



ORIGINAL ARTICLE

Analysis of serum boron, arsenic and aluminium in Hashimoto's Thyroiditis: A pilot study

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Abstract

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Hashimoto's thyroiditis (HT) is a common autoimmune disease with its unclear pathogenesis. HT, widely diagnosed in women, targets thyroid gland and its parenchyma. Thyroid gland is damaged by pro-inflammatory cytokines and mediators due to an imbalanced immune system. Trace elements play vital roles in many physiological and pathological inflammatory process. Dysfunctions of reactive oxygen species production and anti-oxidant protective systems in HT effect alterations of trace/toxic element levels. The biological, anti-inflammatory and anti-oxidant effects of boron (B) on endocrine system have been pointed out in several studies. Arsenic (As) and aluminium (Al), as environmental toxic elements, induce oxidative stress and inflammation also including thyroid gland. The present pilot study was aimed to evaluate alterations of serum B, As and Al in patients with HT. The individuals were categorized in two groups; patients with HT (HT Group, n=30) and healthy controls (HC Group, n=30). Serum element levels were measured using ICP-OES. Serum B and As levels in HT Group were significantly higher than HC Group ($p<0.001$ and $p<0.05$; respectively). There was a significant positive correlation between serum As-Al levels in HT Group. The present study revealed that higher

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serum B levels in HT might present its re-distribution from tissues and the protective effect of B against inflammation due to oxidative stress. Otherwise, higher serum As and Al, and their positive correlation in HT express their hazardous effects on thyroid dysfunction. Further studies should be warranted to determine effects of a variety trace/toxic elements in HT by means of molecular and physiopathological pathways. Monitorization of serum elements should be considered as beneficial biomarkers for thyroid functions.

Introduction

Hashimoto's thyroiditis (HT) disease is a serious autoimmune disease characterized by the immune system cells perceiving the thyroid gland cells as foreign structure and attacking of the thyroid gland by these cells [1,2]. Its annual incidence is 0.3 - 1.5 per 1000 with a clinical presentation between 30 and 50 years of age [3,4]. Approximately 95% of the cases are women and the mechanism causing this difference has not been elucidated yet [5]. HT is affected by both genetic predisposition and environmental factors. Infections, stress, sex steroids, pregnancy, iodine intake, ionizing radiation and genetic predisposition are known possible precipitating factors [6].

The host produces high levels of anti-thyroglobulin and serum thyroid peroxidase antibody (TPOAb) antibodies in an attempt to eliminate its own thyroid gland in HT patients. These antibodies bind to the thyroid gland and initiate to destroy the thyroid cells [1]. The mechanism of autoimmune thyroid destruction likely involves both cellular and humoral immunity. There is intense B lymphocyte and cytotoxic T cell infiltration, which completely destroys the normal thyroid structure into parenchymal alterations [7]. An inflammatory process develops in the thyroid gland during this time period via this autoimmune reaction. Following the attack of immune system cells such as autoreactive T cells migrating to this region, thyroid gland cells are damaged, causing a decrement in thyroid hormone production. Thyroid functions are assessed by thyroid stimulating hormone (TSH), triiodothyronine hormone (T3), thyroxine hormone (T4) and thyroid ultrasonography. The thyroid gland becomes smaller in its size and is not capable of synthesizing sufficient hormones, resulting in hormone deficiency and requiring treatment [8].

Trace elements are vital constituents of biological structures in low concentrations (mg/dL and mg/kg) in body fluids or tissues. Despite their low concentration utilized within the body, they have crucial functions in the structure of various biomolecules, mitochondrial activity, membrane stabilization, regulation of pH, muscle contraction, nerve conduction and energy production [9-11]. They alter and modulate their own functions through the mutual interaction of trace elements, but they can also have a positive or negative impact on the functions of other elements [9,10,12,13]. Due to this fact, trace elements should be taken regularly with foods and/or supplements as essential micronutrients [14].

Trace element and toxic element concentrations in the organism affect the normal physiology of the thyroid gland, and synthesis and metabolism of thyroid hormones. Concentrations of trace elements in the thyroid gland are higher than in other tissues [15]. Trace elements such as iodine, selenium (Se), iron, copper and zinc are important minerals that support and regulate thyroid function. It has also been shown that blood parameters were correlated with the HT disease in the development of autoimmune thyroid dysfunction [16-18].

Studies encompassing both humans and animals have investigated the beneficial impacts of boron (B) on biology. B has vital roles for mineral balance, hormone systems, lipid profile and energy metabolisms, bone structure and function, metabolism of cell membranes and enzymatic mechanisms, antioxidant defence through reactive oxygen species elimination, and immune system [19,20]. B is

regarded as a preventive element that controls essential processes for human health and actively contributes in the immune system and anti-oxidant defence systems. On the other hand, there is still debate on the importance of B in nutrition and its beneficial role in human health [19,21].

Biological organisms are exposed to toxic metals (arsenic (As), aluminium (Al), lead, mercury, cadmium) via inhalation, digestion and skin contact. As and Al induce oxidative stress and inflammation within the whole organism, also including thyroid gland. As is a ubiquitous environmental element particularly found in soil, water, and air. Since toxicity might affect millions of people, it can lead to pathologic diseases in the respiratory, hematopoietic, gastrointestinal, cardiovascular systems [22,23]. High content of As in thyroid tissue might contribute to the replacement of anti-oxidant trace elements including B and Se [24]. Al is an abundant metal found in many parts of the environmental areas [25]. Also, it has been emerged to interfere with some endocrine systems including thyroid gland leading several pathological processes [26].

The present pilot study was planned as a single-center cross-sectional research with the aim of clarifying the effects of serum boron, arsenic and aluminium in euthyroid individuals with Hashimoto's thyroiditis. Furthermore, possible cross-relationships between targeted elements within biological organism would be assessed.

Materials and Methods

Study population

The study included the individuals who were admitted to the Department of Internal Medicine's Outpatient Clinic after receiving approval for their written consent. The ethical approval of the present research was obtained from İstinye University Clinical Research Ethics Committee (2/2021.K-43). The study groups were planned as euthyroid individuals who were diagnosed with Hashimoto's thyroiditis (HT Group, n=30; 17 female and 13 male) not receiving drug treatment and healthy controls (HC Group, n=30; 15 female and 15 male).

Hashimoto's thyroiditis diagnosis was established on TPOAb levels and heterogeneous parenchymal echogenicity of thyroid gland in thyroid ultrasonography data. The thyroid gland ultrasonographies were assessed within physiological findings for healthy controls. The exclusion criteria of the present study were pregnancy, anti-inflammatory diseases other than HT, active infection, antibiotic and/or anti-inflammatory medication. Euthyroid individuals included in HT Group were 39 participants at the onset of study plan, but following the personal consent interval 9 participants were excluded from the study due to these pathologies; diabetes mellitus (n=2), cancer (n=2), autoimmune diseases (n=2), and blood parameters out of reference range (n=3).

Sample analysis

The whole blood samples of the individuals were withdrawn in the morning after 8-10 hours fasting interval into dry blood test tubes to avoid from possible trace and toxic element interactions. Whole blood samples were centrifugated at 3000 rpm for 20 minutes for obtaining serum samples for biochemical and serum trace and toxic element analysis. Hemolyzed blood samples were excluded from the research. Biochemical analysis were held in Central Biochemistry Laboratory. Centrifugated serum samples were kept in Eppendorf tubes at -80°C until the analysis of serum trace and toxic elements.

Analysis of serum B, As and Al levels were determined utilizing Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP - OES) (iCAP 6000-Thermo). ICP-OES is equipped with an emission spectrophotometer, auto sampler and a soft-ware program. ICP-OES was operated under acceptable circumstances with chosen favourable wavelength for B (249.775 nm), As (189.040 nm) and Al

(167.090 nm) with gas flow rate of plasma as 5 L/min, flow rate of argon as 0.5 L/min, flow rate of sample as 1.51 L/min, flow rate of elution, and peristaltic pump speed of 100 rpm. Transport lines were made using a 1.25-mm-i.d. polytetrafluoroethylene tubing. Standard solutions were prepared for each measured element (B, As and Al) using their stock solutions of 1000 µg/dL. Serum levels of analyzed elements, with an average of triplicate measures, were given in micrograms per milliliter (µg/mL) [11,27].

Emission-concentration graphs of serum elements

Calibration graphs were obtained for each element using the standard solutions and distilled water as blank solution (Figure 1).

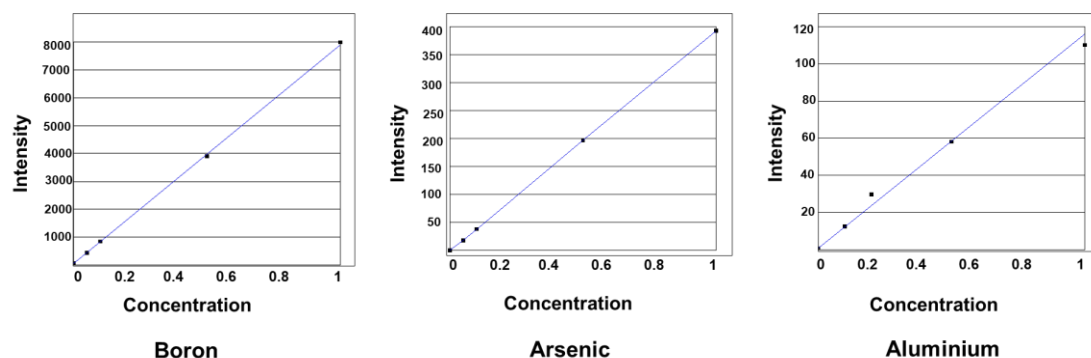


Figure 1. The emission-concentration graphs of serum elements for all standards.

Statistical analysis

Statistical analysis was performed utilizing IBM SPSS version SPSS 21.0. Independent t sample test was used for variables having normal distribution to assess the mean value within study groups. The optimal sample size in groups was calculated as 69 participants for 80% power at a 95% confidence level. Within a 95% confidence interval, the mean and median values were assessed. Parameters among the study groups were evaluated by Pearson correlation analysis. Serum trace and toxic element levels were given as means $\pm$ standard deviation (SD). The limit of significance was accepted as $p < 0.05$.

Results

The demographic details and biochemical markers of study groups were given in Table 1.

Table 1. Demographic details and biochemical characteristics of the study groups.

	HT Group n= 30	HC Group n= 30
Age (years)	39 ± 4	39 ± 5
Sex (F/M)	17 F/13 M	15 F/15 M
BMI (kg/m ²)	22.43 ± 4.39	21.12 ± 4.84
WBC (10 ³ /mL)	7.49 ± 1.85	6.65 ± 1.37
Hemoglobin (g/dL)	13.41 ± 1.64	12.75 ± 1.45
Hematocrit (%)	40.15 ± 4.10	39.33 ± 5.36
Glucose (mg/dL)	94.72 ± 9.25	93.68 ± 8.36
T ₃ (ng/dL)	3.22 ± 0.68	3.00 ± 0.42
T ₄ (ng/dL)	1.18 ± 0.21	1.14 ± 0.13
TSH (mIU/L)	1.39 ± 0.32	1.45 ± 0.86
TPOAb (IU/mL)	322.25 ± 102.82	8.25 ± 3.75 ^{***}
CRP (mg/dL)	3.18 ± 0.37	3.02 ± 0.47

Data are presented in mean ± SD.

^a statistical comparison with Group 1.

^{***}*p*<0.001.

HT Group: Hashimoto's thyroiditis group; **HC Group:** Healthy controls; **BMI:** Body mass index; **WBC:** White blood cell; **T₃:** Triiodothyronine; **T₄:** Thyroxine; **TSH:** Thyroid-stimulating hormone; **TPOAb:** Thyroid peroxidase antibodies; **CRP:** C reactive protein.

Serum B and As levels in HT Group were significantly higher than HC Group (*p*=0.000 and *p*=0.043; respectively). Besides, serum Al levels were higher in HT Group with no significance (*p*=0.661) (Table 2). There was a significant positive correlation between serum As - Al levels in HT Group (*r*:0.657, *p*:0.01).

Table 2. Serum element levels of the study groups.

	HT Group n = 30	HC Group n = 30
B (µg/mL)	0.13 ± 0.03	0.03 ± 0.02 ^{***}
As (µg/mL)	0.27 ± 0.18 ^{b**}	0.18 ± 0.02 ^{a*}
Al (µg/mL)	0.05 ± 0.02	0.04 ± 0.02

Data are presented in mean ± SD.

^a statistical comparison with HT Group

^b correlation with Al

p*<0.05, *p*<0.01, ****p*<0.001

HT Group: Hashimoto's thyroiditis group; **HC Group:** Healthy controls; **B:** Boron; **As:** Arsenic; **Al:** Aluminium.



Discussion

As a severe autoimmune condition, HT is defined by the thyroid gland's cells being attacked by immune system cells [1,2]. The thyroid gland is being destroyed by the anti-thyroglobulin and TPOAb antibodies and is infiltrated by cells of cellular and humoral immunity mechanisms. The thyroid gland is susceptible to trace elements, because it can accumulate them for an extended period. Therefore, endocrine disruption may occur due to prolonged exposure to the high content of essential and toxic metals [7,8,28].

Trace elements are necessary for an optimal thyroid function, metabolism of thyroid hormones and dynamic balance of thyroid gland. Normal thyroid metabolism and physiological functions of thyroid tissue are closely related with trace element status [7,16,17]. Whereas, thyroid gland is vulnerable to selected trace and toxic elements, because this gland is a potent structure for element accumulation. Endocrine disruption may occur from prolonged exposure to high concentrations of both essential and toxic elements [28]. There have been many studies related with the protective effect of B, and hazardous effects of As and Al in biological organism. Based on limited number of research with the impact of trace and toxic elements on HT, this study was conducted to evaluate the effects of boron, arsenic and aluminium in patients diagnosed with HT.

Establishing the basic mechanism underlying B's potentially beneficial function has been challenging due to the various functions of B within the whole biological mechanism. It is likely that B influences a cell signalling system, development and activity of numerous biochemical processes [29]. There is evidence that B affects the activation and metabolism of thyroid hormones by stimulating the receptors of thyroid hormone and the cell membrane [30-32]. Nevertheless, there have been limited data related with the impact of serum B on HT patients. As we could reach the literature, conducted studies with serum B have been designed based on hypothyroidism, hyperthyroidism and thyroid cancer issues. It was reported that a natural diet enriched with B decreased serum TSH levels, which is a leading hormone for thyroid function [17]. It was conducted by Nielsen and Penland [33] that B supplementation in postmenopausal women caused a decrement in serum T3 concentration. Moreover, Armstrong et al. [34] reported in their study based on the long-term effects of B on growth performance and immune function in gilts that serum T3 and T4 concentrations decreased presenting the impact of serum T3 and T4 in completion of physiological growth. On the other hand, a study held by Ibrahim et al. [35] in B supplemented male rams aiming to investigate the effects of B on thyroid activity revealed that serum T3 increased significantly with age. In consistent with this data, Küçük Kurt et al. [36] investigated in male rats that B supplementation also increased serum T3 concentration. In a further study held by Kan et al. [37] in hypothyroidic rats, B supplementation increased serum T3 concentration and had no effect on serum T4 and TSH levels. In the present study, HT Group had no statistical significance with HC Group by means of serum T3, T4 and TSH and significantly higher serum B levels compared with HC Group. The values of serum T3, T4 and TSH within reference range limits might be due to the fact that our study group involved euthyroid individuals with Hashimoto's thyroiditis. Three-fold increased serum B levels in HT Group without supplementation ($p < 0.001$) might be related with anti-inflammatory and protective effect of B against inflammation due to oxidative stress, and also with its re-distribution from tissues. Furthermore, thyroid gland is the primary target in HT patients based on inflammatory processes and oxidative imbalance in this organ. That's why, stored B in several tissues within the organism is secreted into blood circulation pointing out its re-distribution and resulting in higher serum B levels.

As initially functions to disrupt the balance between pro-oxidant and anti-oxidant systems, and also causes cellular and functional abnormalities in tissues and accumulation in various organs. As has been considered to inhibit thyroid homeostasis directly and to interfere with other trace and toxic elements physiopathologic pathways [38]. It was reported that diluted drinking water with As in rats

deteriorated the oxidative balance of blood and various tissues [36]. Benvenga et al. [39] pointed out that As could disrupt thyroid hormone receptors. In their study based on HT patients, Stojšavljević et al. [4] demonstrated significantly increased As in both serum samples and thyroid tissue of HT patients when compared to healthy controls. Ciarrocca et al. [40] reported higher urinary excretion of As, higher serum TSH levels and significant lower serum T3 and T4 levels in traffic policemen in urban areas compared with road workers in rural areas. Consistently with this study by means of the study population involving euthyroid individuals, the present study revealed out statistically higher serum As levels in HT Group ($p<0.05$). Higher serum As levels in HT Group might indicate the oxidant status has been initiated even within normal range of thyroid function markers.

Al can prompt several systemic disorders related with all cell membranes via lipid peroxidation and accumulation in multiple tissues [11]. The disrupting effects of Al on thyroid gland occur by the induction of oxidative stress resulting in alteration in the function of basal membrane of thyrocytes [25]. A single-dose of Al infusion study in rabbits did not alter Al levels of thyroid gland [41]. When literature based on impacts of Al for biological organism were evaluated, long term exposure studies showed the deteriorating effect of Al on various tissues including thyroid gland [25,42,43]. In a five-year follow-up study with aluminium-workers conducted by Alessio et al. [42], serum TSH levels increased within one year of exposure of Al compared with healthy controls. Orihuela et al. [43] investigated that high dose orally Al exposure reduced serum T4 levels in euthyroid rats. Same research group supported this data by another study based on intraperitoneally injection of Al to rats that addressed the induction of oxidative stress state for thyroid gland and disturbed hormone synthesis [25]. In our study, HT Group had higher serum Al levels with no statistical significance. A positive correlation was found ($r=0.657$, $p=0.01$) between serum As and Al levels in HT Group indicating their synergistic effect on thyroid gland.

Conclusion

In conclusion, highly elevated serum boron levels were observed in euthyroid patients with Hashimoto's thyroiditis compared to healthy controls. This noble outcome of the present study has strengthened the anti-inflammatory, protective and modulating impacts of B in thyroid gland. On the other hand, arsenic and aluminium presented an abnormal synergistic effect on thyroid gland.

The present research has some limitations as insufficient number of individuals involved in the study, the lack of analysis of other trace and toxic elements and absence of thyroid tissue and urine samples. Further multi-centric studies are needed to explain relationship between complications of Hashimoto's thyroiditis and trace and toxic elements, and etiopathogenesis of thyroid dysfunction by means of trace elements and their relationship between anti-oxidant systems. Evaluation of serum trace and toxic elements should be considered as beneficial and potential biomarkers for following-up of thyroid functions.

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Conflict of interest

There is no conflict of interest.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

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