Changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with autoimmune thyroid disease

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Abstract

Background: Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disorder, and genetic, environmental, and endogenous factors are responsible for initiation of thyroid autoimmunity. Some AITD patients suffer from a certain degree of glucose-lipid metabolism disorder. This study aims to explore the changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with AITD.

Methods: A total of 91 patients with Hashimoto’s thyroiditis were retrospectively analyzed and divided into hypothyroidism group (n = 42) and normal thyroid group (n = 49), while 50 healthy people were selected as control group. The changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in each group were compared, and their correlations with the thyroid function were analyzed.

Results: The levels of serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-12, IL-10, (FINS), and homeostasis model assessment of insulin resistance (HOMA-IR) were gradually declined in sequence of hypothyroidism group, normal thyroid group, and control group (P < 0.05). In hypothyroidism group, the levels of serum-free triiodothyronine (FT3), free thyroxine (FT4), (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) were significantly lower than those in normal thyroid group (P < 0.05), while the level of serum thyroid stimulating hormone (TSH) was significantly higher than that in normal thyroid group (P < 0.05). However, the fasting blood glucose and 2-hour postprandial blood glucose levels had no statistically significant differences among the three groups (P > 0.05).

Conclusion: Autoimmune thyroid disease patients are prone to fat metabolism disorder, and the serum thyroid hormone level has a close correlation with blood lipid metabolism, insulin metabolism, and inflammatory factors.

Keywords: autoimmune thyroid disease, glucose-lipid metabolism, inflammatory factors, insulin resistance
1 | INTRODUCTION

Autoimmune thyroid disease (AITD) is a kind of common autoimmune disease in clinic, and the diseased organ is the thyroid gland. Multiple factors in the external environment, differences in individual genetic background and abnormal immune function in the body can induce the occurrence of AITD. Clinically, AITD is divided into Hashimoto’s thyroiditis (HT) and Graves’ disease (GD). HT has a higher morbidity rate, and its pathogenesis is certainly related to the humoral immunity and cellular immunity in the body, which induces infiltration of lymphocytes into thyroid tissues and antibody production. Studies have demonstrated that serum cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-12, IL-10, play important roles in the pathogenesis of HT, and the production of a large number of inflammatory factors can increase the expression of HLA-I antigen to some extent and aggravate the immune disorder. After HT occurs, a large number of anti-thyroid antibodies will be produced by B lymphocytes to produce a certain cytotoxic effect, causing damage to thyroid tissues and aggravating the condition. Studies have shown that HT patients suffer from a certain degree of glucose-lipid metabolism disorder, and they are prone to free fatty acid metabolism disorder and hypercholesterolemia, inducing the formation of atherosclerosis. Inflammation and infections induce a variety of alterations in lipid metabolism that may initially dampen inflammation or fight infection, but if chronic could contribute to the increased risk of atherosclerosis. The most common changes are decreases in serum HDL and increases in triglycerides. The increase in serum triglycerides is due to both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride-rich lipoproteins. Considering the close association of inflammation with lipid metabolism, the exact relationship of them in the pathogenesis of AITD remains poorly understood. In the present study, we aimed to evaluate the changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in AITD patients as well as analyze their correlations with the thyroid function, in order to provide more evidences of the role of inflammation and glucose-lipid metabolism in the development of AITD.

2 | DATA AND METHODS

2.1 | General data

The clinical data of a total of 91 HT patients treated in our hospital from June 2015 to January 2017 were retrospectively analyzed, and these patients were divided into hypothyroidism group (n = 42) and normal thyroid group (n = 49) according to the thyroid function at the visit, while 50 healthy people receiving examination in the same period were selected as control group. All healthy subjects were not in infection or inflammatory condition during sampling as the level of CRP was in normal ranges. In hypothyroidism group, there were 18 males and 24 females aged 12-64 years old with an average of (35.42 ± 11.64) years old. In normal thyroid group, there were 21 males and 28 females aged 13-65 years old with an average of (36.02 ± 11.85) years old. In control group, there were 23 males and 27 females aged 12-65 years old with an average of (35.88 ± 11.79) years old. There were no statistically significant differences in the general data, such as age and gender, among the three groups, and they were comparable (P > 0.05). The study was approved by the ethics committee of The Affiliated Hospital of Southwest Medical University, and informed consents were signed by the patients.

2.2 | Diagnostic criteria for Hashimoto’s thyroiditis

(a) The thyroid ultrasound diagnosis shows that there is diffuse swelling accompanied by certain surface roughness and nodules (b) The serum thyroid stimulating hormone (TSH) level significantly increases (c) TGA and MCA examinations show the positive results, and there are high-level antibodies (d) In the thyroid CT scan, there are concentration and irregular sparsity caused by unbalanced iodine uptake (e) The potassium perchlorate excretion test displays that the iodine release rate is greater than 10%. Suspected HT can be diagnosed if patients meet any two of the above criteria, and HT can be definitely diagnosed if they meet four out of the five criteria.

2.3 | Inclusion and exclusion criteria

Inclusion criteria: (a) patients meeting the above diagnostic criteria, (b) patients with complete clinical data, (c) patients who and whose families agreed and signed the informed consent. Exclusion criteria: (a) patients who took hormones or drugs affecting glucose-lipid metabolism, (b) patients complicated with cardiovascular diseases, severe liver or kidney disease, inflammatory bowel disease, rheumatism or rheumatoid diseases, viral hepatitis or diabetes, (c) patients complicated with adrenal cortex dysfunction, (d) pregnant or lactating patients, or (e) patients with incomplete medical records.

2.4 | Methods

At the time of sampling, patients did not take any medications. The laboratory indexes of all subjects, including glucose-lipid metabolism, insulin resistance and inflammatory factors, were collected and measured as follows: (a) Determination of inflammatory factor levels: The next day after admission, 5 mL fasting venous blood was drawn from subjects in the early morning, added with 35 μL 10% ethylenediaminetetraacetic acid for anticoagulation and centrifuged with a centrifuge (Ortho BioVue, Johnson & Johnson Medical Equipment) at centrifugal radius of 10.5 cm, 1500 g and 4°C for 10 minutes. The plasma was separated and stored in a refrigerator at −75°C for detection. The levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-12, and IL-10 were detected via enzyme-linked immunoassay using the kits (Shanghai Yiji Biotechnology Co., Ltd.) according to the instructions. (b) Determination of thyroid function indexes: The levels of TSH, free thyroxine (FT4), and free triiodothyronine (FT3) were detected via assay using the automatic chemiluminescence apparatus (Beckman Coulter, ACCESS2). (c) Determination of blood glucose level: The levels of fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2h-PBG) were detected using the glucose oxidase...
method in strict accordance with the instructions of the kit (Shanghai DiaSys Diagnostic Technology Co., Ltd.). (d) Determination of blood lipid level: The levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), (TC) and triglyceride (TG) were detected using the peroxidase method. (e) Determination of insulin level 11 (FINS) level was detected via chemiluminescence sandwich immunoassay using the full-automatic chemiluminescence immunoassay analyzer (BMbio 400Plus, Yancheng Baiming Biotechnology Co., Ltd.) and the corresponding insulin assay kit, and it was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR; HOMA-IR = FINS×FBG/22.5).

2.5 | Statistical analysis

SPSS 19.0 software (SPSS Inc) was used for data processing. Measurement data were expressed as mean ± standard deviation (SD), and student t test was performed for comparison of the difference. Enumeration data were expressed as the rate, and chi-square test was performed for difference comparison. The correlation with the thyroid function was analyzed via Pearson correlation analysis. P < 0.05 suggested that the difference in data was statistically significant.

3 | RESULTS

3.1 | Changes in thyroid function indexes in each group

There were no statistically significant differences in thyroid function indexes between normal thyroid group and control group (P > 0.05). In hypothyroidism group, the levels of serum FT3 and FT4 were significantly lower than those in normal thyroid group, while the level of serum TSH was significantly higher than that in normal thyroid group (P < 0.05; Table 1).

3.2 | Changes in IL-6, TNF-α, IL-12, and IL-10 levels in each group of participants

The serum IL-6, TNF-α, IL-12, and IL-10 levels gradually declined in sequence of hypothyroidism group, normal thyroid group, and control group, and the differences were statistically significant (P < 0.05; Table 2).

3.3 | Changes in FBG and 2h-PBG levels in each group of participants

There were no statistically significant differences in FBG and 2h-PBG levels among the three groups (P > 0.05; Table 3).

3.4 | Changes in TC, TG, HDL-C, and LDL-C levels in each group of participants

The TC, TG, HDL-C, and LDL-C levels had no statistically significant differences between normal thyroid group and control group (P > 0.05). The serum TC, TG, and LDL-C levels in hypothyroidism group were obviously higher than those in normal thyroid group, showing statistically significant differences (P < 0.05; Table 3).

### TABLE 1 | Changes in thyroid function indexes in each group

|                  | FT3 (pmol/L) | FT4 (pmol/L) | TSH (uIU/mL) |
|------------------|--------------|--------------|--------------|
| Hypothyroidism   | 3.31 ± 1.25* | 6.59 ± 3.89* | 40.07 ± 10.03* |
| Normal thyroid   | 4.26 ± 0.85  | 11.39 ± 1.58 | 2.21 ± 1.15   |
| Control group    | 4.36 ± 0.79**| 11.41 ± 1.72**| 2.15 ± 1.11** |
| F                | 52.364       | 6.721        | 18.706        |
| P                | <0.001       | <0.001       | <0.001        |

*P < 0.05 vs normal thyroid group.
**P > 0.05 vs normal thyroid group.

### TABLE 2 | Changes in IL-6, TNF-α, IL-12, and IL-10 levels in each group of participants

|                  | IL-6 (pg/mL) | TNF-α (ng/mL) | IL-12 (pg/mL) | IL-10 (pg/mL) |
|------------------|--------------|---------------|--------------|--------------|
| Hypothyroidism   | 68.74 ± 13.27| 5.32 ± 0.47   | 1106.53 ± 298.51 | 45.62 ± 11.35 |
| Normal thyroid   | 58.74 ± 12.05**| 1.54 ± 0.32**| 789.62 ± 256.74**| 33.56 ± 7.89** |
| Control group    | 36.51 ± 10.23***| 1.01 ± 0.21***| 593.15 ± 215.69***| 26.35 ± 5.66*** |
| F                | 7.521        | 8.235         | 11.975        | 38.924        |
| P                | <0.001       | <0.001        | <0.001        | <0.001        |

*P < 0.05 vs normal thyroid group.
**P < 0.05 vs hypothyroidism group.
3.5 Changes in FINS and HOMA-IR in each group of participants

The levels of FINS and HOMA-IR gradually declined in sequence of hypothyroidism group, normal thyroid group, and control group, and there were statistically significant differences ($P < 0.05$; Table 3).

3.6 Correlations of thyroid function with glucose-lipid metabolism, insulin resistance and inflammatory factors in HT patients

The serum FT3 and FT4 levels were positively correlated with IL-6, TNF-$\alpha$, IL-12, IL-10, TC, TG, LDL-C, FINS, and HOMA-IR, while the serum TSH level was negatively correlated with IL-6, TNF-$\alpha$, IL-12, IL-10, TC, TG, LDL-C, FINS, and HOMA-IR, displaying statistically significant differences ($P < 0.05$) (Table 4).

4 DISCUSSION

Hashimoto's thyroiditis (HT) is an autoimmune disease reported by Hashimoto Hakaru of Kyushu University in Japan for the first time in 1912. It is widely believed that the pathogenesis of HT is related to the immune dysfunction of thyroid tissues. A large number of specific immune antibodies will destroy the normal function of thyroid tissues, damage the thyroid follicular function, produce a toxic effect on thyroid tissues, and affect the storage, synthesis, and secretion of thyroid hormones. Cytokines, such as IL-1beta, TNF-alpha, and IL-6, play a crucial role in modulating immune response in autoimmune disorder and therefore are considered as markers of hypothyroidism. As hypothyroidism occurs in patients, the clearance rate of LDL-C is reduced. Moreover, the activity of lipoprotein lipase is inhibited by the thyroid hormones, ultimately resulting in the increase in serum TC level. In this study, we investigated the changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in AITD patients as well as analyze their correlations with the thyroid function.

Recent study on children diagnosed with autoimmune thyroid disease indicated that the thyroid function (TSH, FT4, FT3) was evidently impaired. Similar to the previous finding, our result showed decrease in levels of serum FT3 and FT4 in hypothyroidism group compared to that in normal thyroid group, with elevation of serum TSH. Cytokines are involved in the pathogenesis of thyroid diseases working in both the immune system and directly targeting the thyroid follicular cells. Accordingly, we detected IL-6, TNF-$\alpha$, IL-12, and IL-10 levels and found that they were evidently increased in patients with autoimmune thyroid disease, which was consistent with previous finding that Hashimoto thyroiditis (HT), as the most frequent thyroid autoimmune disease, significantly elevated concentrations of IL-4, IL-6, IL-9, IL-13, and IFN-gamma in patients. Interestingly, it has been demonstrated that the levels of pro-inflammatory cytokines TNF-$\alpha$, IL-10, IL-12p70, IFN-$\gamma$, and
TABLE 4 Correlations of thyroid function with glucose-lipid metabolism, insulin resistance, and inflammatory factors in Hashimoto’s thyroiditis patients

|             | FT3  | FT4  | TSH  |
|-------------|------|------|------|
|             | r    | p    | r    | p    | r    | p    |
| IL-6        | -0.543 | <0.001 | -0.447 | <0.001 | 3.575 | <0.001 |
| TNF-α       | -0.368 | <0.001 | -0.233 | <0.001 | 0.781 | 0.005  |
| IL-12       | -0.543 | <0.001 | -0.069 | <0.001 | 0.537 | 0.014  |
| IL-10       | -0.368 | <0.001 | -0.015 | <0.001 | 0.781 | 0.005  |
| TC          | -0.741 | <0.001 | -0.135 | <0.001 | 0.537 | 0.014  |
| TG          | -0.374 | 0.023  | -0.085 | <0.001 | 3.575 | <0.01  |
| LDL-C       | -0.869 | <0.001 | -0.062 | <0.001 | 0.684 | 0.015  |
| FINS        | -0.781 | 0.005  | -0.140 | <0.001 | 0.654 | 0.035  |
| HOMA-IR     | -0.326 | <0.001 | -0.151 | <0.001 | 0.537 | 0.014  |

IL-1β were significantly decreased in offspring of mothers with autoimmune thyroid disease as compared to healthy controls, indicating that maternal thyroid autoimmunity and transplacental passage of autoantibodies against thyroid antigens may affect the generation or expansion of cells with NK activity and the secretion of inflammatory cytokines.11

In hypothyroidism, the thyroid hormones in the body may exert a stimulatory effect on the synthesis and secretion of IL-12, and the IL-2 level is also significantly increased with the increase of the TSH level in the body. It has been shown that the levels of fasting blood glucose (FBG), FINS, and HOMA-IR were apparently elevated in participants with nodular goiter and AITD. By contrast, our study indicated no statistical differences in FBG and 2h-PBG among the three groups. In addition, FINS and HOMA-IR were remarkably reduced in hypothyroidism group, suggesting nodular goiter may affect the level of FBG, FINS, and HOMA-IR, which requires further investigation with a large group of samples. The high-level in patients with hyperthyroidism can accelerate the decomposition and synthesis of blood lipid in the body, so that the lipid synthesis in the body is less than lipid degradation, raising the clearance rate of serum TG. In patients with hypothyroidism, the decline in LDL activity and the number of receptors in liver cells may damage the degradation pathway of LDL-dependent receptor in vivo and increase the serum LDL level in HT patients.2

Notably, we found that there was a close correlation between HT patients and the blood lipid level. Previous evidence showed that the high-lipid diet in primates can reduce the serum FT4 level in their descendants, indicating that the high-level TG is not only the “result” but also the “cause” of hypothyroidism in patients. Under normal physiological conditions, the thyroid hormones can promote the degradation of cholesterol into bile acids and also inhibit the biosynthesis of human cholesterol. It was indicated that a statistically significant relationship was found between thyroid volume and age, fasting glucose, HOMA-IR, BMI, and fasting insulin. Participants with thyroid nodules were older and had higher fasting glucose, BMI, fasting insulin, and HOMA-IR values compared with those without thyroid nodules.11 Consistently, our correlation analysis revealed data significant association of thyroid function with glucose-lipid metabolism, insulin resistance, and inflammatory factors in HT patients. We found that the levels of serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-12, IL-10, (FINS), and homeostasis model assessment of insulin resistance (HOMA-IR) were gradually declined in sequence of hypothyroidism group, normal thyroid group, and control group, further supporting the pathogenic role of inflammatory cytokines as well as lipid metabolism in the pathogenesis and development of AITD.

5 | CONCLUSION

In conclusion, the risk of fat metabolism disorder increases in AITD patients, and the serum thyroid hormone level has a close correlation with blood lipid metabolism, insulin metabolism, and inflammatory factors, which has certain reference value in guiding treatment and correcting metabolic disorder.

CONFLICT OF INTEREST

None.

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