR itself is a multifactorial disease and that it affects non-obese individuals[20].

In the past decade, there was a tremendous interest in elucidating the relationship between thyroid function and insulin levels. It is established that clinical hypothyroidism is considered as an insulin-resistant state[6,21], however, the causal relationship between these two states has not been completely understood. Although it has been reported that hypothyroidism makes glucose inaccessible to insulin[22], an exact pathogenetic mechanism involved in IR in hypothyroidism remains unknown. Recently, Mazaheri *et al.*[16] tried to detect association of autoimmunity against thyroid and IR. When adjusted for age and sex, hypothyroid patients had a higher rate of central obesity than general population. Moreover, the high prevalence of IR (44%) in their patients who all were euthyroid for a long time before the study, indicated a mechanism other than the role of low thyroid hormones for IR in hypothyroidism. Higher central fat in their subjects might explain the high prevalence of IR among participants, however, a significantly higher fasting insulin level was detected in a subgroup of patients with Hashimoto thyroiditis and highly elevated levels of anti-TPO antibodies, which might support the concept of IR role in autoimmunity, which is partially in accordance with our study results although we did not measure waist circumference as a measure of central obesity.

Hashimoto disease could be considered a T helper 1 disease in which proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) play a crucial role[23,24]. There is a connection between the level of anti-TPO antibodies and proinflammatory cytokines such as TNF-α and IL-6, which appear at higher concentrations in individuals with IR[25]. The production of proinflammatory cytokines might result in an immunity complex, which then activates the complement pathway and ultimately the T cells, thus leading to an increase in antibodies produced against the antigens specific to the thyroid such as TPO[23]. Therefore, anti-TPO antibodies, which play a predictive role in the progress of hypothyroidism, can have either direct cytotoxic effect on thyroid cells through the IgG1 class[24], or indirect destructive effect on thyrocytes through activating TH1 cells and increasing inflammatory response *via* release of inflammatory cytokines[26].

Moreover, the present study showed the euthyroid subjects positive for anti-TPO and/or anti-Tg antibodies to have higher total serum cholesterol and LDL cholesterol but lower serum HDL concentration as compared to the antibody negative group, which is also partially in accordance with Mazaheri *et al.*[16]. However, except for the Hashimoto thyroiditis subgroup with highly positive antibody levels, they did not find any difference between patients with and without autoimmunity regarding their lipid profile. We could explain these differences with the fact that some of their study participants were using levothyroxine in therapy, which definitely interfered with the results obtained. There is a growing body of literature suggesting the effect of levothyroxine on lipid profile, suggesting that its administration indeed helps reduce total cholesterol and LDL to a limited extent[27]. Tamer *et al.*[28] suggest that thyroid autoimmunity disorder correlates with hyperlipidemia and atherosclerosis independently of thyroid function, which could also be explained in the light of our study results, i.e. thyroid autoimmunity might be at least partially a consequence of IR, which promotes dyslipidemia.

Finally, our study had several limitations that should be pointed out, e.g., a relatively limited sample size, short follow up and greatly outnumbered female to male subjects, which made the results impossible to generalize to male patients with Hashimoto thyroiditis.

In conclusion, despite limitations, we do believe that IR triggers thyroid antibody production and Hashimoto disease development, and if so, that it might even lead to progression to hypothyroidism, which needs to be evaluated in further larger scale follow up studies.

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Sažetak

POVEZANOST SUBKLINIČKE INZULINSKE REZISTENCIJE S AUTOIMUNIM BILJEZIMA ŠTITNE ŽLIJEZDE U EUTIROIDNIH ISPITANIKA

K. Blaslov, D. Gajski, V. Vucelić, P. Gaćina, G. Mirošević, J. Marinković, M. Vrkljan i *K. Rotim*

Hashimotov tireoidits obilježavaju anti-TPO i anti-Tg antitijela koja postupno dovode do uništenja stanica štitne žlijezde. Kako se hipotireoza povezuje s inzulinskom rezistencijom (IR) cilj ovoga istraživanja bio je ispitati postoji li povezanost IR s prisutnošću tireoidnih antitijela te je li stupanj IR povezan s koncentracijom autoantitijela u eutiroidnih ispitanika. U istraživanje je bilo uključeno 164 eutiroidnih ispitanika bez šećerne bolesti koji su podijeljeni u dvije skupine ovisno o prisutnosti Hashimotova tireoiditisa. Svi ispitanici podvrgnuti su 5-satnom testu opterećenja glukozom. Stupanj IR izračunat je standardiziranom metodom HOMA-IR (engl. *Homeostatic Model Assessment of Insulin Resistance*). Skupina ispitanika s Hashimotovim tireoiditisom imala je više vrijednosti HOMA-IR (p=0,003), ali i nižu koncentraciju glukoze (p=0,04). HOMA-IR pozitivno je korelirao s anti-TPO (p<0,001). Linearna logistička regresija pokazala je da koncentracija anti-TPO poraste za 18,13 (p=0,001) sa svakom jedinicom porasta HOMA-IR. IR je mogući okidač za razvoj autoantitijela štitnjače i razvoj Hashimotove bolesti, što treba evaluirati u budućim prospektivnim istraživanjima.

Ključne riječi: *Inzulinska rezistencija; 5-satni OGTT; Hashimotov tireoiditis*