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The physiochemical effect of selenium levels on thyroid function in women with thyroid disorders

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Abstract
Background: The main function of the thyroid gland is to control the rate of metabolism. Thyroid problems are a variety of disorders that may lead to an imbalance in the secretion of thyroid hormones such as (T4, T3) in addition to (TSH) and may eventually lead to thyroid tumors. Selenium plays a major role in the physiology and function of the thyroid gland, as the thyroid gland contains large amounts of selenium in the form of selenocysteine, which is an amino acid specifically incorporated into selenoproteins. In this study, the diagnosed groups were divided equally into four groups, with 20 samples for each group of women. One of these groups was the control group. Selenium deficiency was found to lead to thyroid dysfunction. The average concentration of the hormone (TSH) in the hyperthyroid group was found to have dropped sharply, with a significant difference of 0.13 mIU/mL from the normal level of 2.42 mIU/mL. Thyroxine (T4) secretion increased to 117.5 pmol/L, with a significant difference from the normal level. Triiodothyronine (T3) concentration also increased from 1.6 pmol/L to 1.97 pmol/L. These differences in the levels of these hormones are due to the decrease in selenium levels to 110.05 µg/L, compared to the normal level of selenium, which is 134.5. (µg/L), while the hypothyroidism group led to a selenium deficiency to 98.45 (µg/L), a significant increase in the serum TSH level from the normal state, to 9.845 (mIU/mL), and a clear decrease in the secretion of the hormone (T4) in this group at a rate of 91.35 (pmol/L) in the control group to 77.05 (pmol/L), and a decrease in the hormone (T3) from 1.6 (pmol/L) in the control group to a rate of 1.4 (pmol/L). The goiter group witnessed a sharp drop in the level of selenium, reaching approximately 50% of the normal limit, as it recorded 70.80 (µg/L), which may be the main reason for the goiter, with an approximate stability in the levels of the thyroid hormones (T4) and (T3), and an increase in (TSH) in this group at a concentration rate of 3.18 (mIU/mL) above the normal level. All of these results lead to a general disturbance in thyroid function and hormone levels due to selenium deficiency.

Keywords: Selenium deficiency, TSH, thyroid, thyroxine (T4), (T3)

Introduction

Selenium (Se) is a very important trace element, first isolated by the Swedish scientist Jöns Jacob Berzelius in 1817 (Lanzolla, *et al*., 2020) [1]. Although it is not an essential nutrient for plants, it is an essential nutrient for humans and many other organisms (Dottore, *et al*., 2016) [2]. In tissues, selenium is a component of amino acids such as selenomethionine and selenocysteine, with the amino acid selenocysteine being responsible for the main known biological activity of selenoproteins (Kahaly, *et al*., 2017) [3]. As is well known, the thyroid gland is the organ with the highest selenium content (Douglas, *et al*., 2020) [4]. Selenoproteins may play an important and fundamental role in the cellular defense system against hydrogen peroxide (H2O2), primarily, and other reactive oxygen species (ROS). Excessive production of free radicals, leading to tissue oxidative stress (OS), has been associated with many diseases and cancers, particularly thyroid cancer (Dottore, *et al*., 2017) [5]. The main pathological mechanism of hyperthyroidism is stimulation of the thyroid hormone (TSH) receptor by autoantibodies that bind directly to it and promote thyroid cell proliferation and activity, leading to hyperthyroidism (Wang, *et al*., 2023) [6]. The symptoms of thyroid toxicity are often nonspecific, so patients with hyperthyroidism may present in various ways. Symptoms include heat intolerance, tachycardia, hyperactivity, weight loss, and inappropriate feelings of anxiety and fear. Diffuse goiter may be visible or palpable, with a systolic murmur above it. Systolic blood pressure may also be elevated, and hepatomegaly or splenomegaly may also be observed (Zheng, *et al*., 2016) [7]. The complex pathogenic interaction of Graves' disease specifically involves, among other things, oxidative stress, for which selenium and other antioxidant agents have been proposed for the management of hyperthyroidism in Graves' disease (Gallo, *et al*., 2022) [8]. As is well known, autoimmune thyroid disease (AITD) is a typical organ-specific autoimmune condition caused by multiple factors, including genetics, environment, and lifestyle. Selenium (Se) may have an indirect role in this, as it can directly regulate thyroid antibody levels, which can lead to AITD if levels in the thyroid gland are abnormal. Selenium is also involved in the biosynthesis of thyroid hormones in the body (Gallo, *et al*., 2022) [8]. Recently, several studies and research have shown that selenium supplements are beneficial in regulating serum levels of thyroid-stimulating hormone (TSH), as well as triiodothyronine (T3), thyroxine (T4), TGAb, and TPOAb, specifically, which in turn have a significant immunomodulatory effect (Kim, *et al*., 2022) [9].

The aim of this study

was to determine the extent to which selenium (Se) levels affect thyroid activity and the susceptibility to thyroid disease in humans in particular.

Materials and Method

Ethical approval

Ethical approval University of Mosul, College of Science. Ethical Committee approval code is MUH0001. Written consents of the participants were provided.

Sample Collection, Diagnosis, and Experimental Design

Samples were collected through medical examination and testing of (164) females of varying ages, ranging from 25 to 60 years old, weighing between 60 and 90 kg. From patients attending government hospitals, laboratories, and private medical clinics in Mosul, 80 samples were identified and selected.

They were then divided into four groups, each containing 20 samples. The division was as follows:

Group 1: The control group, which includes healthy females who do not suffer from thyroid disease.
Group 2: Includes females suffering from hyperthyroidism.
Group 3: Includes females suffering from hypothyroidism.
Group 4: Includes females suffering from thyroid tumors.

Selenium levels in the samples under study were measured using the Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method, based on the principle of commercial reagent kits from Sunlong Biotech (China). The Microelisa stripplate provided in this kit has been pre-coated with an antibody specific to SELENBP1. Standards or samples are added to the appropriate Microelisa stripplate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)- conjugated antibody specific for SELENBP1 is added to each Microelisa stripplate well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain SELENBP1 and HRP conjugated SELENBP1 antibody will appear blue in color and then turn yellow after the addition of the stop solution. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of SELENBP1, while thyroid function was diagnosed using Cobas e 411 device from Germany, which employs Electrochemiluminescence Immunoassay (ECLIA) technology. Its principle involves using ruthenium-labeled antibodies that bind to the target hormones. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. The process was carried out according to the manufacturer's instructions and protocols.

Statistical Analysis

To analyze the test results and determine the mean and standard deviation, a one-way analysis of variance (ANOVA) was conducted to determine the mean and standard deviation using a completely randomized design (CRD). The study aimed to determine the effect of serum selenium concentrations on the thyroid gland and to identify thyroid disorders by comparing the study group with the control group. To determine these differences between the other groups, Duncan's multiple range test was used for all studied variables. Differences were considered statistically significant at a probability level of $P < 0.05$. Statistical analysis was conducted using the Statistical Analysis System program to calculate the mean and standard deviation (Leo, *et al*., 2017) [10].

Results and Discussion

It is noted, according to Table (1), that the average concentration of selenium in the serum was (134.5 (µg/L)) for the control group. At this concentration, the average concentration of thyroid-stimulating hormone (TSH) secreted by the pituitary gland was 2.42 (mIU/mL), which is very normal for the control group consisting of 20 samples. Tests also showed that the average concentration of thyroxine (T4) reached 91.35 (pmol/L) in the control group, while the average concentration of triiodothyronine (T3), also known as (T3), was 1.6 (pmol/L). There are two types of T3 in the body: free T3, which is present freely in the blood, not bound to anything, and bound T3, which is the most common type in the body. Most of the T3 in the body is bound to a protein (Liontiris, *et al*., 2017) [11]. In general, according to the mentioned table, the concentrations of thyroid hormone secretions appear normal when the selenium concentration is 134.5 (µg/L), and these results may be similar to most studies, including Josef's study (Köhrle, *et al*., 2023) [12].

Table 1. The effect of selenium on thyroid hormone secretion in the control group.

Parameter *N=20	Mean ± SD [1]/Mean (CI) [2*]	Median (Min.–Max.)
TSH (mIU/mL)	2.5 ± 1.1	2.42 (0.32-4.52)
T4 (pmol/L)	91.5 ± 16.8	91.35 (63.07–119.35)
T3 (pmol/L)	1.6 ± 0.9	1.6 (0.96–2.25)
Selenium (µg/L)	134.4 ± 20.2	134.5 (75.8–193.2)

Where N* represents the mean number of samples, (CI) 2* (Continuous Integration), probability level $P < 0.05$

The effect of selenium concentrations on the hyperthyroidism group

The study showed that the average concentration of the hormone (TSH) in the hyperthyroidism group recorded a very sharp decline, with a highly significant statistical difference, reaching 0.13 (mIU/mL) (Table (2)), compared to the control group, which was 2.42 (mIU/mL). This led to an increase in the secretion of the hormone thyroxine (T4) in this group, with a rate of 91.35 (pmol/L) in the control group to 117.5 (pmol/L) in the hyperthyroidism group, with a clear significant difference.

Table 2. The rate of selenium's effect on thyroid hormone secretions in the Hyperthyroidism Group

Parameter *N=20	Mean ± SD [1]/Mean (CI) [2*]	Median (Min.–Max.)
TSH (mIU/mL)	0. 13± 0.04	0.13*(0.02-0.24)*
T4 (pmol/L)	117.5 ± 19.7	117.5 (96.0 –139.0)
T3 (pmol/L)	2.0 ± 1.5	1.97 (1.22 –2.72)
Selenium (µg/L)	110.0 ± 18.4	110.05 (99.5 –120.6)

Where N* represents the mean number of samples, (CI) 2* (Continuous Integration), probability level $P < 0.05$.

The amount of secretion of the hormone triiodothyronine (T3) also increased from 1.6 (pmol/L) to a rate of 1.97 (pmol/L) compared to the control group. These differences in the secretion rates of all these hormones are generally due to the difference in the concentration of the element selenium, which decreased in the serum of the samples from the hyperthyroidism group. to (110.05) (µg/L) compared to the control group, which recorded a selenium concentration of (134.5) (µg/L). As it is known, most of the selenium-associated proteins (Wang, *et al*., 2023) [6], were identified by the three deiodinase enzymes (DIO, EC: 1.21.99.4 and

EC: 1.21.99.4), which are essential for the activation of local cells in the thyroid gland and the inhibition of T4 and T3 hormones in the thyroid gland as well as the target tissues for TH hormone activity, in addition to various selenium proteins involved in cellular redox controls in thyroid tissue and quality control of thyroglobulin (TG) biosynthesis, which is the main product of thyroid follicles, which is an essential protein for the synthesis, storage and secretion of thyroid hormone (Köhrle and Frädrich, 2022) [13]. Selenium deficiency affects the production of this hormone and consequently the function of the thyroid gland and the production and secretion of thyroid hormone (Figure 1). Many different studies have confirmed that it is possible to prevent or treat disorders associated with the thyroid hormone, even through dietary (assisted) selenium supply or medications containing selenium (Winthe, *et al*., 2020).

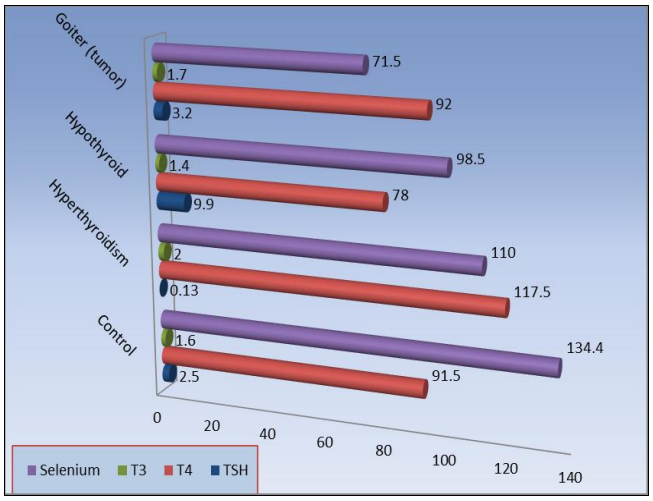

Fig 1: shows the effect of selenium deficiency on thyroid function in the three groups under study and in comparison, with the control group.

The effect of selenium concentrations on the hypothyroidism group

It is clear, according to Table (3), that selenium deficiency affected the hypothyroidism group (20 samples), as it led to a clear decrease in the secretion of thyroxine (T4) in this group, from 91.35 (pmol/L) in the control group to 77.05 (pmol/L) in the hypothyroidism group, with a significant statistical difference. The amount of triiodothyronine (T3) secretion also decreased from 1.6 (pmol/L) in the control group to 1.4 (pmol/L). At the same time, this led to an increase in the level of thyroid-stimulating hormone (TSH) in the serum, with a very significant difference from the normal state in the control group, 2.42 (mIU/mL), to 9.845 (mIU/mL) in the hypothyroidism group (Figure 1). This is certainly due to a decrease in the concentration of the selenium excretion recorded in this group was (98.45) (µg/L), which differs from the normal selenium concentration of (134.5) (µg/L) in the control group.

Table 3. The effect of selenium on thyroid hormone secretion in the Hypothyroid group

Parameter *N=20	Mean ± SD [1]/Mean (CI) [2*]	Median (Min.–Max.)
TSH (mIU/mL)	*9.9 ± 2.02*	*9.845 (5.24 -14.45)*
T4 (pmol/L)	78.0 ± 11.2	77.05 (52.6 –101.5)
T3 (pmol/L)	1.4 ± 1.2	1.42 (0.81–2.04)
Selenium (µg/L)	98.5 ± 14.8	98.45 (71.6 –125.3)

Where N* represents the mean number of samples, (CI) 2* (Continuous Integration), probability level P < 0.05

As previously mentioned, selenium is a component of a group of proteins that are linked to the production and secretion of thyroid hormones (T4) and (T3). These results may be consistent with many studies, as a group of researchers discussed in a study conducted on women, that consuming a sufficient amount of selenium may stimulate the formation of (T3) by selenium-deiodinating proteins (Liu, *et al*., 2022) [15]. Another study conducted on a large study group that included approximately 14,200 adult employees of both sexes in Brazil showed a (negative) relationship between selenium intake and subclinical hypothyroidism (Andrade, *et al*., 2018) [16]. In another study conducted on healthy thyroid individuals (aged 60 to 74) who took nutritional supplements containing selenium and yeast specifically (100, 200, or 300 micrograms of selenium daily for several years), a significant decrease in serum TSH and fT4 concentrations was observed. Finally, hypothyroidism may lead to symptoms of hypothyroidism such as constipation, lethargy, fatigue, depression, high cholesterol levels, low heart rate, hair weakness and loss, weight gain, and others. All of these symptoms are caused by decreased metabolic rates in the body as a result of hypothyroidism resulting from low selenium levels in the body (Zheng, 2016; Gabulov and Jabrailova, 2019) [17, 18].

The effect of selenium concentrations on the thyroid gland enlargement group(tumor)

This study showed that thyroid swelling or enlargement (tumor) may be the result of a sharp decrease in selenium levels and ratios to the minimum by a percentage that may be close to 50%. According to Table (4) and Figure (1), selenium levels were recorded at 70.80 (µg/L) compared to the normal level of 134.5 (µg/L) in the control group, according to the test results in Table (1).

Table 4 The rate of selenium's effect on the secretion of thyroid hormones in the group of thyroid gland enlargement (tumor)

Parameter *N=20	Mean ± SD [1]/Mean (CI) [2*]	Median (Min.–Max.)
TSH (mIU/mL)	3.2 ± 0.99	3.18 (0.21-6.15)
T4 (pmol/L)	92.0 ± 10.4	92.15 (58.7–125.6)
T3 (pmol/L)	1.7 ± 1.6	1.70 (0.90 –2.50)
Selenium (µg/L)	71.5 ± 8.8	70.80 (61.3 –80.3)

Where N* represents the mean number of samples, (CI) 2* (Continuous Integration), probability level P < 0.05.

It was also noted that in the thyroid gland enlargement group, the concentration of the hormone (TSH) increased in this group, with an average concentration of 3.18 (mIU/mL) compared to the normal level in the control group of 2.42 (mIU/mL). As for the thyroxine (T4) hormone, it was recorded in this group at 92.15 (pmol/L), which may be close to the normal level of this hormone in the control group, which is 91.35. (pmol/L), while for the hormone (T3), it recorded a rate of concentrations of 1.70 (pmol/L), which is significantly higher than the normal level of 1.60 (pmol/L). Concentrations of the thyroid hormones (T4) and (T3) that are equal to the normal level with a very sharp decrease in selenium levels may be a real and clear indicator of goiter when conducting immunological tests for the thyroid gland. These results may be similar to the results of some studies such as the study of Rui *et al*. (Rua, *et al*., 2023) [19], as this study and many other studies confirmed

that selenium deficiency (Figure (1) may actually lead to goiter and autoimmune deficiency diseases. This is due to the role of selenium in the production of thyroid hormones. In general, selenium is necessary for converting the hormone thyroxine (T4) to its active form (T3), and it also works as an antioxidant to protect the thyroid gland from tissue damage. Studies have also found that selenium deficiency leads to thyroid failure. Producing enough hormones, which in turn stimulates the pituitary gland to secrete more thyroid-stimulating hormone (TSH) to try to compensate for the deficiency. This continuous stimulation can ultimately lead to an enlarged thyroid gland (AlRasheed, 2019; Razaghi, 2021) [20, 21].

Conclusion

This study demonstrated that selenium deficiency led to a general disturbance in thyroid function and serum thyroid-stimulating hormone (TSH) levels. There were statistically significant differences in the levels and concentrations of thyroxine (T4) and thyroxine (T3) in the study groups compared to the control group. It was found that a decrease in selenium concentrations to a minimum of 50% was the primary cause of thyroid enlargement (tumor), regardless of thyroid hormone levels.

Conflict of Interest

The authors declare that they have no financial or personal relationships with any party that might constitute a conflict of interest with respect to the research and information contained in this paper.

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