



Effect of Trace Elements on Thyroid Gland Review

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Abstract:

The research aimed to study the role of some trace elements such as (selenium, cadmium, zinc, copper, iron), vitamins (C and E), and the enzyme glutathione peroxidase in the spread of thyroid diseases in the regions of central and southern Iraq. During research and studies, it has been shown that environmental pollution plays an important role in the concentrations of these elements and enzymes. This study recommends the following recommendations: Estimation of other trace elements in the blood serum of people with thyroid diseases, such as (nickel, manganese, lead, etc.). The importance of eating foods containing elements such as (selenium and zinc) and vitamins that people with thyroid diseases need. Measuring the level of other antioxidant enzymes such as (SOD) to know the state of oxidation and other antioxidants except for the enzyme glutathione peroxidase. Treating liquid discharges coming out of factories, workshops and industrial units before putting them into the river. Conducting studies on the content of selenium, cadmium, zinc, copper and other trace elements in fish, aquatic life/herbs and plants.

Key words: *trace elements; thyroid gland, vitamins (C and E), glutathione peroxidase enzyme.*

Introduction

Some trace elements, such as selenium, cadmium, zinc, copper, and iron, play a major role in the spread of thyroid diseases in the regions of central and southern Iraq.

Most studies indicate that a decrease in selenium concentration leads to many pathological conditions, and one of these pathological conditions that arise when there is a deficiency in thyroid cells is thyroid disease. Selenium is the main component of the enzyme (Hepatic-type-1-iodothyronine deiodinase) that converts Thyroxin 4T to active T₃, which is responsible for the effectiveness of the thyroid gland [1], Which, when absent, leads to hypothyroidism, as T₄ does not convert to T₃. That is, when the concentration of selenium in the body decreases, it affects the formation of this active enzyme, since this enzyme is classified as a Seleno Enzyme, as selenium is one atom in the molecule of this enzyme, which is present in the liver, kidney, and thyroid [2]. That is, reducing the concentration of this enzyme (1-iodothyronine) leads to reducing its effectiveness, i.e., reducing the conversion of T₄ to T₃, and thus reducing the metabolism of thyroid hormones, which has a role. On physiological effects [3]. Studies have shown that people with hyperthyroidism suffer from a decrease in the concentration of selenium in their blood serum because this element is a major component of the enzyme glutathione peroxidase [GSH-PX], the main thyroid antioxidant enzyme in thyroid cells [3]. When there is a high level of free radicals, this will lead to the formation of reactive oxygen species, which leads to an increase in the action of the enzyme glutathione (GSH-PX), which in turn preserves or protects the body and thyroid cells from oxidative damage. In this case, the concentration will increase. (T₃) so that the enzyme [GSH-PX] can control free radicals [4]. Selenium is considered an element that forms a compatibility with non-enzymatic antioxidants such as vitamins C and E. That is, selenium deficiency affects the effectiveness and concentration of these vitamins [5], and the same relationship is with other trace elements such as zinc and iron. This is in order to protect the components of the cell and the cell wall from the dangers of damage by free radicals [6]. Selenium deficiency will lead to damage to thyroid cells and a disturbance in the formation of hormones, with increased production of the active thyroid hormone (T₃) to prevent cell damage and control harmful compounds. of thyroid cells [7]. People with hyperthyroidism also suffer from an increase in the concentration of the heavy element cadmium, which leads to poisoning of the cells in which it is present or accumulates. The element cadmium works in the cells of the body to secrete (antagonist) important trace elements, which leads to a decrease in the work and effectiveness of many enzymes and hormones, such as selenium, because it binds with selenium and secretes it through the blood circulation and excretes it from the body through urine, which reduces the effectiveness and activity of the most important enzymes, which is the enzyme Glutathione peroxidase, the antioxidant enzyme and the most important enzyme defending thyroid cells[8].

In addition, the presence of cadmium at a concentration higher than the permissible concentration in the body will lead to damage to thyroid cells, and the formation of hydrogen peroxide, which is considered the most effective type of oxygen (Ros), which drives and stimulates the production of thyroid hormone in the thyroid gland. This shows the relationship between cadmium poisoning and the increase in cadmium. Thyroid hormone (T₃) production [9].

Zinc is considered an important element in the functioning of more than (300) enzymes, and a low concentration of zinc in blood serum leads to a decrease in the concentration of the enzyme glutathione peroxidase (GSH-Px). The concentration of T₃ and T₄ in the blood serum decreases, and we see that the effectiveness of hepatic 1.5 deiodinase decreases by (67%), meaning that the conversion of T₄ to active T₃ will decrease. However, selenium deficiency, as some studies indicate, affects (47%) the effectiveness of this enzyme [10], in addition to the fact that zinc excretion through urine is little in hypothyroidism [11], The effect of

cadmium on the depletion of this effective element must be mentioned, which has a role no less than the role that selenium plays in the body, especially the thyroid gland [12].

Copper is the main component in the effectiveness of the catalytic enzyme (Cu/Zn- Super Oxide dismutase) and the enzyme glutathione peroxidase (GSH-PX), which resist active oxygen, in addition to that in the case of (hypothyroidism) the concentration of the enzyme decreases Glutathione peroxidase (GSH-Px) and a decrease in the concentration of (Cu) in the blood serum lead to a decrease in the effectiveness of the SOD enzyme, i.e. an increase in concerns about cell damage due to free radical formation. Therefore, a lack of (Cu) increases the fear of developing hypothyroidism. This is because the effectiveness of both (GSH-Px) and (Cu/Zu SOD) decreases with a deficiency of Cu and free radicals are scavenged by copper is done by binding it to albumin, which participates in oxidation reactions, and one of the radicals that copper scavenges is the (OH[·]) radical [13]. This means that when copper is deficient, this will lead to the failure of each of these antioxidant enzymes to function in their normal form. These radicals increase in the body, especially in thyroid cells [14].

An increase in the concentration of iron ions in the blood leads to a decrease in the activity of (GSH), (GSH-Px) and (SOD) in people with increased thyroid secretion (hyperthyroidism). This is due to the increase in the level of oxidation and radicals that cause damage to the cell wall and thus a defect in the blood. Balance of elements and imbalance in metabolism resulting from this disease. Research confirms that the level of stored iron (Ferritin) increases in people with hyperthyroidism [15].

1. Thyroid gland

The thyroid gland is one of the largest endocrine glands present in the body of a living organism [16], and it is called endocrine because it does not contain ducts and its secretions flow directly into the bloodstream [17]. Endocrine glands include the hypothalamus, the pituitary gland, the adrenal glands, the gonads (such as the testes and ovaries), the parathyroid glands, the pancreas, and the thyroid gland, which is located in the neck area directly under the larynx and on either side of the trachea [18;19]. The thyroid gland is adjacent to and connected to the thyroid cartilage (this is why the thyroid gland moves up and down during the swallowing process) [20]. In the fetus, the thyroid gland arises at the base of the tongue and then migrates down the neck during formation and development [21]. It consists of a right and left lobes that are strongly connected to the trachea by the isthmus and located below the cricoid cartilage [22;23;24], The right lobe is usually larger than the left lobe as shown in Figure No. (1). The height of each lobe ranges about (2 cm) , its width is (2.5-1.5) cm, and its thickness is (2-4) cm.

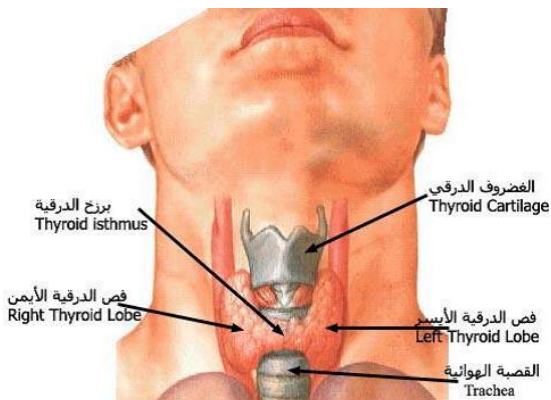


Image No. (1): Location of the thyroid gland

The weight of the gland ranges between (15-25) grams, and its front appearance shows a shape resembling a butterfly or the letter H [25]. It is attached by fibrous tissue in front of the pharynx and trachea and on either side of them [26].

1.1. Thyroid disorders

Thyroid diseases are common diseases, affecting 13% of adults, with a higher incidence in women and the elderly. Thyroid diseases arise from dysfunction in the thyroid gland itself or in the pituitary gland, which regulates the secretion of T3 and T4 hormones by means of thyroid stimulating hormone (TSH). The hypothalamus regulates the secretion of the pituitary gland by means of the thyroid-releasing hormone thyrotropin (TRH). Therefore, any change in hormone levels from the normal level reflects the patient's health condition [27].

1.1.1. Hypothyroidism

It is a medical condition that leads to a deficiency in the secretion of thyroid hormones and may result from:

1. A state of decreased secretion of thyroid hormones as a result of a decrease in the amount of iodine taken daily [28].
2. Autoimmune disease, where antibodies attack and destroy the gland instead of stimulating it to secrete hormones. As a result, a state of thyroiditis develops, which causes the destruction and destruction of the gland's follicles and the occurrence of fibrosis in them with the cessation of the secretion of thyroid hormones [29].

The lack of secretion of thyroid hormones leads to enlargement of the thyroid gland, which is called Goiter or Myxoedema [30], which is one of the clinical problems with a wide spread in all countries of the world, and the cause of the occurrence of thyroid enlargement is iodine deficiency, which prevents the production of hormones. Thyroid, which leads to increased production of TSH. This hormone, in turn, prompts the gland cells to secrete huge, unspecified amounts of colloidal fluid inside the follicle with disturbed growth of the gland, after which the size of the follicles clearly increases. Which leads to enlargement of the thyroid gland and its weight increases to (300-500) grams or more in humans [30].

A study also showed that suffering from hypothyroidism can lead to hyperoxidation, which causes damage to body tissues, so it was suggested to take antioxidants to protect body tissues from damage and reduce the level of oxidative stress [31].

A study indicated that suffering from hypothyroidism greatly affects public health, and one of the most important effects is the disturbances resulting from an imbalance in the antioxidant system, as suffering from hypothyroidism leads to a reduction in the level of antioxidants [32].

1.1.2. Hyperthyroidism

Hyperthyroidism occurs for several reasons, the most important of which are:

1. Autoimmune diseases that involve the organism's body forming antibodies against its normal cells. These antibodies can stimulate the thyroid gland, increasing its activity, or vice versa [33].
2. Thyroid hyperautonomus, as the thyroid gland can develop tumors in certain areas of it, and these areas have an autonomous function, as they are independent in their function and not subject to the control of thyroid-stimulating hormone, as in the case of follicular adenomas [34].
3. Substances similar to thyroid-stimulating hormone can act as thyroid-stimulating hormone and lead to increased gland activity. Likewise, exogenous medications and hormones that are taken in the form of drugs can cause hyperthyroidism, especially the large doses used to treat hypothyroidism [35]. It has been found that hyperthyroidism leads to suppressing free radicals, reducing trans-fat peroxides, and increasing the level of antioxidants [36].

2. Importance of trace elements

2.1. Selenium

Selenium belongs to group six in the periodic table and is located between sulfur and trillium, and has the same physical and chemical properties as them. Selenium was known as an essential element for some living organisms during the year 1957. It was confirmed that selenium is available in yeast and some grains and is a substance that prevents liver damage in mice and atrophy. Muscles in sheep and cattle. Researchers attributed the cause of these diseases to a lack of selenium [37]. Humans need selenium in very small concentrations (55 µg/day), despite the prevailing belief in the past that this element has toxic properties on the human and animal bodies, but after a period of time, knowledge was reached about the importance and benefit of this element for living organisms at specific concentrations [38].

2.1.1. Physiological importance of selenium

Selenium is one of the essential elements for humans, and it plays an important role in many physiological processes as a basic component of enzymes that act as antioxidants. It also works to maintain muscle cells and red blood cell cells, transfer energy, and isolate toxic elements in the body. It also plays an “important” role in the production of sperm cells. And the formation of antibodies [39], and also “selenium is an essential” element in the formation and effectiveness of the enzyme glutathione peroxidase, which works to remove different types of peroxides [40]. Selenium deficiency leads to inhibition of the activity of the enzyme (the hepatic enzyme that removes iodine from iodothyronine) hepatic-type-iodothyronine deiodinase (1hepatic-type-iodothyronine deiodinase), which is responsible for converting thyroxine (T4) to triiodothyronine (T3), the active enzyme in the functioning of the thyroid gland [38]. In a study on patients with hypothyroidism who suffer from the ineffectiveness of the enzyme glutathione, the effectiveness of this enzyme was improved by controlling the selenium concentration, which led to improving the effectiveness of the enzyme [41]. There are studies that indicate that the effectiveness and concentration of selenium are affected by the concentrations of toxic heavy elements. When these toxic elements are present in concentrations higher than the permissible limit in the body, this does not only affect selenium, but also negatively affects other important elements as well, in addition to other enzymes that depend on selenium. Its effectiveness on selenium and other trace elements such as zinc and iron. There are studies that indicate the existence of areas where thyroid diseases are widespread due to the fact that their environment suffers from a lack of selenium concentration in addition to other important elements [42].

2.1.2. Selenium and its relationship to other diseases

From the above, it becomes clear to us that selenium is one of the necessary and important elements for the human body. When its concentration is less than the normal limit, it causes clinical symptoms, while when its concentration is in quantities higher than the normal limit, it leads to an imbalance and negative effects on the organism’s body, accompanied by toxic symptoms and conditions. Such as the effect on the nervous system, difficulty speaking, disturbance in the functioning of the digestive tract, muscle spasm, vomiting and severe diarrhea, and there are many studies indicate that there is a close relationship between cancer and a deficiency of this element, considering that selenium is a strong defender against oxidizing substances such as prostate cancer, as it was estimated that the concentration of selenium in their blood serum was in very low percentages. Also, skin cancer in America is widespread in the regions whose soil suffers from a scarcity of selenium [43]. In the Lixian region in China, daily concentrations of selenium were given to people suffering from cancer for a period of five years. After this period, the death rate due to this disease decreased by (13%) among those who took it. This element as therapy [44] in another study, selenium was taken as a treatment for cancer by giving

selenium as a treatment to one group and leaving another group without treatment. After a period of treatment had passed, it was found that (35) cases of their health were not good in the group that did not take the treatment, while there were only (13) cases that appeared in the groups. Women who take selenium, this represents a decrease in the incidence of prostate cancer by an average of 63%, and this shows the extent of the effect of this element on cancer., As for those suffering from colon cancer and the end of the gastrointestinal tract, selenium was estimated and the activity of the GSH-PX enzyme was measured in their blood and plasma. Finally, they concluded that there is a direct relationship between the concentration of selenium and the effectiveness of the enzyme (GSH-PX). For those with the disease, when the concentration of the element decreases, their effectiveness of the enzyme decreases. As for those suffering from thyroid cancer, the concentration of more than 11 trace elements such as (selenium, zinc, lead, cobalt, etc.) was estimated in the thyroid tissue as well. They indicated that the selenium concentration was less than its natural concentration, as well as the other elements that play a role in the work of this gland [45].

Another disease related to selenium is Keshan Disease, which is widespread in large areas of China, whose soil suffers from a lack of selenium concentration. One of the symptoms of this disease is an enlarged heart size and poor heart function [46]. The effect of selenium on those suffering from this disease and its effect on other enzymes such as 1,5-deiodinase, GSH-PX, and tri-iodo thyronine were studied, and it was concluded that there is a direct relationship between selenium and iodine for the spread of this disease [46].

As for Kashin-Beak disease, which is widespread in northern China, northern Korea, and eastern Siberia, it affects children between 5 and 13 years of age, and its symptoms include degeneration of the articular cartilage. Some of the causes of this disease are due to selenium deficiency in blood serum [47]. Likewise, selenium deficiency it plays an important role in contracting AIDS, because selenium is part of the immune system in the human body and also works to strengthen the work of this system [48].

Selenium is an important and essential element in protecting the heart from diseases. When selenium deficiency leads to a loss of the effectiveness of the GSH-PX enzyme, this causes the breakdown of the heart cell membrane and also leads to the accumulation of free radicals and ultimately affects the heart muscle [49].

2.1.3. Selenium in foods and plants

The level of selenium in plants depends on the level of concentration of this element in the soil, that is, the levels of selenium in the soil determine its content in foods. Eggs produced from selenium-poor areas contain a selenium concentration of 0.05mg/gm, and in milk the selenium concentration contains 0.005mg/gm. gm, while milk in selenium-rich areas contains a selenium concentration of 0.07 mg/gm, and eggs contain a selenium concentration of 0.4-0.5 mg/gm. As for the liver and kidneys of sheep raised in relatively rich soil with selenium, it varies between 0.15-0.8 mg/gm [50]. To increase the concentration of selenium in agricultural lands, Sodium Selenate was used and distributed in the soil by spraying or irrigation [51]. Fish meat is considered one of the meats rich in selenium, and in areas that suffer from the problem of selenium deficiency, each individual in these areas is given up to 100 µg/day of selenium in food in the form of pills. The most recorded areas of selenium deficiency in food are China and Russia [52].

2.1.4. Selenium in milk

The concentration of selenium in mothers' blood serum is low compared to adults. It is known that selenium is responsible for the effectiveness of the enzyme (glutathione peroxidase) and to protect the child from fears of exposure to diseases caused by a deficiency of this element. Breast milk that contains this element reduces the child's infection with many diseases [53]. Therefore, mothers who already suffer from a selenium deficiency compensate their children by adding selenium to powdered milk. The amount of selenium taken daily by infants

is approximately (10 mg/day). The concentration of selenium in mother's milk is estimated at 7.62-11.91mg/L and in cow's milk is 11.26mg/L. The selenium concentration varies according to age. At birth, the concentration in the human body is 50mg/L, but at the age of 20 years it reaches approximately 100mg/L. In addition to what was mentioned, milk contains a large number of enzymes and elements [54].

2.2. Cadmium

2.2.1. Cadmium and its Biological effect

Cadmium is found in body tissues and fluids in small concentrations (0.5-1. 8µg.l-1) [55], but it is found in the kidneys and liver in higher concentrations linked to proteins that transport trace elements in the body. An excess of cadmium in livestock leads to stunting of growth. And damage to the liver and kidneys and infertility, and in mice it leads to small blood cell anemia [13] in addition to that increasing its concentration leads to chronic disease (Itai-Itai). That 6-10% of cadmium the digested cadmium is absorbed in the gastrointestinal tract, and cadmium is accumulated in the kidneys, bones, liver, female ovaries, follicles, and placenta [56]. The effect of increasing the concentration of cadmium on antioxidant enzymes leads to an increase in the production of active oxygen (ROS), such as superoxide ions, hydroxyl radicals, and hydrogen peroxide. The enzyme Metallothionein is known to have an "important and essential" role in protecting cells from Toxic heavy elements such as cadmium. The researcher Luce confirms that old cells in the human thyroid gland are more sensitive to the toxic effects of toxic heavy elements such as cadmium up to concentrations (100-175 µg) and its sensitivity up to 3.7 µg is more in the cells. The reason is that old cells have the ability to form more MT. In addition, the enzyme (GSH-PX) and the sulfhydryls, Dim ethyl sulfoxide and xamethylene bisacetamide, hypoxanthine N,N-dimethyl form amide, hemin, Ouabain, sodium butyrate, defend cells, The researcher (Arvidson) (Arvidson, 1996) indicates that the accumulation of cadmium in the olfactory causes the disease (anosmia), which reduces the state of smell in humans, and this condition is recorded in people who are exposed to cadmium as a result of pollution. During a study, it was reached Cadmium has a toxicity three times higher than arsenic and approximately 188 times higher than cobalt, copper, and indium [57].

2.2.2. Cadmium and its relationship to thyroid disease:

Studies confirm that when its concentration is higher than the permissible limit in the body, it will negatively affect the effectiveness of enzymes and cell function. In cases of hyperthyroidism, toxic elements, including cadmium, will play an important role in causing this condition. The disease, and negatively affects the effectiveness of the enzyme 5-iodinase 5-monode). The accumulation of cadmium in thyroid cells is greater than in other parts of the body, so humans are more susceptible to disease. The thyroid gland is protected from other diseases when exposed to high concentrations of this element [58].

Experiments conducted by Peter and his group demonstrated that in people with hypothyroidism, cadmium directly affects thyroid secretion and leads to this disease. Cadmium has a significant impact on the concentration of elements that make up enzymes, such as selenium, which is considered one of the elements that make up the enzyme (GSH-PX). Germany is considered one of the major industrialized countries with the highest rate of thyroid diseases. Researcher Muller and his group confirm that pollution The environmental impact of this element and its spread in the environment has become a source for the spread of diseases [59].

One of the important characteristics of cadmium is that it spreads quickly in the soil, and through the nutrient cycle, cadmium is effective in transmitting to plants and then to humans and animals. Exposed plants contain 10 to 20 times more cadmium than uncovered plants in Germany, for example. Cadmium was measured in South Korea, China and Japan in legumes (beans, peas) and its concentrations ranged (55.7 ng/g), in grains (9.2 ng/g)

and in corn grains (about 55.7 ng/g), but in carrots there is a high percentage of cadmium. And lead, where the percentage of lead is estimated at (0.019 mg/kg) and cadmium at (0.015 mg/kg) (1998) [60].

2.3. Zinc

2.3.1. Zinc and its biological importance

The importance of zinc has been known for more than a century, and the importance of this element and its necessity for animal growth has been known since 1934. Zinc deficiency in animals such as mice leads to growth failure, hair loss, reduced enzyme activity, and digestive disorder. Studies have shown that zinc deficiency in humans leads to stunted growth (Dewaof), and the production and action of insulin is also linked to zinc levels. Apparently, zinc is necessary for Complete control over insulin levels and thus glucose levels through a study conducted on rats [61].

Zinc has a direct role in the formation of thyroid hormones and some enzymes, and in the absence of this element, this will lead to a malfunction of this hormone and other enzymes. Studies indicate that when the concentration of zinc increases, this increase will lead to a malfunction of Antioxidant defense systems in thyroid cells and leads to a change in the membrane property of red blood cells [62]. Zinc is an essential element in the formation of the hormone (testosterone), and this hormone is specific to women, which is why women need zinc more than men, especially in areas polluted with heavy metals. Zinc is an effective and important part in the action of the enzyme (superoxide demutase), which acts as an enzyme that combats free radicals and converts them into hydrogen peroxide and oxygen, which protects sensitive membranes from oxidative damage. Zinc is an important element in nutrition. Foods rich in zinc include wheat bran, while foods with moderate concentrations include flour, bread, leafy vegetables, meat, fish, eggs, and grains [63].

2.4. Iron

2.4.1. Iron and its biological effect

The toxic effects of iron salts in human food have been known since the seventeenth century. Iron is known to be an indispensable element for the normal function of hemoglobin in red cells and myoglobin in the heart muscle. Other valuable and vital functions of iron have been proven in enzymes such as catalase and peroxidase. Iron in the body is produced as a result of a lack of iron intake in food, poor absorption of iron, or increased loss of iron from the body. When the deficiency increases, the individual suffers from anemia, and the face appears pale with headaches and rapid fatigue [64]. Iron affects the The effectiveness of both enzymes, glutathione peroxidase, and superoxide dismutase. There are studies that indicate that iron helps reduce the size of Goiters. Low iron concentration (anemia) is the closest condition to exposure to hypothyroidism, and iron plays an important role not only in transporting oxygen to cells, but also as a cofactor with some enzymes that is involved in the processes of energy metabolism and thermoregulation. There is Signs that iron deficiency (anemia) causes physiological changes in the body [65], and there is a relationship between people with iron deficiency (anemia) and a decrease in the effectiveness of their hormones (T3, T4), and it can be improved the effectiveness of these hormones when taking thyroid medications (Thyroxin, pointing to the role of iron in hyperthyroidism and its effect on the concentration and effectiveness of (T4, T3), in addition to the effect of iron on the level of concentration (GSH-PX enzyme) (GSH). However, when the iron concentration increases in thyroid diseases, it will lead to an increase in iron in these cells, and this causes poisoning of these cells [65]. Foods rich in iron are meat, liver, kidneys, heart, egg yolk, cocoa, minerals, fish, poultry, and flour. Foods poor in iron are milk and its products, white sugar, white flour, rice, and fresh fruits [66].

2.5. Copper

2.5.1. Copper and its biological effect

Copper is distributed in various tissues of the body, and the human body contains about 100 kg/ μg of the body, concentrated in the liver, brain, kidneys, heart, and hair. Foods can affect the concentration of copper in the blood, as high or low amounts of copper intake give similar levels in the blood [67]. Copper is included in the synthesis of many enzymes as a cofactor, especially in antioxidant enzymes, including (Super Oxide Dismutase), (SOD) and the enzyme tyrosine. Copper has a major role in the processes of growth and reproduction and protecting thyroid tissue from free radicals, Studies indicate that a high level of copper in the body leads to the emergence of pathological conditions such as Wilson disease [68]. In a study on rats, it was noted that copper is necessary for iodine metabolism and has an effect on the synthesis of thyroid hormone. Although Copper has a major role in the functioning of the thyroid gland [69]. Kralik and his group [70] indicate that the concentration of thyroid hormone in the serum and the effectiveness of 5-monodeiodinase and (T3) are affected by a decrease in the proportion of this element [71] and causes hypothyroidism [72]. A deficiency in copper also affects the functioning of the immune system and reduces its activity, and an increase in it also leads to a defect in the activity of this system [73].

Kaji., *et al* indicated in a study that the presence of copper in cells can play an important “defensive” role in protecting the body’s cells from high concentrations of heavy elements such as cadmium from the dangers of poisoning [74], when the concentration of selenium in the body decreases, the human body leads to the accumulation of copper in the eye, and this is a pathological condition such as Wilson’s disease, schizophrenia, and the formation of a green ring in the cornea [75]. As for those suffering from the disease (Bronchial asthma) A decrease in the level of copper in their blood serum was observed when Varal and his group studied the effect of this element on mice infected with this disease. In addition to what we mentioned, copper is involved as an auxiliary factor in building red blood cells, and Copper deficiency leads to anemia and decreased lifespan of red blood cells. Milk and its products, honey, and white sugar are poor sources of copper, and non-leafy vegetables, fresh fruits, and purified grains contain about (2 $\mu\text{g}/\text{gm}$) of copper, while white flour contains (1.7 $\mu\text{g}/\text{gm}$) of copper [76].

conclusion

The results showed that the oven is the only source of thyroid issues. The environment (soil, water), as well as nutrition, mostly determine the concentration and kind of elements found in the human body. Pregnant women and smokers are more susceptible to thyroid disease.

References:

1. Arthur, J. R., Nicol, F., Grant, E., & Beckett, G. J. (1991). The effects of selenium deficiency on hepatic type-I iodothyronine deiodinase and protein disulphide-isomerase assessed by activity measurements and affinity labelling. *The Biochemical journal*, 274 (Pt 1)(Pt 1), 297–300. <https://doi.org/10.1042/bj2740297>
2. Arthur, J. R., Nicol, F., Hutchinson, A. R., & Beckett, G. J. (1990). The effects of selenium depletion and repletion on the metabolism of thyroid hormones in the rat. *Journal of inorganic biochemistry*, 39(2), 101–108. [https://doi.org/10.1016/0162-0134\(90\)80018-s](https://doi.org/10.1016/0162-0134(90)80018-s)
3. Schoenmakers, C. H., Pigmans, I. G., Hawkins, H. C., Freedman, R. B., & Visser, T. J. (1989). Rat liver type I iodothyronine deiodinase is not identical to protein disulfide isomerase. *Biochemical and biophysical research communications*, 162(2), 857–868. [https://doi.org/10.1016/0006-291x\(89\)92389-9](https://doi.org/10.1016/0006-291x(89)92389-9)
4. Arthur, J. R., Nicol, F., & Beckett, G. J. (1990). Hepatic iodothyronine 5'-deiodinase. The role of selenium. *The Biochemical journal*, 272(2), 537–540. <https://doi.org/10.1042/bj2720537>

5. Decherf, S., Seugnet, I., Kouidhi, S., Lopez-Juarez, A., Clerget-Froidevaux, M. S., & Demeneix, B. A. (2010). Thyroid hormone exerts negative feedback on hypothalamic type 4 melanocortin receptor expression. *Proceedings of the National Academy of Sciences of the United States of America*, 107(9), 4471–4476. <https://doi.org/10.1073/pnas.0905190107>
6. Kim, W. G., & Cheng, S. Y. (2013). Thyroid hormone receptors and cancer. *Biochimica et biophysica acta*, 1830(7), 3928–3936. <https://doi.org/10.1016/j.bbagen.2012.04.002>
7. Song, Y., Yao, X., & Ying, H. (2011). Thyroid hormone action in metabolic regulation. *Protein & cell*, 2(5), 358–368. <https://doi.org/10.1007/s13238-011-1046-x>
8. Astapova, I., & Hollenberg, A. N. (2013). The in vivo role of nuclear receptor corepressors in thyroid hormone action. *Biochimica et biophysica acta*, 1830(7), 3876–3881. <https://doi.org/10.1016/j.bbagen.2012.07.001>
9. Harrus, D., Déméné, H., Vasquez, E., Boulahtouf, A., Germain, P., Figueira, A. C., Privalsky, M. L., Bourguet, W., & le Maire, A. (2018). Pathological Interactions Between Mutant Thyroid Hormone Receptors and Corepressors and Their Modulation by a Thyroid Hormone Analogue with Therapeutic Potential. *Thyroid : official journal of the American Thyroid Association*, 28(12), 1708–1722. <https://doi.org/10.1089/thy.2017.0551>
10. Kralik, A., Eder, K., & Kirchgessner, M. (1996). Influence of zinc and selenium deficiency on parameters relating to thyroid hormone metabolism. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme*, 28(5), 223–226. <https://doi.org/10.1055/s-2007-979169>
11. Macvanin, M. T., Gluvcic, Z., Zafirovic, S., Gao, X., Essack, M., & Isenovic, E. R. (2023). The protective role of nutritional antioxidants against oxidative stress in thyroid disorders. *Frontiers in endocrinology*, 13, 1092837. <https://doi.org/10.3389/fendo.2022.1092837>
12. Nakamura, H., Noh, J. Y., Itoh, K., Fukata, S., Miyauchi, A., & Hamada, N. (2007). Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. *The Journal of clinical endocrinology and metabolism*, 92(6), 2157–2162. <https://doi.org/10.1210/jc.2006-2135>
13. Jenkinson, S. G., Lawrence, R. A., Burk, R. F., & Williams, D. M. (1982). Effects of copper deficiency on the activity of the selenoenzyme glutathione peroxidase and on excretion and tissue retention of ⁷⁵SeO₃(2-). *The Journal of nutrition*, 112(1), 197–204. <https://doi.org/10.1093/jn/112.1.197>
14. Hawk, S. N., Uriu-Hare, J. Y., Daston, G. P., Jankowski, M. A., Kwik-Urbe, C., Rucker, R. B., & Keen, C. L. (1998). Rat embryos cultured under copper-deficient conditions develop abnormally and are characterized by an impaired oxidant defense system. *Teratology*, 57(6), 310–320. [https://doi.org/10.1002/\(SICI\)1096-9926\(199806\)57:6<310::AID-TERA4>3.0.CO;2-#](https://doi.org/10.1002/(SICI)1096-9926(199806)57:6<310::AID-TERA4>3.0.CO;2-#)
15. Seymen, H. O., Seven, A., Civelek, S., Yiğit, G., Hatemi, H., & Burçak, G. (1999). Evaluation of antioxidant status in liver tissues: effect of iron supplementation in experimental hyperthyroidism. *Journal of basic and clinical physiology and pharmacology*, 10(4), 315–325. <https://doi.org/10.1515/jbcpp.1999.10.4.315>
16. Pan, Z., Zhu, T., Zhu, J., & Zhang, N. (2022). Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. *Iranian journal of public health*, 51(10), 2149–2158. <https://doi.org/10.18502/ijph.v51i10.10974>
17. Zhang, S., Qiu, X., Wang, T., Chen, L., Li, J., Diao, J., Li, Y., Qin, J., Chen, L., & Jiang, Y. (2022). Hypertensive Disorders in Pregnancy Are Associated With Congenital Heart Defects in Offspring: A

- Systematic Review and Meta-Analysis. *Frontiers in cardiovascular medicine*, 9, 842878. <https://doi.org/10.3389/fcvm.2022.842878>
18. Miller, F. R., & Netterville, J. L. (1999). Surgical management of thyroid and parathyroid disorders. *The Medical clinics of North America*, 83(1), 247–xi. [https://doi.org/10.1016/s0025-7125\(05\)70100-0](https://doi.org/10.1016/s0025-7125(05)70100-0)
 19. Wang, T., Chen, L., Yang, T., Huang, P., Wang, L., Zhao, L., Zhang, S., Ye, Z., Chen, L., Zheng, Z., & Qin, J. (2019). Congenital Heart Disease and Risk of Cardiovascular Disease: A Meta-Analysis of Cohort Studies. *Journal of the American Heart Association*, 8(10), e012030. <https://doi.org/10.1161/JAHA.119.012030>
 20. Hahka, T. M., Slotkowski, R. A., Akbar, A., VanOrmer, M. C., Sembajwe, L. F., Ssekandi, A. M., Namaganda, A., Muwonge, H., Kasolo, J. N., Nakimuli, A., Mwesigwa, N., Ishimwe, J. A., Kalyesubula, R., Kirabo, A., Anderson Berry, A. L., & Patel, K. P. (2024). Hypertension Related Co-Morbidities and Complications in Women of Sub-Saharan Africa: A Brief Review. *Circulation research*, 134(4), 459–473. <https://doi.org/10.1161/CIRCRESAHA.123.324077>
 21. Cromb, D., Slator, P., Hall, M., Price, A., Alexander, D., Counsell, S., & Hutter, J. (2024). Advanced magnetic resonance imaging detects altered placental development in pregnancies affected by congenital heart disease. *Research square*, rs.3.rs-3873412. <https://doi.org/10.21203/rs.3.rs-3873412/v1>
 22. Liu, Y., Chen, S., Zühlke, L., Black, G. C., Choy, M. K., Li, N., & Keavney, B. D. (2019). Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *International journal of epidemiology*, 48(2), 455–463. <https://doi.org/10.1093/ije/dyz009>
 23. Zaidi, S., & Brueckner, M. (2017). Genetics and Genomics of Congenital Heart Disease. *Circulation research*, 120(6), 923–940. <https://doi.org/10.1161/CIRCRESAHA.116.309140>
 24. Laurberg, P., Andersen, S., & Karmisholt, J. (2005). Cold adaptation and thyroid hormone metabolism. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme*, 37(9), 545–549. <https://doi.org/10.1055/s-2005-870420>
 25. Paier, B., Pavia, M. A., Jr, Hansi, C., Noli, M. I., Haggmüller, K., & Zaninovich, A. A. (1997). Cadmium inhibits the in vitro conversion of thyroxine to triiodothyronine in rat brown adipose tissue. *Bulletin of environmental contamination and toxicology*, 59(1), 164–170. <https://doi.org/10.1007/s001289900460>
 26. Lezama-García, K., Mota-Rojas, D., Martínez-Burnes, J., Villanueva-García, D., Domínguez-Oliva, A., Gómez-Prado, J., Mora-Medina, P., Casas-Alvarado, A., Olmos-Hernández, A., Soto, P., & Muns, R. (2022). Strategies for Hypothermia Compensation in Altricial and Precocial Newborn Mammals and Their Monitoring by Infrared Thermography. *Veterinary sciences*, 9(5), 246. <https://doi.org/10.3390/vetsci9050246>
 27. Shimasaki, T., Masaki, T., Mitsutomi, K., Ueno, D., Gotoh, K., Chiba, S., Kakuma, T., & Yoshimatsu, H. (2013). The dipeptidyl peptidase-4 inhibitor des-fluoro-sitagliptin regulates brown adipose tissue uncoupling protein levels in mice with diet-induced obesity. *PloS one*, 8(5), e63626. <https://doi.org/10.1371/journal.pone.0063626>
 28. Tan, C. L., & Knight, Z. A. (2018). Regulation of Body Temperature by the Nervous System. *Neuron*, 98(1), 31–48. <https://doi.org/10.1016/j.neuron.2018.02.022>
 29. Mizukami, Y., Michigishi, T., Kawato, M., Sato, T., Nonomura, A., Hashimoto, T., & Matsubara, F. (1992). Chronic thyroiditis: thyroid function and histologic correlations in 601 cases. *Human pathology*, 23(9), 980–988. [https://doi.org/10.1016/0046-8177\(92\)90258-5](https://doi.org/10.1016/0046-8177(92)90258-5)

30. Kovacevic, B., Vucevic, D., Cerovic, S., & Eloy, C. (2022). Peripheral Versus Intraparenchymal Papillary Thyroid Microcarcinoma: Different Morphologies and PD-L1 Expression. *Head and neck pathology*, 16(1), 200–212. <https://doi.org/10.1007/s12105-021-01337-1>
31. Zhi, J., Zhao, J., Gao, M., Pan, Y., Wu, J., Li, Y., Li, D., Yu, Y., & Zheng, X. (2018). Impact of major different variants of papillary thyroid microcarcinoma on the clinicopathological characteristics: the study of 1041 cases. *International journal of clinical oncology*, 23(1), 59–65. <https://doi.org/10.1007/s10147-017-1170-6>
32. Sparano, C., Rotondi, M., Verdiani, V., Brunori, P., Castiglione, F., Bartoli, C., Perigli, G., Badii, B., Vezzosi, V., Simontacchi, G., Livi, L., Antonuzzo, L., Maggi, M., & Petrone, L. (2022). Classic and Follicular Variant of Papillary Thyroid Microcarcinoma: 2 Different Phenotypes Beyond Tumor Size. *Journal of the Endocrine Society*, 6(12), bvac157. <https://doi.org/10.1210/jendso/bvac157>
33. Zhang, Z. W., Yang, Y., Wu, H., & Zhang, T. (2023). Advances in the two-dimensional layer materials for cancer diagnosis and treatment: unique advantages beyond the microsphere. *Frontiers in bioengineering and biotechnology*, 11, 1278871. <https://doi.org/10.3389/fbioe.2023.1278871>
34. Glinoe D. (1998). Thyroid hyperfunction during pregnancy. *Thyroid : official journal of the American Thyroid Association*, 8(9), 859–864. <https://doi.org/10.1089/thy.1998.8.859>
35. Stanbury, J. B., Ermans, A. E., Bourdoux, P., Todd, C., Oken, E., Tonglet, R., Vidor, G., Braverman, L. E., & Medeiros-Neto, G. (1998). Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid : official journal of the American Thyroid Association*, 8(1), 83–100. <https://doi.org/10.1089/thy.1998.8.83>
36. Hu, Y., Feng, W., Chen, H., Shi, H., Jiang, L., Zheng, X., Liu, X., Zhang, W., Ge, Y., Liu, Y., & Cui, D. (2021). Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. *Clinical and translational science*, 14(4), 1390–1402. <https://doi.org/10.1111/cts.12993>
37. Zhou, Q., Xue, S., Zhang, L., & Chen, G. (2022). Trace elements and the thyroid. *Frontiers in endocrinology*, 13, 904889. <https://doi.org/10.3389/fendo.2022.904889>
38. Clark, L. C., Dalkin, B., Krongrad, A., Combs, G. F., Jr, Turnbull, B. W., Slate, E. H., Witherington, R., Herlong, J. H., Janosko, E., Carpenter, D., Borosso, C., Falk, S., & Rounder, J. (1998). Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *British journal of urology*, 81(5), 730–734. <https://doi.org/10.1046/j.1464-410x.1998.00630.x>
39. Sheehan, T. M., & Halls, D. J. (1999). Measurement of selenium in clinical specimens. *Annals of clinical biochemistry*, 36 (Pt 3), 301–315. <https://doi.org/10.1177/000456329903600302>
40. Barysheva E. S. (2018). Experimental Simulation of the Effects of Essential and Toxic Trace Elements on Thyroid Function. *Bulletin of experimental biology and medicine*, 164(4), 439–441. <https://doi.org/10.1007/s10517-018-4007-z>
41. Wu, H. Y., Xia, Y. M., Ha, P. C., & Chen, X. S. (1997). Changes in myocardial thyroid hormone metabolism and alpha-glycerophosphate dehydrogenase activity in rats deficient in iodine and selenium. *The British journal of nutrition*, 78(4), 671–676. <https://doi.org/10.1079/bjn19970182>
42. Wróblewski, M., Wróblewska, J., Nuskiewicz, J., Pawłowska, M., Wesołowski, R., & Woźniak, A. (2023). The Role of Selected Trace Elements in Oxidoreductive Homeostasis in Patients with Thyroid Diseases. *International journal of molecular sciences*, 24(5), 4840. <https://doi.org/10.3390/ijms24054840>
43. Gheorghiu, M. L., & Badiu, C. (2020). Selenium involvement in mitochondrial function in thyroid disorders. *Hormones (Athens, Greece)*, 19(1), 25–30. <https://doi.org/10.1007/s42000-020-00173-2>

44. Blot W. J. (1997). Vitamin/mineral supplementation and cancer risk: international chemoprevention trials. *Proceedings of the Society for Experimental Biology and Medicine*. Society for Experimental Biology and Medicine (New York, N.Y.), 216(2), 291–296. <https://doi.org/10.3181/00379727-216-44180>
45. Zaichick VYe, Tsyb, A. F., & Vtyurin, B. M. (1995). Trace elements and thyroid cancer. *The Analyst*, 120(3), 817–821. <https://doi.org/10.1039/an9952000817>
46. Moreno-Reyes, R., Suetens, C., Mathieu, F., Begaux, F., Zhu, D., Rivera, M. T., Boelaert, M., Nève, J., Perlmutter, N., & Vanderpas, J. (1998). Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. *The New England journal of medicine*, 339(16), 1112–1120. <https://doi.org/10.1056/NEJM199810153391604>
47. Umemura T. (2000). Experimental reproduction of itai-itai disease, a chronic cadmium poisoning of humans, in rats and monkeys. *The Japanese journal of veterinary research*, 48(1), 15–28.
48. Uriu, K., Morimoto, I., Kai, K., Okazaki, Y., Okada, Y., Qie, Y. L., Okimoto, N., Kaizu, K., Nakamura, T., & Eto, S. (2000). Uncoupling between bone formation and resorption in ovariectomized rats with chronic cadmium exposure. *Toxicology and applied pharmacology*, 164(3), 264–272. <https://doi.org/10.1006/taap.2000.8908>
49. Stojisavljević, A., Rovčanin, B., Jagodić, J., Krstić, Đ., Paunović, I., Gavrović-Jankulović, M., & Manojlović, D. (2021). Alteration of Trace Elements in Multinodular Goiter, Thyroid Adenoma, and Thyroid Cancer. *Biological trace element research*, 199(11), 4055–4065. <https://doi.org/10.1007/s12011-020-02542-9>
50. Kim, M. J., Kim, S. C., Chung, S., Kim, S., Yoon, J. W., & Park, Y. J. (2020). Exploring the role of copper and selenium in the maintenance of normal thyroid function among healthy Koreans. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)*, 61, 126558. Advance online publication. <https://doi.org/10.1016/j.jtemb.2020.126558>
51. Li, W., Kagan, H. M., & Chou, I. N. (1994). Alterations in cytoskeletal organization and homeostasis of cellular thiols in cadmium-resistant cells. *Toxicology and applied pharmacology*, 126(1), 114–123. <https://doi.org/10.1006/taap.1994.1097>
52. Shopsis C. (1994). Antagonism of cadmium cytotoxicity by differentiation inducers. *Cell biology and toxicology*, 10(3), 191–205. <https://doi.org/10.1007/BF00757562>
53. Gilani, S. H., & Alibhai, Y. (1990). Teratogenicity of metals to chick embryos. *Journal of toxicology and environmental health*, 30(1), 23–31. <https://doi.org/10.1080/15287399009531407>
54. Ghosh, N., & Bhattacharya, S. (1992). Thyrotoxicity of the chlorides of cadmium and mercury in rabbit. *Biomedical and environmental sciences : BES*, 5(3), 236–240.
55. Gupta, P., & Kar, A. (1999). Cadmium induced thyroid dysfunction in chicken: hepatic type I iodothyronine 5'-monodeiodinase activity and role of lipid peroxidation. *Comparative biochemistry and physiology. Part C, Pharmacology, toxicology & endocrinology*, 123(1), 39–44. [https://doi.org/10.1016/s0742-8413\(99\)00007-9](https://doi.org/10.1016/s0742-8413(99)00007-9)
56. Falnoga, I., Tusek-Znidaric, M., Horvat, M., & Stegnar, P. (2000). Mercury, selenium, and cadmium in human autopsy samples from Idrija residents and mercury mine workers. *Environmental research*, 84(3), 211–218. <https://doi.org/10.1006/enrs.2000.4116>
57. Alyahya, A., AlNaim, A., AlBahr, A. W., Almansour, F., & Elshebiny, A. (2021). Knowledge of Thyroid Disease Manifestations and Risk Factors Among Residents of the Eastern Province, Saudi Arabia. *Cureus*, 13(1), e13035. <https://doi.org/10.7759/cureus.13035>

58. Rydzewski, B., Sułkowski, W., & Miarzyńska, M. (1998). Olfactory disorders induced by cadmium exposure: a clinical study. *International journal of occupational medicine and environmental health*, 11(3), 235–245.
59. Perrone, L., Salerno, M., Gialanella, G., Feng, S. L., Moro, R., Di Lascio, R., Boccia, E., & Di Toro, R. (1999). Long-term zinc and iron supplementation in children of short stature: effect of growth and on trace element content in tissues. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)*, 13(1-2), 51–56. [https://doi.org/10.1016/S0946-672X\(99\)80023-6](https://doi.org/10.1016/S0946-672X(99)80023-6)
60. Shimada, H., Bare, R. M., Hochadel, J. F., & Waalkes, M. P. (1997). Testosterone pretreatment mitigates cadmium toxicity in male C57 mice but not in C3H mice. *Toxicology*, 116(1-3), 183–191. [https://doi.org/10.1016/s0300-483x\(96\)03544-5](https://doi.org/10.1016/s0300-483x(96)03544-5)
61. Zimmermann, M., Adou, P., Torresani, T., Zeder, C., & Hurrell, R. (2000). Iron supplementation in goitrous, iron-deficient children improves their response to oral iodized oil. *European journal of endocrinology*, 142(3), 217–223. <https://doi.org/10.1530/eje.0.1420217>
62. Rosenzweig, P. H., & Volpe, S. L. (1999). Iron, thermoregulation, and metabolic rate. *Critical reviews in food science and nutrition*, 39(2), 131–148. <https://doi.org/10.1080/10408399908500491>
63. Beard, J. L., Brigham, D. E., Kelley, S. K., & Green, M. H. (1998). Plasma thyroid hormone kinetics are altered in iron-deficient rats. *The Journal of nutrition*, 128(8), 1401–1408. <https://doi.org/10.1093/jn/128.8.1401>
64. Seymen, O., Seven, A., Candan, G., Yigit, G., Hatemi, S., & Hatemi, H. (1997). The effect of iron supplementation on GSH levels, GSH-Px, and SOD activities of erythrocytes in L-thyroxine administration. *Acta medica Okayama*, 51(3), 129–133. <https://doi.org/10.18926/AMO/30797>
65. Boisier, X., Schön, M., Sepúlveda, A., Basualdo, A., Cornejo, P., Bosco, C., Carrión, Y., Galleano, M., Tapia, G., Puntarulo, S., Fernández, V., & Videla, L. A. (1999). Derangement of Kupffer cell functioning and hepatotoxicity in hyperthyroid rats subjected to acute iron overload. *Redox report : communications in free radical research*, 4(5), 243–250. <https://doi.org/10.1179/135100099101534963>
66. Boisier, X., Schön, M., Sepúlveda, A., Basualdo, A., Cornejo, P., Bosco, C., Carrión, Y., Galleano, M., Tapia, G., Puntarulo, S., Fernández, V., & Videla, L. A. (1999). Derangement of Kupffer cell functioning and hepatotoxicity in hyperthyroid rats subjected to acute iron overload. *Redox report : communications in free radical research*, 4(5), 243–250. <https://doi.org/10.1179/135100099101534963>
67. Sokol, R. J., Twedt, D., McKim, J. M., Jr, Devereaux, M. W., Karrer, F. M., Kam, I., von Steigman, G., Narkewicz, M. R., Bacon, B. R., & Britton, R. S. (1994). Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. *Gastroenterology*, 107(6), 1788–1798. [https://doi.org/10.1016/0016-5085\(94\)90822-2](https://doi.org/10.1016/0016-5085(94)90822-2)
68. Esipenko, B. E., & Marsakova, N. V. (1990). Vliianie medi na obmen joda, uglevodov i belkov v organizme kys [The effect of copper on the metabolism of iodine, carbohydrates and proteins in rats]. *Fiziologicheskii zhurnal*, 36(2), 35–43.
69. Oliver J. W. (1975). Interrelationships between athyroidic and copper-deficient states in rats. *American journal of veterinary research*, 36(11), 1649–1653.
70. Walther, L. E., Winnefeld, K., & Sölch, O. (2000). Determination of iron, copper, zinc, magnesium and selenium in plasma and erythrocytes in neurosurgical patients. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)*, 14(2), 92–95. [https://doi.org/10.1016/S0946-672X\(00\)80037-1](https://doi.org/10.1016/S0946-672X(00)80037-1)

71. Kaji, T., Fujiwara, Y., Koyanagi, E., Yamamoto, C., Mishima, A., Sakamoto, M., & Kozuka, H. (1992). Protective effect of copper against cadmium cytotoxicity on cultured vascular endothelial cells. *Toxicology letters*, 63(1), 13–20. [https://doi.org/10.1016/0378-4274\(92\)90103-q](https://doi.org/10.1016/0378-4274(92)90103-q)
72. Jamall, I. S., & Roque, H. (1989). Cadmium-induced alterations in ocular trace elements. Influence of dietary selenium and copper. *Biological trace element research*, 23, 55–63. <https://doi.org/10.1007/BF02917177>
73. Vural, H., Uzun, K., Uz, E., Koçyigit, A., Cigli, A., & Akyol, O. (2000). Concentrations of copper, zinc and various elements in serum of patients with bronchial asthma. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)*, 14(2), 88–91. [https://doi.org/10.1016/S0946-672X\(00\)80036-X](https://doi.org/10.1016/S0946-672X(00)80036-X)
74. Arvidson B. (1986). Autoradiographic localization of cadmium in the rat brain. *Neurotoxicology*, 7(3), 89–96.
75. Ghent, W. R., Eskin, B. A., Low, D. A., & Hill, L. P. (1993). Iodine replacement in fibrocystic disease of the breast. *Canadian journal of surgery. Journal canadien de chirurgie*, 36(5), 453–460.
76. Kammersgaard, T. S., Pedersen, L. J., & Jørgensen, E. (2011). Hypothermia in neonatal piglets: interactions and causes of individual differences. *Journal of animal science*, 89(7), 2073–2085. <https://doi.org/10.2527/jas.2010-3022>