Short Communication

The Role of Trace Element (Zn, Se, Cu, and Cr) Levels with an Increased Risk of Developing Hashimoto Disease

Haneen Sayar, Alaa A. Saleh, Dawood Salman Ali

Medical Laboratory Techniques Department, Health & Medical Techniques College, Southern Technical University, Basrah, Iraq

Abstract

Background: Autoimmune Hashimoto thyroiditis destroys thyroid cells via cell- and antibody-mediated immunological mechanisms. This disease causes hypothyroidism. Dietary iodine deficiency is the most common cause of hypothyroidism. **Objectives:** The objective of this study is to investigate the association between trace element levels, specifically zinc (Zn), selenium (Se), copper (Cu), and chromium (Cr), and the risk of developing Hashimoto's disease in female patients. **Materials and Methods:** Between September 2022 and April 2023, 50 women with Hashimoto thyroiditis and 46 healthy controls visited the teaching hospital in Basrah, Southern Iraq. In order to measure thyroperoxidase autoantibodies (TPOA), enzyme-linked fluorescence immunoassay (ELFA) was used. Enzyme-linked fluorescence immunoassay was used to measure thyroid hormone levels [FT3, FT4, and thyroid stimulating hormone (TSH), TPOA]. Atomic absorption spectrometry was also used to analyze the levels of trace elements (Zn, Se, Cr, and Cu). **Results:** The result shows a significant decrease in FT4 and FT3 levels compared to the control group and significantly higher thyroid peroxidase antibodies level. Instead, the levels of TSH are raised. When comparing the levels of trace elements (Cu, Cr, Se, and Zn) the result shows significantly lower levels of Cr and Zn. In contrast, Cu and Se levels are insignificantly different between the two groups. **Conclusion:** The study findings indicate that low levels of Zn and Cr are associated with an increased risk of developing Hashimoto's disease in female patients. These results suggest that Zn and Cr may play a crucial role in the pathogenesis and progression of Hashimoto's disease.

Keywords: Anti-TPO antibodies, biomarkers, Hashimoto disease, hypothyroidism, trace elements

Introduction

Autoimmune Hashimoto thyroiditis destroys thyroid cells via cell- and antibody-mediated immunological processes. It causes most hypothyroidism in industrialized nations. Lack of iodine in the diet is the major cause of hypothyroidism worldwide.[1]

People acquire anti-thyroid peroxidase (anti-TPO) antibodies most often. The body produces plenty of antithyroglobulin (anti-Tg) and thyroid stimulating hormone (TSH) receptor blocking antibodies (TBII). Antibodies destroy thyroid tissue.[2]

Lymphocyte infiltration and fibrosis indicate autoimmune development in Hashimoto disease. Laboratory data showing increased TSH with normal or low thyroxine led to the diagnosis.[3]

Thyroid antibodies include TPO antibodies. Thyroid peroxidase produces T3, T4, and TSH. Immune cells create antibodies to fight foreign proteins. Antigens are non-host proteins. Antibody generation is essential for infection prevention. Autoantibodies are created when the immune system misidentifies our proteins as foreign antigens.[1]

Patients with primary hypothyroidism typically have low FT4 and high TSH levels. Most cases of primary hypothyroidism can be traced back to an inadequate intake of iodine. Iodine-rich regions are more likely to

Address for correspondence: Haneen Sayar, Medical Laboratory Techniques Department, Health & Medical Techniques College, Southern Technical University, Basrah 61001, Iraq.
E-mail: hanen.med95@gmail.com

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have Hashimoto's thyroiditis; hence TPO-Ab testing is also advised.[4]

Because they are necessary cofactors for enzymes, trace elements are crucial to cellular metabolism and maintaining homeostasis. In order to prevent deficiencies and toxicity, their amounts within cells and in the blood are controlled by gastrointestinal absorption and excretion via the kidneys and intestines.[5]

Zinc exists as Zn^{+2} in the body, but only after being covalently linked to other molecules. Zinc is necessary for the synthesis of over 2700 enzymes in the human body.[6]

Follicular cells in the thyroid secrete the hormones thyroxine (T4) and triiodothyronine (T3). These peptides have important functions in homeostasis, such as the regulation of the basal metabolic rate, through their effects on lipid and carbohydrate metabolism. Growth, development, thermogenesis, and oxidative metabolism all rely on them in some way.[7]

Zinc is a critical transcription factor for the gene expression of the proteins involved in the synthesis of the thyroid hormones, in addition to its role as a cofactor for type I and II deiodinases, which contributes to the activation of the thyroid hormones by converting T4 to T3. Similarly, zinc is essential to the construction of T3 receptors.[8]

Copper (Co) is a redox active element that helps keep one's thyroid working properly and her/his lipids metabolized properly. Calcium levels are controlled and T4 absorption is blocked by cobalt. Animal studies have shown a correlation between hypothyroidism and high Co levels, and hyperthyroidism and low Co levels. Co has been proven in certain studies to stimulate thyroid hormone production and have a beneficial influence on thyroid hormone levels.[9]

Selenium (Se) plays a crucial role in the synthesis and metabolism of thyroid hormones. Most Se is found in the thyroid gland. Several selenoproteins, including glutathione peroxidase, iodothyronine deiodinase, thioredoxin reductase, selenoprotein P, selenoprotein K, etc., are responsible for the biological effects of Se.[9]

The human body needs chromium (III) to function properly. Chromium (III) ion is required for nutritional support of the thyroid gland to aid insulin in weight reduction because insulin prevents phosphorylation and thus opposes the action of epinephrine and can limit thyroid hormone production.[10]

The aim of this study was to investigate the relationship between trace elements level and Hashimoto thyroiditis in female patients.

Materials and Methods

Study design and patients

This is a case–control study which included 50 women with Hashimoto thyroiditis. The median age of the participants in the study was 35. This study also includes 46 healthy individuals with normal thyroid function test as control group. A group of patients visited Al-Faiha specialized diabetes, endocrine, and metabolism center (FDEMC) and AL-Sader teaching Hospital. Doctors at Al-Faiha specialized diabetes, endocrine, and metabolism center (FDEMC) and AL-Sader teaching Hospital examined the patients for this study between September 2022 and April 2023 in Basrah, Southern Iraq. We excluded men and also excluded patients with Graves' disease, thyrotoxicosis, renal failure, a thyroid tumor, children, patients aged 55 and under, and patients aged 18 and above were not included in the study. A total of 5 mL of blood sample for the measurement of serum TPOA, FT3, FT4, and TSH was drawn from each patient and control subject, and then all the samples were placed in sterile gel tubes and allowed to coagulate at room temperature for 30 min before being centrifuged for 15 min at a speed of 3000 rpm to separate the components. The serum should be separated and kept at a temperature of –20ºC until use. TPOA, FT3, FT4, and TSH were assayed by an automated enzyme-linked fluorescence immunoassay (ELFA), according to the operational automated of Biomerieux, France. The trace element (Zn, Se, Co, and Cu) was also measured using atomic absorption spectrometry according to shimadzu company, Japan.

Statistical analysis

The statistically significant differences were determined using SPSS version 26 (SPSS, IBM Company, Chicago, Illinois).

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before conducting the study. The study protocol and the subject information and consent form were reviewed and approved by a local committee on publication ethics at Basra Directorate under the reference No. 840/12 on August 14, 2022.

Results

Table 1 shows highly significant increase in the levels of TPOA in the patients group (450.44 ± 400.43) compared to control group (0.89 ± 0.14) ($P \leq 0.001$).

Table 2 shows a comparison of the trace elements (Cu, Cr, Se, and Zn) between control and patients group. It was noticed that Cr and Zn show significant decrease in patients compared to the control (1.57 ± 0.76 vs. 1.21 ± 0.58, $P = 0.01$) (1.07 ± 0.59 vs. 0.81 ± 0.40, $P = 0.02$) respectively. In contrast, there in non-significant difference in the levels of Cu and Se in the two groups (1.11 ± 0.64 vs. 1.18 ± 0.54, $P = 0.40$) and (107.80 ± 17.10 vs. 104.49 ± 19.81, $P = 0.28$), respectively.

Table 1: Differences in TPOA, FT4, FT3, and thyroid stimulating hormone, between patients group and control group

Parameters	Control group (n = 46)	Patients group (n = 50)	P value
	Mean ± SD	Mean ± SD	
TPOA	0.89 ± 0.14	450.44 ± 400.43	<0.001
FT3	4.65 ± 0.59	4.19 ± 1.15	0.01
FT4	15.39 ± 2.45	11.63 ± 4.05	<0.001
TSH	2.16 ± 1.14	16.25 ± 13.23	<0.001

Compared with healthy control: *** P<0.001, ** P<0.01
TSH = thyroid stimulating hormone

Table 2: Differences in trace elements (Cu, Cr, Se, and Zn) between control and patients group

Parameters	Control group (n = 46)	Patients group (n = 50)	P value
	Mean ± SD	Mean ± SD	
Cu	1.11 ± 0.64	1.18 ± 0.54	0.40^{NS}
Cr	1.57 ± 0.76	1.21 ± 0.58	0.01
Se	107.80 ± 17.10	104.49 ±1 9.81	0.28^{NS}
Zn	1.07 ± 0.59	0.81 ± 0.40	0.02

Discussion

When comparing thyroid hormones between the control group and the patients group, a significant decrease was observed in both FT3 and FT4 in patients group compared to control (4.65 ± 0.59 vs. 4.19 ± 1.15, P = 0.01) and (15.39 ± 2.45 vs. 11.63 ± 4.05, P < 0.001), respectively. On the one hand, there is a significant increase in serum levels of TSH in patients group compared to control (2.16 ± 1.14 vs. 16.25 ± 13.23, P < 0.001), but on the other hand, there is a significant increase in serum levels of TPOA in patients group compared to control (450.44 ± 400.43 vs. 0.89 ± 0.14, P < 0.001).

Anti-thyroid peroxidase (anti-TPO) antibodies are the most common form of anti-thyroid antigen antibodies. TSH receptor blocking antibodies (TBII) and antithyroglobulin (anti-Tg) are also created in the body in high levels. Antibodies like these can inhibit or completely halt hormone production by binding to thyroid tissue. Only about 15% of those with obvious disease had negative results for serum antibodies. A positive TPO antibody test is diagnostic inference of the clinical illness.[11]

This research is consistent with Liu *et al* found that autoimmunity is a controversial factor in hypothyroidism.[12] Hashimoto's thyroiditis can be diagnosed by analyzing TPOA and learning about its levels in patients.

Hashimoto disease is characterized by lymphocyte infiltration and fibrosis, which point to an autoimmune mode of development. The current diagnosis was reached due to laboratory results of elevated TSH in the presence of either normal or low thyroxine levels.[13]

When comparing of between control and patients' group, it noticed that Cr could show significant decrease in patients compared to the control. This research corresponds to previous study.[14]

The effects of an overabundance of Cr (III) on the thyroid gland are poorly understood. The connection between the very hazardous hexavalent form of chromium and thyroid structure and function has not been studied as thoroughly. Cr (VI) undergoes reduction to Cr (III) after penetrating cellular membranes and in the gastrointestinal environment; therefore, its characteristics may play a role in this.[14]

Hanif *et al*. found that The majority of the literature on the endocrine effects of chromium focuses on the element in its reduced form,[15] which is not agreed with this study.

Patients with hypothyroidism had chromium levels that were considerably higher than the control group's (Cr 12.31 1.229 µgg/g vs. 8.422 0.886 µgg/g). Among the many, Rezaei stands out revealing an association between high Cr levels and an increased danger of hypothyroidism.[16]

Research done by Stojsavljevi *et al.* 2018. High amounts of Cr were seen in 23 patients with hypothyroidism compared to 70 healthy people. In contrast, Błażewicz *et al*., found that, contrary to what is known at the time, Cr content in the control group was two to three times greater than in patients with hypothyroidism.[17]

When Zn levels were examined between the control group and the patients, the patients were found to have significantly lower Zn levels. This study is in line with.[18]

The levels of thyroid hormones (TSH, T4, and T3), as well as their precursors (TRH), are all affected by zinc deficiency. It is also required for the conversion of T4 to T3 in tissues outside of the thyroid and it is involved in the binding of T3 to the nuclear receptor and the receptor to DNA. Changes in thyroid function have been recorded in people who are zinc deficient, but hypothyroidism can cause zinc deficiency and also contributes to it.[19] However, the result of this study was incompatible with.[20]

Extremely low zinc levels were seen in hyperthyroidism, whereas elevated zinc levels were seen in hypothyroidism. Unlike plasma zinc levels, erythrocyte zinc concentration correlated positively with plasma prealbumin and retinol-binding protein. Superoxide dismutase activity in erythrocytes was not correlated with copper or zinc levels.

In contrast, Cu and Se levels do not differ significantly between the two groups. Copper levels were found to be considerably higher in persons with Hashimoto's disease compared to healthy controls in a study conducted by Rasic-Milutinovic *et al*.[21] Thyroid hormone levels may

also be affected by the ratio of copper to selenium, with a higher selenium level and lower copper encouraging a decrease in L-thyroxine or causing euthyreosis at lower FT4 values.

Copper levels were not significantly different between hypothyroidism patients and control people, according to the majority of authors' research.[22]

Correct copper levels are necessary for the prevention of thyroid problems and can be used in the treatment of thyroid disease because copper levels are altered in patients with hypothyroidism. Copper was not associated with T3, T4, or TSH levels in hypothyroidism patients. Rashid *et al*. also observed the same results.[23]

Decreased activity of glutathione peroxidases, which is linked to the severity of oxidative damage, or of deiodinases, and can lead to worsening of thyroid activity, selenium insufficiency may affect thyroid function where low selenium levels influence blood levels of thyroid hormones. With a mean SD plasma selenium concentration of 98.79 13.63 µg/L, 26.08% of the sample exhibited deficient selenium levels (selenium deficiency cut-off 90.0 µg/L). The levels of selenium and thyroid hormone 4 (T4) were strongly inversely linked with their research, Khorasani *et al*.[23]

Conclusion

The conclusion from the results of the research that trace elements have an important and significant role in affecting the activity of the thyroid gland, and an imbalance in the levels of trace elements in the human body can lead to a functional defect that leads to the development of Hashimoto's disease, as we explained in the discussion on the research.

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Conflicts of interest

There are no conflicts of interest.

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