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Insulin resistance in the patients with euthyroid Hashimoto thyroiditis.

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Abstract

Objectives: The relationship between Insulin Resistance (IR) and both clinical and subclinical hypothyroidism is well documented. Hashimoto's Thyroiditis (HT) is the most common cause of hypothyroidism. In this study, we aim to reveal whether a relationship exists between insulin resistance and euthyroid Hashimoto's thyroiditis.

Material and method: The study included 55 patients with Positive Thyroid Autoantibodies (PTA) euthyroid Hashimoto's Thyroiditis (HT) and 55 healthy control groups. Insulin, Thyroid Stimulant Hormone (TSH), thyroid autoantibodies such as Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg), Homeostasis Model Assessment (HOMA) index, and fasting blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol levels of patients and a control group were compared.

Results: Age, gender, Body Mass Index (BMI), Thyroid Stimulating Hormone (TSH), Free Thyroxine (FT4), and Free Triiodothyronine (FT3) did not differ between patients and the control group. Fasting glucose levels (p: 0.006); insulin levels (p: 0.011); Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values (p: 0.011); low-density lipoprotein cholesterol levels (p: 0.008); high-density lipoprotein cholesterol levels (p: 0.041); triglyceride levels (p: 0.008); and total cholesterol levels (p: 0.002) were significantly higher among patients with positive thyroid autoantibodies than control subjects. We found a positive correlation among thyroid stimulating hormone, anti-thyroid peroxidase, anti-thyroglobulin, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) levels (p<0.001).

Conclusion: High thyroid autoantibodies levels are related to high fasting blood glucose levels, insulin levels, lipid parameters, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values. These findings indicate a possible relationship between insulin resistance and autoimmune thyroiditis and thyroid stimulating hormone levels. Patients with positive thyroid autoantibodies should be followed closely for diabetes mellitus and cardiovascular events.

Keywords: Thyroid autoantibodies, Insulin resistance, Autoimmunity.

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Introduction

Hashimoto's thyroiditis is a chronic autoimmune inflammatory disease and the most common cause of hypothyroidism in adults. It is characterized by histological infiltration of T and B cells into the thyroid gland. Autoimmune diseases detect the body's own tissue as foreign and work to destroy it. Therefore, the immune system begins to produce Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg) antibodies in order to destroy the thyroid gland. It is not known why the body begins to behave like this. Thyroid peroxidase antibodies are positive in 95% of cases of Hashimoto's thyroiditis and 85% of Graves' disease [1].

Insulin resistance is defined as a reduction in expected effects. There may be defects in the stages ranging from production of the insulin in pancreatic β-cells to the effects of insulin in target cells [2]. Insulin resistance is considered one of the primary defects underlying the development of diabetes mellitus type 2 and also plays an important role in the pathogenesis of atherosclerosis and metabolic syndrome [3]. Both insulin resistance and diabetes mellitus-related atherosclerosis are chronic inflammatory diseases [3]. T-Helper 1 (Th1) and CD8 lymphocytes infiltrate visceral adipose tissue in insulin resistance and B lymphocytes cause T cell-mediated inflammation in adipose tissue in insulin resistance [4,5].

The purpose of this study is to reveal the relationship between two chronic inflammatory diseases: Hashimoto's thyroiditis and insulin resistance.

Material and Methods

Patients presenting at internal medicine policlinics between January 1, 2014 and December 31, 2014 were scanned. A total of 55 newly diagnosed euthyroid Hashimoto's thyroiditis patients (mean (SD) age: 28.8 ± 8.3) years; thyroid stimulating hormone (TSH), FT3, and FT4 in normal range) without a history of operations, smoking, or comorbid disease; and 55 healthy euthyroid control subjects (mean (SD) age: 27.5 ± 7.8 years) were included in this prospective case-control study. 47 patients showed both positive Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg), while 8 patients had only positive Anti-Thyroid Peroxidase (Anti-TPO). We aimed to compare Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values (insulin, body mass index, and glucose) as measured in patients with euthyroid Hashimoto's thyroiditis and healthy controls. Diagnosis of Hashimoto's thyroiditis was based on thyroid autoantibody positivity and Ultrasonography (USG) findings. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values was calculated as fasting glucose (mg/dL) × fasting insulin (mI U/L)/405. A Tanita analyzer TBF-300 was used for measuring body composition. Venous blood samples were obtained for biochemical examination after 12-14 hours of fasting. Thyroid ultrasonography was made by the same physician. Patients with a history of chronic diseases, due their well-known effects on insulin resistance such as Diabetes Mellitus (DM Types 1-2), Hypertension (HT), Hyperlipidaemia (HL), ischemic heart disease or smoking were excluded from the study. Signed patient consent documents were obtained from each subject. The Helsinki Declaration, which covers biomedical research on humans, was complied with during the study. The study was approved by the University Ethics Committee.

Statistical analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc. Chicago, IL, USA). A Kolmogorov-Smirnov test was used for normality test. Differences between normally distributed data were analysed with Student t-test; and Chi-square test and when necessary Fisher's exact test were used to calculate differences between string data. Insulin, homeostasis model assessment-insulin resistance, FT3, thyroid peroxidase, and thyroglobulin levels were not normally distributed, so a Mann-Whitney U test was used to evaluate differences in these parameters. Pearson's correlation was used for correlation analyses between continuous variables. P<0.05 was considered statistically significant.

Results

Patients with euthyroid Hashimoto's thyroiditis and control subjects were determined to be homogenous in terms of demographic characteristics and anthropometric measurements as shown in Table 1.

Thyroid Stimulating Hormone (TSH), FT3, and FT4 levels were found to be similar between the two groups (data not shown). Anti-Thyroid Peroxidase (Anti-TPO) (p<0.001) and Anti-Thyroglobulin (Anti-Tg) levels (p<0.001) were found to be significantly higher in patients group than control subjects as shown in Table 2.

Table 1. *Demographic characteristics, anthropometric measurements in patients vs. control subjects.*

	Antibody positive (Patients n: 55)	**Antibody negative (Controls n: 55)**	**P value**
Age (year)	28.8	27.5	0.773
Gender (M/F)	4/51	4/51	1.000
Body mass index (kg/m^2)	22.8	23.6	0.309
TG, mean (SD), or median (IR*)	5.2 (2.8)	2.27 (0.9)	<0.0001
IR: Insulin Resistance.			

Table 2. *Thyroid function tests and autoantibodies in patients vs. Control subjects.*

	Antibody positive (Patients n: 55)	**Antibody negative (Controls n: 55)**	**P value**
TSH (mIU/ml) mean (SD)	0.8 ± 1.4	1.0 ± 1.8	0.019
FT3 (pg/ml) mean (SD)	0.5 ± 0.47	0.6 ± 0.46	1
FT4 (ng/dl) mean (SD)	1.8 ± 1.52	1.7 ± 1.45	0.035
Anti-TPO (IU/mL) mean (SD)	312.5 ± 259.4	0.72 ± 0.3	<0.0001
Anti-Tg (IU/mL) mean (SD)	212.2 ± 140.4	0.8 ± 1.2	<0.0001

TSH: Thyroid Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Tetreiodothyronine; Anti-TPO: Anti-Thyroid Peroxidase Antibodies; Anti-Tg: Anti-Thyroglobulin.

Fasting glucose levels (p: 0.006), insulin levels (p: 0.011); Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values (p: 0.011); low-density lipoprotein cholesterol levels (p: 0.008); high-density lipoprotein cholesterol levels (p: 0.041); triglyceride levels (p: 0.008); and total cholesterol levels (p: 0.002) were found to be significantly higher in patients than control subjects as shown in Tables 3 and 4.

Table 3. *Fasting Glucose, Insulin and Homeostasis Model Assessment (HOMA) Index levels in patients vs. control subjects.*

	Antibody positive (Patients n: 55)	**Antibody negative (Controls n: 55)**	**P value**
Fasting glucose (mg/dl)	92.49	87.87	0.006
Mean (SD)	8.6	8.6	-
Insulin (mIU/ml)	8.25	6.76	0,011
Mean (SD)	4.3	3.3	

HOMA index	1.85	1.47	0.011
Mean (SD)	0.9	0.8	

HOMA: Homeostasis Model Assessment.

Table 4. *Lipid parameters and mean blood pressure measurements in patients vs. control subjects.*

	Antibody positive (Patients n:55)	**Antibody negative (Controls n:55)**	**P value**
LDL (mg/dl)	105.24	92.07	0,008
Mean (SD)	28.4	22.1	
HDL (mg/dl)	59.47	54.33	0.041
Mean (SD)	14.9	10.7	
Triglyceride (mg/dl)	92.04	73.98	0.008
Mean (SD)	43	24.6	
Total cholesterol (mg/dl)	180.58	163.2	0.002
Mean (SD)	30.9	26.3	
SBP (mmHg)	118	117.5	>0.05
Mean (SD)	13.8	13.2	

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Positive correlations were found between Thyroid Stimulating Hormone (TSH), Anti-TPO, Anti-Thyroglobulin (Anti-Tg) levels and insulin, Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), and Body Mass Index (BMI) levels ($p<0.001$) as shown in Table 5.

Table 5. *Correlation Results (p/r values).*

	TSH	**Anti-Tpo**	**Anti-Tg**	**Insulin**	**BMI**	**HOMA-IR**
	p/r	**p/r**	**p/r**	**p/r**	**p/r**	**p/r**
TSH(uIU/ml)	1/1	0.664/0.06	0.476/0.098	0.004/0.935	0.002/0.989	0.002/0.941
Anti-Tpo (IU/mL)	0.664/0.06	1/1	0.840/-0.028	0.001/0.924	0.001/0.905	0.001/0.93
Anti-Tg (IU/mL)	0.476/0.098	0.840/-0.028	1/1	0.001/0.956	0.001/0.847	0.001/0.958
Insulin (mIU/ml)	0.004/0.935	0.001/0.924	0.001/0.956	1/1	0.001/0.921	0.001/0.993
BMI (kg/m^2)	0.002/0.989	0.001/0.905	0.001/0.847	0.001/0.921	1/1	0.001/0.924
HOMA-IR	0.002/0.941	0.001/0.93	0.001/0.958	0.001/0.993	0.001/0.924	1/1

TSH: Thyroid Stimulating Hormone; Anti-TPO: Anti-Thyroid Peroxidase Antibodies; Anti-Tg: Anti-Thyroglobulin; BMI: Body Mass Index; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance.

Discussion

Our study is the first in the literature demonstrating the relationship between thyroid autoantibodies and insulin resistance.

Firstly, we found a positive correlation between Thyroid Stimulating Hormone (TSH) levels and fasting insulin levels, fasting glucose levels, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values in patients with euthyroid Hashimoto's thyroiditis. Many factors that increase insulin resistance are released from adipose tissue. Tumour Necrosis Factor-alpha (TNF-α), C-Reactive protein (CRP), Interleukin (IL)-6, Interleukin (IL)-2, leptin, ghrelin, resistin, and adiponectin are all products released from adipocytes that increase insulin resistance [6]. Tumour necrosis factor-alpha, C-reactive protein, Interleukin (IL)-2, and Interleukin (IL)-6 are proinflammatory cytokines. There are Thyroid Stimulating Hormone (TSH) receptors on adipocytes. Thyroid Stimulating Hormone (TSH) induces proliferation of adipocytes and also production of proinflammatory markers in adipocytes by these receptors [7]. Due to this, clinical hypothyroidism and subclinical hypothyroidism are both risk factors for insulin resistance, as shown in several studies [8-13]. We found one study showing the relationship between Thyroid Stimulating Hormone (TSH) levels and insulin resistance in euthyroid subjects [14]. Our study is the second demonstrating this relationship in the literature. High Thyroid Stimulating Hormone (TSH) levels have been found in obese euthyroid patients in several studies [15-17]. We found a positive correlation between Thyroid Stimulating Hormone (TSH) levels and body mass index levels in non-obese euthyroid patients with a max body mass index level of 29.9 kg/m^2. Our study is also the first in the literature showing this relationship.

Hashimoto's thyroiditis is an organ specific autoimmune disease and chronic inflammatory condition. T helper cells, Tumour Necrosis Factor (TNF)-α, interferon-γ and interleukin 2 play important roles in the pathogenesis of Hashimoto's thyroiditis [18,19]. A genetic defect in the suppressor T-cell function was found in patients with Hashimato's thyroiditis [20]. $CD4^+$ T helper cells are not suppressed because of this genetic defect and produce cytokines such as interferon (IFN)-g, interleukin (IL)-2, and tumour necrosis factor (TNF)-α [21]. We reviewed the literature and found a study about thyroid autoantibodies and insulin resistance. Tina et al. demonstrated insulin resistance in patients with Hashimato's thyroiditis and

highly elevated levels of Anti-Thyroid Peroxidase (Anti-TPO) antibodies of more than 1000 IU/ml [22]. In our study, we showed insulin resistance in patients with both elevated Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg) levels. The mean age of our patients, as well as their body mass index levels, is lower than those in Tina et al.'s study [22].

Some studies have demonstrated that IFN-g regulates inflammation and TNF-α promotes lipogenesis and induces lipolysis in adipose tissue [23]. For high CD4 and CD8 T-cells, both T helper 1 and T helper 2 were found in adipose tissue [4,5,24]. We also found a relationship between thyroid autoantibodies and hyperlipidaemia as shown in Table 4. Certain pro-inflammatory cytokines such as IL-2, TNF-α, and T helpers play important roles in the pathogenesis of Hashimoto's thyroiditis, hyperlipidaemia, and insulin resistance.

These mechanisms may explain the relationship between thyroid autoantibodies and insulin resistance in our study.

It is not clear how thyroid autoimmunity affects insulin resistance. It is possible that increased IFN-g and TNF-a may cause insulin resistance in patients with thyroid autoimmunity.

A limitation of our study is that we did not measure inflammatory parameters such as CRP or interleukins.

Conclusion

In conclusion, Thyroid Stimulating Hormone (TSH) levels and thyroid autoimmunity are related to insulin resistance. Patients with Hashimoto's thyroiditis should be monitored for early-onset diabetes mellitus type 2 and cardiovascular diseases. Larger scale randomized studies are needed to clarify the mechanisms of thyroid autoantibodies in insulin resistance.

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