Insulin resistance in hypothyroid patients under Levothyroxine therapy: a comparison between those with and without thyroid autoimmunity

Tina Mazaheri1*, Faranak Sharifi2 and Koorosh Kamali3

Abstract

Background: A chronic inflammation resulting from an imbalance between pro-inflammatory and anti-inflammatory cytokines in Hashimoto’s thyroiditis (HT) might be responsible for IR in hypothyroidism. This study was performed to investigate a probable association between autoimmune background of hypothyroidism and IR.

Methods: In this clinical study, 63 subjects with Hashimoto’s thyroiditis and 49 subjects with post-ablation hypothyroidism were enrolled. All the participants were euthyroid for more than one year through Levothyroxine therapy. Serum concentrations of Thyroid-stimulating Hormone (TSH), Free Thyroxin (FT4, FT3), Anti-Thyroid Peroxidase Antibodies (Anti-TPO Abs), Total Cholesterol (TC), HDL-Cholesterol (HDL-C), Triglyceride (TG), Fasting Blood Glucose (FBG), and insulin levels were measured and Oral Glucose Tolerance Test (OGTT) was performed for all of the subjects. Participants with anti TPO levels more than 1000 IU /ml were classified as having highly positive antibodies.

Results: No significant differences regarding to plasma insulin, glucose and lipid concentration, were detected between subjects with and without Hashimoto’s thyroiditis. However, subjects with highly positive Anti TPO Abs had higher prevalence of elevated fasting insulin level than those with lower titers of Anti TPO Abs and subjects without autoimmune background (94.1% vs. 62.8% and 71.4% respectively, P = 0.05). Subjects with highly positive titers of Abs also had a lower serum HDL-c levels than the rest of the subjects (40.6 ± 2.1 vs. 47.2 ± 1.7 and 47.4 ± 1.4, P = 0.04).

Conclusions: There is no obvious association between thyroid autoimmunity and metabolic indexes of hypothyroid patients. Only patients with Ani TPO antibody levels more than 1000 IU/ml may experience higher insulin level and less HDL-c with the same BMI.

Keywords: Hypothyroidism, Autoimmunity, Insulin resistance

Introduction

Hypothyroidism has been reported in 1% to 10% of the adult population [1] and is accompanied by a number of important health implications including increased risk of dyslipidemia, altered peripheral glucose disposal due to insulin resistance and cardiovascular disorders [2,3]. Insulin resistance is a key factor in the pathogenesis of type 2 diabetes mellitus (DM), metabolic syndrome and atherosclerosis [1,4]. It is established that hypothyroidism constitutes to insulin resistant state [5,6]. Furthermore, some studies have shown that even a subtle increase in plasma TSH levels within the physiological range may affect insulin secretion [7] and may be associated with insulin resistance and metabolic syndrome [8]. However, the exact mechanism connecting hypothyroidism to IR is still unclear. The fact that overt hypothyroidism and even subclinical hypothyroidism have been associated with disorders of glucose and insulin metabolism [9,10] and that thyroid replacement therapy has been unable to restore Insulin Mediated Glucose Uptake (IMGU) to its physiological state suggests that molecular and cellular interactions other than the thyroid hormones are involved in the insulin resistance state [11].

Since Hashimoto’s thyroiditis is the most common cause of hypothyroidism in areas with sufficient iodine intake [12], a chronic inflammation resulting from an imbalance between pro-inflammatory and anti-inflammatory cytokines
[13] in this disease might be the mechanism responsible for IR in hypothyroidism. Considering these theory non-autoimmune and non-inflammatory causes of hypothyroidism would not contribute to IR.

To illustrate a probable association between autoimmune background of hypothyroidism and IR this study was conducted. In this study we compared insulin resistance and dysglycemia in hypothyroid patients with and without autoimmunity after attainment of a euthyroid state through levothyroxine therapy.

**Materials and methods**

**Subjects**

A total of 112 adult hypothyroid patients including 63 subjects with Hashimoto’s thyroiditis and 49 people with post ablation hypothyroidism who were randomly selected from Valiasr Hospital outpatient endocrine clinic, an academic general hospital in Zanjan, enrolled in this study. Diagnosis of hypothyroidism was conducted if serum TSH concentration was more than 5 IU/ml, and serum T4 concentration was less than 64.5 nmol/l. Individuals with serum TSH level more than 10 IU/ml accompanied by normal T4 and T3 levels, were considered as subclinical hypothyroid. All hypothyroid patients with enlarged rubbery thyroid and high serum Anti-TPO Abs concentration were categorized as Hashimoto’s thyroiditis while those with history of thyroid surgery or radioiodine ablation performed in more than a year period of time and without any anti-thyroid antibodies in their blood were recognized as post ablation hypothyroid.

Having a list of all hypothyroid patients of the clinic, they were categorized under Hashimoto’s thyroiditis and post-ablation hypothyroidism based on their documented medical history. Inclusion criteria were hypothyroid participants who underwent Levothyroxine therapy in an appropriate dosage by which the patient was euthyroid at least for one year. Patients with diabetes mellitus, cardiovascular disease, cerebral vascular disease, corticosteroid consumption, pregnancy, chronic liver disease, thyroid cancer, renal dysfunction and any autoimmune disease like lupus erythematosus and Rheumatoid arthritis were excluded from the study. None of the selected individuals were under medication known to affect glucose or lipid metabolism.

At the beginning of the study anti-thyroid antibodies including anti thyroglobulin and Anti TPO levels were measured again for all the eligible participants and those with positive anti-thyroid antibodies in the post ablation hypothyroid group were excluded from the study.

After exclusion of two subjects due to DM in Hashimoto’s thyroiditis group and 16 subjects from post-ablation hypothyroid group including 6 people with mild elevated Anti TPO Abs, four people with history of thyroid cancer, five subjects who did not complete the study and one person with DM, 112 patients were studied.

All the participants were informed orally about the aim of study and informed consents were obtained from them. This study was approved by the ethical committee of Zanjan University of Medical Sciences in Iran.

**Measurements**

Clinical examination and Anthropometric Measurements carried out for all the patients by the researcher. Height was measured with a stadiometer to the nearest 0.5 cm. Body weight was recorded by calibrated digital scale while wearing light clothes. Blood pressure values were measured twice on the left upper arm; in the sitting position with a random zero sphygmomanometer after a 10-min rest. Waist circumference between the iliac crest and the lowest rib at umbilicus level was measured using flexible tape. Body Mass Index (BMI) was also calculated accordingly. Demographic information and family history of diabetes and hypertension were obtained from the participants. Duration of replacement therapy with Levothyroxine-sodium, plasma TSH levels in the first diagnosis of hypothyroidism state and TSH plasma levels at the time of study were explored and documented specifically. In order to select only euthyroid patients, those with TSH or FT3 values below or above the normal range were excluded from further analysis.

Blood samples were collected from the ante-cubital vein of the participants after at least 12 hours of fasting. Serum concentrations of TSH, FT4, FT3, Anti TPO Abs, Total Cholesterol (TC), HDL-cholesterol (HDL-C), Triglyceride (TG), glucose and insulin were measured. Afterwards, an Oral Glucose Tolerance Test (OGTT) with 75 gr of glucose was performed for all the participants.

Obesity was defined as BMI ≥30 kg/m², central obesity as a waist circumference ≥102 cm in men and ≥88 cm in women, low HDL as serum HDL cholesterol ≤40 mg/dl in men and ≤50 mg/dl in women. Serum triglycerides ≥150 mg/dl, total cholesterol level ≥240 mg/dl, fasting insulin ≥6 uIU/mL and fasting plasma glucose ≥100 mg/dl were considered as hypertriglyceridemia, hypercholesterolemia, elevated fasting insulin level and hyperglycemia respectively. Hypertension defined as systolic blood pressure more than 130/85 mmHg. TPO Ab level of more than 80 U/ml was positive. People with anti TPO levels more than 1000 IU /ml were categorized as having highly positive antibodies and analyzed separately.

**Laboratory measurements**

Biochemical variables measurements were done at the laboratory of Val-i-e-asr Hospital, using commercial kits: Plasma glucose was measured by the glucose peroxidase colorimetric enzymatic method, with a sensitivity of 5 mg/dl. Serum cholesterol and triglyceride (TG) were measured by
colorimetric method with a sensitivity of 5 mg/dl. Low-density lipoprotein (LDL-C) estimation was calculated using the Friedewald formula. Insulin resistance was estimated by the homeostasis model assessment index (HOMA-IR = (fasting glucose (mmol/l) × fasting insulin (uIU/mL))/22.5). TSH concentrations were measured by Immuno Chemiluminescence assay. Anti-TPO was determined by radioimmunoassay (RIA) system (SorinBiomedia, Italy).

**Statistics**

Statistical analyses were done using SPSS 16.5 software package. Data are expressed as mean ± SE or medium where is appropriate. Differences between two groups were tested using Student’s unpaired t-test (or Mann–Whitney according to sample distribution). For an analytic comparison of the variables between three groups with and without a normal distribution, Fisher test and Kruskal–Wallis test, were utilized respectively. χ2 test was performed to assess the significance of differences between proportions. To determine the correlation between the serum anti TPO antibody concentration and other variables Regression analysis was employed. P < 0.05 was considered to specify statistical significance.

**Results**

A total of 112 hypothyroid patients including 98 (88%) women and 14 (12%) men with the mean age of 41.8 ± 12.8 years were studied. Basal clinical and laboratory characteristics of the two groups of patients with Hashimoto’s thyroiditis and post-ablation hypothyroidism are compared in Table 1. Based on the data, no significant difference regarding to clinical and biochemical variables was found between the hypothyroid patients with and without autoimmune background. Although serum levels of TG and HOMA-IR were relatively higher in patients with Hashimoto’s thyroiditis, the difference was not statistically significant.

Regarding to HOMA-IR, 50 subjects (44.6%) of hypothyroid patients were insulin resistant including 26 (41.2%) patients with Hashimoto’s thyroiditis and 24 (48.9%) patients with post ablation hypothyroidism (P = 0.232).

Patients with Anti TPO antibody levels more than 1000 IU/ml were classified as having highly positive antibodies, and were separately analyzed. Table 2 shows the difference between the three groups of patients for frequency of obesity, central obesity, hypercholesterolemia, hypertriglyceridemia, low-HDL cholesterol and hyperglycemia. The prevalence of hyperinsulinemia was significantly higher in Hashimoto patients with higher levels of Anti TPO antibodies more than 1000 IU/ml (Table 2).

Table 3 illustrates an overview of the biochemical and anthropometric parameters in the group with highly positive anti thyroid antibodies and compares it with other hypothyroid patients. The data reveals that beside HDL-c which was significantly lower in patients with high levels of anti thyroid antibody, other parameters like insulin resistance were not different between the three groups.

Table 4 refers to the relationship between the serum level of Anti TPO antibody and other variables. The mean duration of hypothyroidism in our patients was 5.5 ± 7.9 years. Participants were categorized into two groups based on Levothyroxine therapy duration. Glucose concentration and insulin resistance index of subjects who had been diagnosed with hypothyroidism and had received treatment within the past 5 years does not significantly differ from subjects who had been diagnosed earlier and undergone levothyroxine therapy for more than 5 years.

Patients were divided into three groups based on their current TSH levels while taking Levothyroxine for treatment. Patients with serum TSH levels of below 1.88, 1.88 to 3.40, and 3.41 to 5 showed no significant difference in terms of insulin resistance and hyperglycemia. Also no meaningful difference in terms of the presence of metabolic syndrome was detected among the groups (P = 0.39).

**Discussion**

The results of current study revealed a high prevalence of insulin resistance in hypothyroid patients whereas they were in euthyroid state for more than one year with Levothyroxine therapy (44.8%). Moreover, the prevalence of elevated fasting insulin level was more significant in those with highly positive Anti TPO antibodies (94.1%).

### Table 1 Comparison of the biochemical and anthropometric parameters in two groups of patients based on their background autoimmunity (serum levels of Anti-TPO Abs)

| Parameter      | Post ablative hypothyroid (n:49) | Hashimoto’s thyroiditis (n:63) | P value |
|----------------|----------------------------------|--------------------------------|---------|
| Age (year)     | 43.9 ± 1.7                       | 39.9 ± 1.5                     | 0.103   |
| WC (cm)        | 89.5 ± 3.1                       | 92.6 ± 1.4                     | 0.696   |
| BMI (kg/m²)    | 28.5 ± 0.6                       | 28.1 ± 0.6                     | 0.741   |
| SBP            | 113.3 ± 3.1                      | 114.6 ± 2.2                    | 0.677   |
| DBP            | 72.2 ± 2                         | 76.1 ± 1.8                     | 0.126   |
| TC (mmol/L)    | 189.2 ± 6                        | 179.1 ± 5.6                    | 0.266   |
| TG (mmol/L)    | 134.4 ± 7.3                      | 147.9 ± 11.6                   | 0.935   |
| HDL (mmol/L)   | 47.4 ± 1.4                       | 45.6 ± 1.4                     | 0.232   |
| FPG (mmol/L)   | 93 ± 1.6                         | 90.5 ± 1.7                     | 0.452   |
| OGTT           | 1129 ± 3.7                       | 1082 ± 4.5                     | 0.181   |
| Insulin (uIU/mL) | 8.9 ± 0.6                        | 10.7 ± 1.1                     | 0.615   |
| HOMA-IR        | 2.1 ± 0.2                        | 2.4 ± 0.3                      | 0.913   |

WC: Waist Circumference; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total cholesterol; TG: Triglyceride; HDL: High Density Lipoprotein; FPG: Fasting Plasma Glucose, OGTT: Oral Glucose Tolerance Test.
However, no significant differences were found regarding plasma insulin, glucose and lipid concentration between patients with and without Hashimoto’s thyroiditis diagnosed as the cause of their hypothyroidism.

In recent years, tremendous interest has been raised in the effect of thyroid function on insulin levels. It is established that clinical hypothyroidism is considered as an insulin-resistant state [5,6]. Following their studies on patients with hypothyroidism, Handisurya [14] and Stanicka [15] have concluded that hypothyroidism makes glucose inaccessible to insulin [16]. However; an exact pathogenetic mechanism involved in insulin resistance in hypothyroidism is still unknown. In current study with enrolling different groups of hypothyroid patients, we tried to detect any association of autoimmunity against thyroid and insulin resistance. Adjusting for age and sex, hypothyroid patients had more frequency of central obesity than general population of Zanjan, the city that this study was conducted (67% vs. 40%) [17]. Having high prevalence of insulin resistance (44%) in our patients, who all were euthyroid for a long time before the study, reveals another mechanism other than the role of low thyroid hormones for the insulin resistance in hypothyroidism. Higher central fat in the subjects may explain the higher prevalence of insulin resistance among participants; however; a significantly more prevalence of elevated fasting insulin level was detected in a subgroup of patients with Hashimoto’s thyroiditis and highly elevated levels of Anti TPO antibodies more than 1000 IU/ml which might support the concept of autoimmunity role in insulin resistance. Regarding the metabolic indexes and insulin resistance, no differences were found between hypothyroid patients with and without autoimmunity against thyroid.

Positive effect of Lefthothyroxine on insulin resistance is still under investigation. Robert Krysiak et al. [18] have illustrated that a six-month treatment with levothyroxine does not have a significant effect on HOMA-IR in patients with hypothyroidism. Our results could support this finding as although we have not considered the level of glucose, lipid and insulin levels of our hypothyroid patients before the initiation of treatment, they had yet much more frequency of insulin resistance after a long time of treatment as compared to the general population [19]. Thus, a significant effect of replacement therapy

Table 2 Difference between the two groups of patients for frequency of obesity, central obesity, hypercholesterolemia, hypertriglyceridemia, low-HDL cholesterol and hyperglycemia

| Parameters                  | Post ablative hypothyroid (n:49) | Hashimoto’s thyroiditis (n:46) | Hashimoto’s thyroiditis with highly positive TPO abs (n:17) | P value |
|-----------------------------|---------------------------------|--------------------------------|------------------------------------------------------------|---------|
| Obesity                     | 20(40.8%)                       | 14(30.4%)                      | 5(31.3%)                                                   | 0.339   |
| Central obesity             | 37(75.5%)                       | 28(60.9%)                      | 11(64.7%)                                                  | 0.301   |
| Hypertension                | 6(12.2%)                        | 6(13%)                         | 3(17.6%)                                                   | 0.851   |
| Hypercholesterolemia        | 6(12.2%)                        | 5(10.9%)                       | 1(5.9%)                                                    | 0.767   |
| Hypertriglyceridemia        | 17(34.7%)                       | 19(41.3%)                      | 4(28.6%)                                                   | 0.639   |
| Low-HDL cholesterol         | 15(30.6%)                       | 14(30.4 %)                     | 8(47.1%)                                                   | 0.414   |
| Hyperglycemia               | 13(26.5%)                       | 13(28.3%)                      | 4(23.5%)                                                   | 0.931   |
| Elevated fasting insulin level | 36(71.4%)                  | 27(62.8%)                      | 16(94.1%)                                                  | 0.05    |

Table 3 Comparison of the biochemical and anthropometric parameters in three groups of patients based on their serum levels of Anti-TPO Abs

| Parameters                  | Negative Anti-TPO Abs N: 49 | Positive Anti-TPO Abs N: 46 | Highly positive Anti-TPO Abs N: 17 | P value |
|-----------------------------|-------------------------------|-----------------------------|-----------------------------------|---------|
| Age (year)                  | 43.9 ± 1.8                    | 40.9 ± 1.7                  | 37.2 ± 3.2                        | 0.13    |
| WC (cm)                     | 89.5 ± 3.2                    | 91.6 ± 0.7                  | 96.2 ± 3.1                        | 0.58    |
| BMI (kg/m²)                 | 28.5 ± 0.6                    | 27.7 ± 0.7                  | 30 ± 1.2                          | 0.41    |
| SBP                         | 113.2 ± 3.1                   | 113.9 ± 2.6                 | 117.1 ± 5.8                       | 0.91    |
| DBP                         | 72.1 ± 2                      | 74.5 ± 2.2                  | 78 ± 2.6                          | 0.33    |
| TC (mmol/L)                 | 189.2 ± 6                     | 179.9 ± 6.5                 | 176.9 ± 11.7                      | 0.46    |
| TG (mmol/L)                 | 134.4 ± 7.4                   | 148.8 ± 13.6                | 145.2 ± 24.4                      | 0.94    |
| HDL (mmol/L)                | 47.4 ± 1.4                    | 47.2 ± 1.7                  | 40.6 ± 1.2                        | 0.04    |
| FPG (mmol/L)                | 93 ± 1.6                      | 90.8 ± 2.1                  | 89.6 ± 2.9                        | 0.66    |
| OGTT                        | 112.9 ± 3.7                   | 113.3 ± 5.4                 | 92.9 ± 6.4                        | 0.09    |
| Insulin (uIU/mL)            | 8.9 ± 0.6                     | 10.54 ± 1.5                 | 11.07 ± 1                         | 0.20    |
| HOMA-IR                     | 2.1 ± 0.2                     | 2.4 ± 0.4                   | 2.5 ± 0.3                         | 0.29    |
with Levothyroxine on insulin metabolism in hypothyroid patients seems to be unlikely.

Whether the treatment with Levothyroxine can affect autoimmune background against thyroid or not is not clear. Based on some studies [18,20] treatment with Levothyroxine may attenuate the level of Anti TPO antibody in hypothyroid patients and patients whose hypothyroidism is due to Hashimoto’s disease may benefit more from Levothyroxine therapy [18]. On the other hand, some other studies indicate that treatments with Levothyroxine have not always successfully restored the immunoglobulin to its normal levels [9].

Hypothyroidism could be considered as T helper1 disease [21] in which pro-inflammatory cytokines such as TNF-α and IL-6 play a crucial role [22,23]. There is a connection between the level of TPO Abs and pro-inflammatory cytokines like TNF-α and IL-6 [24]. The antibodies produced against the antigens specific to the thyroid like TPO, result in an immunity complex, which activates the complement pathway and ultimately the T cells, thus leading to an increase in the production of pro-inflammatory cytokines [24]. Therefore, Anti-TPO Abs, which play a predictive role in the progress of hypothyroidism can have either direct cytotoxic effect for thyroid cells through the IgG1 class [24,25], or indirect destructive effect on thyrocytes through activating TH1 cells and increasing inflammatory responses via release of inflammatory cytokines [26]. In addition, the secretory function of monocytes and lymphocytes is associated with the TPO Abs titer which can be accounted for the fact that the interaction between the monocytes and T cells activates B lymphocytes and produces TPO Abs [18]. Monocytes, lymphocytes and cytokines produced by these cells play an essential role in triggering autoimmunity disorders [27,28]. The monocytes, macrophages, lymphocytes coupled with the cytokines secreted by these cells – in particular, TNF-α and IL-6 – contribute to insulin resistance and atherosclerotic plaques [16,29].
performance the results might be affected by this and it would be more beneficial to include subjects who have been recently diagnosed with hypothyroidism and have not received any treatment yet in a separate study.

Conclusions

The present study demonstrated that there is no obvious association between thyroid autoimmunity and metabolic indexes of hypothyroid patients. Only patients with Anti TPO antibody levels more than 1000 IU/ml may experience higher insulin level and less HDL-c with the same BMI. More studies with higher sample size of patients with highly positive antibodies would be more informative.

Abbreviations

HIT: Hashimoto’s thyroiditis; TSH: Thyroid-Stimulating Hormone; FT: Free thyroid; Anti-TPO Abs: Anti-Thyroid Peroxidase Antibodies; IR: Insulin resistance; HOMA: Homeostasis model assessment; FBG: Fasting Blood Glucose; OGTT: Oral Glucose Tolerance Test; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; TG: Triglyceride; WC: Waist circumference; BMI: Body Mass Index; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

TM made contributions to conception and design, helped in both data acquisition and statistical analysis and drafted the manuscript. FS involved in data acquisition and revise the manuscript critically for important intellectual content. KK performed the statistical analysis. All authors read and approved the final manuscript.

Authors’ information

TM: medical student in Zanjan University of Medical Sciences, Zanjan, Iran. FS: Professor in Metabolic Disease Research Center, Zanjan University of Medical Sciences, Zanjan, Iran. KK: Health statistics in Department of public health, Zanjan University of Medical Sciences, Zanjan, Iran.

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Author details

1Zanjan University of Medical Sciences, Zanjan, Iran. 2Metabolic Diseases Research Center, Zanjan University of Medical Sciences, Zanjan, Iran. 3Department of public health, Zanjan University of Medical Sciences, Zanjan, Iran.

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References

1. Chen G, Wu J, Lin Y, Huang B, Yao J, Jiang Q, Wen J, Lin L. Associations between cardiovascular risk, insulin resistance, β-cell function and thyroid dysfunction: a cross-sectional study in She ethnic minority group of Fujian Province in China. Eur J Endocrinol 2010, 163(5):775–782.
2. Duntas LH. Thyroid disease and lipids. Thyroid 2002, 12:287–293.
3. Klein I, Darai S. Thyroid disease and the heart. Circulation 2007, 117:1725–1735.
4. Shoelson SE, Lee J. Coflin AB: inflammation and insulin resistance. J Clin Invest 2006, 116:1793–1801.
5. Dimitriadis G, Mitropou L, Lambiadari V, Bounti E, Maratou E, Panagiotakos DB, Koukou E, Tzanella M, Thallasinos N, Raptis SA. Insulin action in adipose tissue and muscle in hypothyroidism. J Clin Endocrinol Metab 2006, 91:4930–4937.
6. Cetour-Rose P, Theander-Carillo C, Asensio C, Klein M, Visser TJ, Burger AG, Meier CA, Rohner-Jeanjean F. Hypothyroidism in rats decreases peripheral glucose utilization, a defect partially corrected by central leptin infusion. Diabetologia 2005, 48:624–633.
7. Ortega E, Koska J, Fannacchelli N, Bunt JC, Rakoff J. Free triiodothyronine plasma concentrations are positively associated with insulin secretion in euthyroid individuals. Eur J Endocrinol 2008, 158:217–221.
8. Heima NE, Eokhoff EM, Oosterwerff MM, Lips PT, Van Schoor NM, Simsek S. Thyroid function and metabolic syndrome in older persons: a population based study. Eur J Endocrinol 2013, 168:S95–66.
9. Dimitriadis G, Baker B, Marsh H, Mandarino L, Rizza R, Bergman R, Raymond M, Gerich J. Effect of thyroid hormone excess on action, secretion, and metabolism of insulin in humans. Am J Physiol 1985, 248:E593–E601.
10. Dimitriadis G, Maratou E, Bounti E, Kollas A, Tiagka K, Alexakis M, Peppa M, Raptis SA, Hadjidakis DJ. IGF-I increases the recruitment of GLUT4 and GLUT3 glucose transporters on cell surface in hyperthyroidism. Eur J Endocrinol 2008, 158(3):361–366.
11. Peppa M, Koliaki C, Nikolopoulos P, Raptis SA. Skeletal muscle insulin resistance in endocrine disease. J Biomed Biotechnol 2010, 2010:157850.
12. Ganiel MA, Sarwaha RC, Aggarwal P, Singh S. Prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: a case-control study. Eur J Endocrinol 2010, 162:1117–1122.
13. Szpyr-Kravitz M, Marai I, Shoenfeld Y. Coexistence of thyroid autoimmunity with other autoimmune diseases: friend and foe? additional aspects on the mosaic of other autoimmune diseases. Autoimmunity 2005, 38:247–255.
14. Handsuyna A, Pacini G, Tura A, Gessl A, Kautzky-Willer A. Effects of T4 replacement therapy on glucose metabolism in subjects with subclinical (SH) and overt hypothyroidism (OH). ClinEndocrinol (Oxf) 2008, 69(6):963–969.
15. Stanicka S, Vondra K, Pelikanova T, Weck P, Hill M, Zamrazil V. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. J ClinChem Lab Med 2005, 43(7):715–726.
16. Wei Y, Chen K, Whaley-Connell AT, Stemp CS, Idbah JA, Sowers JR. Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species. Am J PhysiolRegulIntegr Comp Physiol 2008, 294:R673–R680.
17. Sharifi F, Mousavinasab SN, Saeini M, Dimohammad M. Prevalence of metabolic syndrome in an adult urban population of the West of Iran. Exp Diabetes Res 2009, 2009:136501.
18. Kysia R, Okopien B. The effect of levothyroxine and selenomethionine on lymphocyte and monocyte cytokine release in women with hashimoto’s thyroiditis. J Clin Endocrinol Metab 2011, 96(7):2206–2215.
19. Szukowska M, Gills-Januszewska E, Pach D, Szafarzewicz K, Szyszki Z. The prevalence of the metabolic syndrome using three proposed definitions. Polish multicenter study on diabetes epidemiology. Epidemiology 2005, 16:571–572.
20. Schmidt M, Voell M, Rahlf I, Dietlein M, Koe C, Faust M, Schicha H. Long-term follow-up of antithyroid peroxidase antibodies in patients with chronic autoimmune thyroiditis (Hashimoto’s thyroiditis) treated with levothyroxine. Thyroid 2008, 18(7):755–760.
21. Brown RS. Autoimmune thyroid disease: unlocking a complex puzzle. Curr Opin Pediatr 2009, 21:523–528.
22. Ajan RA, Watson PF, Weetman AP. Cytokines and thyroid function. Ad Neuroimmunol 1996, 6:359–386.
23. Guo J, Rapport B, McIlachlan SM: Balance of Th1/Th2 cytokines in thyroid autoantibody synthesis in vitro. Autoimmunity 1999, 30(1):1–9.
24. Nielsen CH, Bru TH, Leslie RQ, Hegedus LA. Role for autoantibodies in enhancement of pro-inflammatory cytokine responses to a self-antigen, thyroid peroxidase. Clin Immunol 2009, 133(2):218–227.
25. Ravetch JV, Kinet JP. FC receptors. Annu Rev Immunol 1991, 9:457–492.
26. Chistiakov DA. Autoimmune thyroid disease: unlocking a complex puzzle. J Autoimmune 2005, 21:–.
27. Nicholson LB, Ravene BJ, Munder M. Monocyte dependent regulation of autoimmune inflammation. Curr Med Res 2009, 923–29.
28. Piccirillo CA. Regulatory T cells in health and disease. Cytokine 2008, 43(3):395–401.
29. Wilson HM, Barker RN, Enog LP. Macrophages: promising targets for the treatment of atherosclerosis. Curr Vasc Pharmacol 2009, 7:234–248.
30. Akyoz DY, Kerimoglu U, Okur H, Canpinar H, Karacaoguller E, Yetgin S, Kansu E, Gedik O. Effects of prophylactic thyroid hormone replacement in euthyroidHashimoto’s thyroiditis. Endocr J 2005, 52:357–343.
31. Danese MD, Ladenson PW, Meinert CL, Powe NR: Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 2000, 85:2993–3001.

32. Saxena A, Kapoor P, Saxena SH, Kapoor AK: Effect of levothyroxine therapy on dyslipidemia in hypothyroid patients. IJMU 2013, 8:39–49.

33. Anagnostis P, Efstathiadou ZA, Slavakis A, Selamatidou D, Poulasoudidou M, Katergari S, Karathanasi E, Dogramatzis F, Kita M: The effect of L-thyroxine substitution on lipid profile, glucose homeostasis, inflammation and coagulation in patients with subclinical hypothyroidism. Int J Clin Pract 2014, 68:7857–863.

34. Mutlu S, Parlak A, Aydogan U, Aydogdu A, Soykut B, Akay C, Saglam K, Taktikkanar A: The effect of levothyroxine replacement therapy on lipid profile and oxidative stress parameters in patients with subclinical hypothyroidism. Arch Pharm Res 2013, 2013:1–9.

35. Tamer G, Mert M, Tamer I, Mesci B, Kilic D, Arik S: Effects of thyroid autoimmunity on abdominal obesity and hyperlipidaemia. Endokrynol 2011, 62(5):421–428.

36. Topaloglu O, Gokay F, Kucukler K, Burnik FS, Mete T, Yavuz HC, Berker D, Guler S: Is autoimmune thyroiditis a risk factor for early atherosclerosis in premenopausal women even if in euthyroid status? Endocrine 2013, 44(1):145–151.

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