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Effect of Minerals (CD, PB, CR, ZN, And CU) On the Efficiency of Thyroid Gland Function

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Annotation: Background: The Thyroid gland is very crucial to overall health, and its derailment may trigger a host of health complications. These disruptions can be caused internally or by an external stimulant that stimulates a pathway to the end result of either destroying the gland or to increase the activity of the gland. Prolonged stress on the thyroid caused by chronic use of heavy metals may cause damage to the gland by developing antibodies against the thyroid; this process is central in the development of autoimmune thyroid disease.

The Purpose of the Investigation: To research the role and influence of some heavy metals, i.e., cadmium, lead, chromium, zinc, and copper, on the status of thyroid glands, and to determine whether the routine analysis of these metals is reasonable in case of thyroid dysfunction.

Subjects, Materials, and Methods: 30 healthy controls, 30 patients with hyperthyroidism, and 30 patients with hypothyroidism were enlisted as subjects. All subjects were between the ages of 25 and 65 years of age, and the sample had 24 females and eight males in each group. This was done through clinical and laboratory tests. Laboratory tests included the determination of S.TSH, Total S.T3, and Total S.T4 (at the visits of patients to the Specialized Center of Endocrinology and Diabetes and Al-Sadr General Hospital), and the first values were taken based on the archival medical histories. These tests used enzyme-linked fluorescent immunoassay (ELFA); S.TPO concentration was measured through enzyme-linked immunosorbent assay (ELISA). Flame Atomic Absorption Spectrophotometry (FAAS) and Graphite Furnace Atomic Absorption Spectrophotometry (GFAAS) were used to determine the content of metal (lead, cadmium, chromium, copper, and zinc) levels in serum. The research was performed between the months of November 2020 and January 2021.

Findings: It was found that both hypo- and hyperthyroid patients had a high level of lead, cadmium, and copper ($p < 0.05$) and significantly lower levels of chromium and zinc ($p < 0.05$) in comparison with healthy controls. The results showed that in hyperthyroid patients, TSH was negatively correlated with lead ($r=-0.41$, $p=0.05$) and cadmium ($r=-0.56$, $p=0.05$), and no correlation was observed between TSH and lead, cadmium, chromium, copper, and zinc in hypothyroidism. The results in both hypo- and hyperthyroid groups showed no significant relationship ($p < 0.05$) between thyroid hormones (T3 and T4) or TPO-Ab and the above heavy metals.

Conclusion: We could suggest that the dysfunction of the thyroid gland, be it hypothyroidism or hyperthyroidism, is connected to the changes in the levels of heavy metals (Pb, Cd, Cr, Cu, Zn); some of them are increased (Pb, Cd, Cu), and some of them are reduced (Cr, Zn). These results can be supported by comparative studies against healthy subjects. Nevertheless, the research cannot conclusively identify a causal relationship or a particular mineral change to either thyroid disease, other than probably Cd. Therefore, it is necessary to investigate more specific research and conduct bigger studies in order to consider routine heavy metal evaluation in patients with thyroid dysfunction.

Keywords: Thyroid Gland, Gland, Damage, Elisa, Faas, Gfaas, Hyperthyroid, Cadmium, Chromium, Copper.

Introduction

The thyroid gland is one of the central endocrine glands, and it has the main role of secretion of hormones which regulate metabolism and promote growth and development in the entire human body. This gland controls a number of physiological processes through the constant release of a controlled amount of thyroid hormones into the blood. An organism increases the production of hormones as needed when energy requirements are beyond basal consumption levels, as in the case of rapid growth, cold temperatures, or pregnancy. Being the largest of the glands located in the cervix, it is positioned in front of the integumentary and muscular layers. It is bilobed, taking the form of a butterfly, and the two lobes lie along the trachea. Morphologically, the gland usually increases in size in females, especially during gestation [1,2,3,4,5].

The most common hormone the thyroid secreted is thyroxine (T4), which diffuses into the bloodstream then it is then carried to the peripheral tissues, especially in the liver and kidneys, where it is converted into a biologically active triiodothyronine (T3). This change is necessary to the functionality of the hormone because T3 exhibits an approximate fifteen-fold greater affinity of thyroid hormone receptors in comparison to its precursor. As a result, T4 is a prohormone, which provides a constant amount of T3 by conversion in the periphery; this process is essential in the regulation of cardiovascular, gastrointestinal, metabolic, neurologic, skeletal, and muscular homeostasis. Maintaining a well-balanced level of T4 and T3, in its turn, is an essential aspect of good health [6,7,8,9]. The tiny fraction that does not bind, about 0.02% of T4 and 0.3% percent of T3, is able to enter cell membranes to cause its genomic actions (Wassner, 2018). In the normal physiological state, the thyroid gland secreted about eighty percent of circulating T4 and twenty percent T3; however, T3 is four times as potent as T4 in regulating the target tissues, which highlights its overriding role in the regulation of metabolism.

Calcitonin or thyrocalcitonin is a peptide hormone synthesized by parafollicular C cells that are located in the thyroid matrix. Its key action is to keep calcium in equilibrium: it will inhibit bone resorption under the influence of osteoclasts when the systemic levels of calcium exceed the normative levels: in this way, it will reduce the release of calcium ions in the skeleton bank. At the same time, calcitonin decreases renal reabsorption of calcium and thus stimulates its excretion in urine, and reduces phosphorous levels in the same circumstances. A negative feedback loop regulates the release of the thyroid-stimulating hormone (TSH), wherein the release of the hormone is reflexively regulated by the release of T3 and T4 into circulation; a further negative feedback loop is the release of the thyrotropin-releasing hormone (TRH) by the hypothalamus [9,10,11,12]

Under normal endocrine conditions, TRH released by the hypothalamus activates the secretion of TSH by the anterior pituitary, which simplifies the synthesis and release of T4 and T3 by the thyroid gland. TSH secretion is sensitive to small changes in the concentration of thyroid hormones and therefore enables the early diagnosis of endocrine maladjustment, which can be a precursor of actual hormonal disorders. The determinants of the relationship between TSH and T4 are genetically determined and are further modified by the environment, including age, exposure to tobacco, and autoimmune status, among other factors that form a dynamic equilibrium that maintains endocrine homeostasis [13,14,15].

Ethical approval

The Scientific Committee of the Biochemistry Department of the College of Medicine, University of Baghdad, Iraq, gave ethical clearance. Data were determined through a descriptive study carried out in the period between November 2020 and January 2021, and the subjects were recruited in the Baghdad Health Department in the Rusafa area, the Specialized Centre of Endocrinology and Diabetes, the Al-Sadr General Hospital, and the Baghdad Teaching Hospital.

This study included the use of questionnaires as a method of gathering information covering healthy volunteers as well as cohorts of patients.

The evaluation of thyroid, renal, and hepatic activities was conducted in 90 participants, and the assessment of thyroid activity before was done in patients diagnosed in the Special Center on Endocrinology and Diabetes.

Study design

The analytical cross-sectional design was used in the study.

Subjects

The first recruitment produced 157 respondents out of whom 90 were finally recruited based on initial screening, but 67 were excluded due to recent diagnosis, BMI over 40 years, and the largest Kurdish or African ethnic group.

The sample population (183) included 90 individuals (25-65 years old) living in Baghdad who were tested on renal and hepatic functions; none of them reported having received specific care in case of heavy-metal poisoning. They were categorized into three groups following the laboratory and consultations at the Specialized Center of Endocrinology and Diabetes and Al-Sadr General Hospital.

First group: 30 healthy persons were confirmed in relation to clinical examination and laboratory values (serum TSH, total T4, and total T3) and were used as the controls.

Second group: 30 patients that once had hypothyroidism identified in the mentioned centers and who had been taking levothyroxine (100150 mg) over the period of 5-25 years.

Third group: 30 patients with known hyperthyroidism, who have been under carbimazole (5mg) therapy between 3-20 years.

It is necessary to add that all thyroid-gland tests were conducted after the therapy was initiated, due to the impossibility to recruit the patients at the very first diagnosis; this shortcoming is admitted.

Inclusion criteria

Respondents that had either primary hyperthyroidism or hypothyroidism and met the specifications of the research.

Exclusion criteria

1. Breast cancer patients, as the increase in the level of thyroid-antibodies is registered in this scenario (Pan et al., 2020).

2. Patients with renal or hepatic malady. Renal impairment is also known to decrease urinary excretion of metals, but an improvement of renal function augmented excretion (Jin et al., 2018). Copper enters hepatocytes and is incorporated either into endogenous Cu+binding proteins, includative as ceruloplasmin, to be secreted, or unnecessary copper is lost by secretion into the bile to achieve homeostasis (Linder, 2020).

3. Asthmatic smokers and people drinking alcohol heavily. The increased alcohol consumption with the use of cigarettes significantly increases the level of heavy metals in the blood, especially in severe smokers (Choi et al., 2020).

4. Patients with thyroidectomy because of the failure to establish the underlying pathological situation that led to the removal of the gland.

Blood sampling

The participants were sampled in the mornings on 8:00 am to 11:00 am. Every sample (10 mL) was collected by venipuncture using a disposable syringe and a 3 mL aliquot in an EDTA bottle to determine Pb (lead) and Cd (cadmium), and a 7 mL aliquot in a gel-containing tube to allow separation of the serum.

Pb and Cd analyses were done using the EDTA-containing tubes. Gel tubes were left to clot at 37 °C for about 10-15 minutes and centrifuged at 2000 x g for another 10-15 minutes. Serum was aliquated and frozen at -20 o C in sterilised Eppendorf tubes; 0.5ml of serum was further analysed as serum TSH, T4, T3, TPO-Ab, copper, chromium, zinc, AST, ALT, ALP, urea, and creatinine.

Results

Table 1 General Characterization of the study's subject of Age, BMI expressed S.TPO and S.TSH, S.T4 and S.T3 (In basal and after treatment) expressed as mean ± Standard error (SE) without any statistical comparison.

Parameters	Healthy subjects Mean±SD	Hypothyroidism Patients Mean±SD	Hyperthyroidism Patients Mean±SD
	No. =30	No. =30	No. =30
Age Years	46.87 ±2.20	48.57 ±2.53	47.07 ±2.22
BMI Kglm	30.44 ±0.93	28.86 ±0.74	31.17 ±1.10
S.TPO pg/ml	442 ±11.30	500.53± 28.14	489.7 ±19.87
S.TSH	1.83 ±0.15	22.147 ±4.37	0.38 ±0.18
basal (IU/ml)			
S.T4 basal (nmol/l)	103.83 ±4.30	65.87 ±3.04	155.2 ±10.51
S.T3 basal (nmol/l)	1.38 ±0.05	1.29 ±0.0.08	3.25 ±0.37
S.TSH after		4.41±1.96	1.10±0.33
treatment (IU/ml)			
S.T4after treatment (nmol/l)		128.8±6.3	129.6±10.14
S.T3 after		1.45±00.07	2.03±0.16
treatment (nmol/l)			

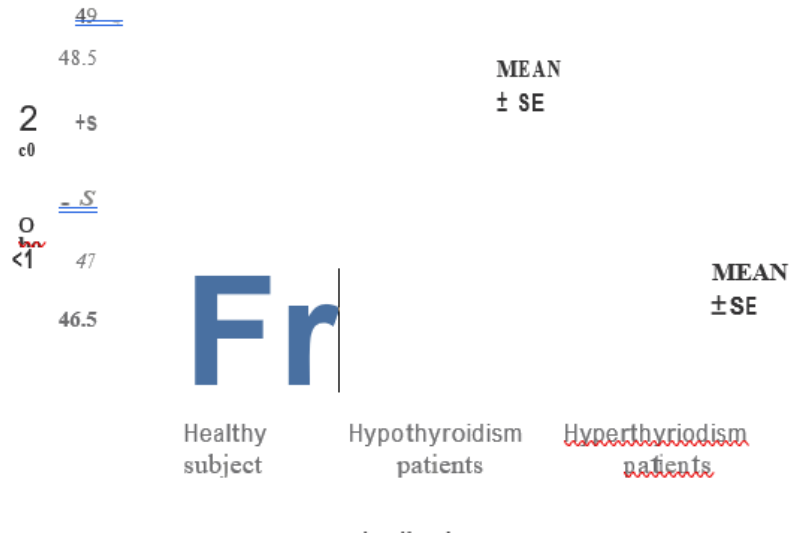

Figure 1- Mean±SD Distribution of Age in study groups

Table 2- Mean ± SE Age and BMI for hypothyroidism patients and healthy subjects.

Parameters	Healthy subject Mean±SD	Hypothyroidism Patient Mean±SD	T-TEST Sig.
	No.=30	No.=30	
Age			P >0.05
Years	46.87 ±2.20	48.57 ±2.53	N.Sig.
BMI			P >0.05
Kg/m	30.44 ±0.93	28.86 ±0.74	N.Sig.
S.TPO pg/ml	442 ±11.30	500.53± 28.14	P <0.05 Sig.

Table 3- Mean ± Standard error (SE) Age and BMI for hyperthyroidism patients and healthy subjects.

Healthy subject Hyperthyroidism Patient T-TEST Parameters Mean±SD Sig.

No.=30 No.=30

Age P >0.05 years 46.87 ±2.20 47.07 ±2.22 N. Sig.

BMI P >0.05

Kg/m 30.44 ±0.93 31.17 ±1.10 N. Sig.

S.TPO P <0.05 pg/ml 442 ±11.30 489.7 ±19.87 Sig.

Table 4- The heavy metals (Cu, Pb, Cd, Cr, Zn) status of hypothyroidism patients compared to healthy subjects represent as Mean ± Standard error (SE).

Elements	Healthy subject Mean±SE No.=30	Hypothyroidism Patient Mean±SE No.=30	T-TEST Sig.
S.Cu µg/dl	110.67±2.11	143.60±1.80	P<0.05 Sig.
S.Zn ug/dl	98.77±1.39	73.33±1.83	P <0.05 Sig.
S.Pb ug/dl	14.60±0.24	26.13±0.62	P <0.05 Sig.
S.Cd µg/dl	0.13±0.01	0.29±0.01	P <0.05 Sig.
S.Cr ug/dl	0.17±0.01	0.15±0.01	P<0.05 Sig.

Table 5- The heavy metals (Cu, Pb, Cd, Cr, Zn) status of hyperthyroidism patients compared to healthy subjects represent as Mean ± Standard error (SE).

Elements	Healthy subject Mean±SD	Hyperthyroidism Patient Mean±SD	T-TEST Sig.
	No.=30	No.=30	
S.Cu	110.67±2.11	141.60±1.60	P <0.05
µg/dl			Sig.
S.Zn	98.77±1.39	76.77±1.97	P <0.05
µg/dl			Sig.
S.Pb	14.60±0.24	27.50±0.55	P <0.05
ug/dl			Sig.
S.Cd ug/dl	0.13±0.01	0.32±0.01	P <0.05 Sig.
S.Cr	0.17±0.01	0.14±0.01	P <0.05
ug/dl			Sig.

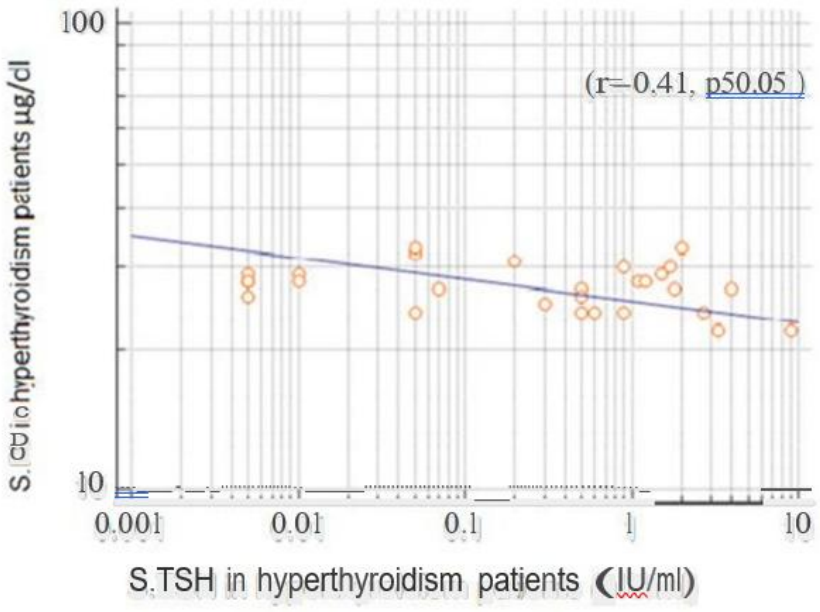

Figure 2- correlation between S. TSH and S.Cd in hyperthyroidism patients

Discussion

Ageing is associated with changes in pituitary-thyroid axis function as well as an increase in the prevalence of autoimmune and nodular thyroid disease (Gauthier et al. 2020). Previous research indicated that ageing in the absence of thyroid dysfunction was linked with decreased TSH secretion. (Duntas et al. 2018) (Chaker et al. 2018)

Thyroid function can affect the BMI; the alteration in thyroid function is mainly primary, while the change in body weight is secondary. The thyroid function disorders, in conjunction with the strong influence of various environmental factors, can increase body weight and lead to obesity. [16,17] As long as it is not a goal of the research study, the effect of age and weight on thyroid function is not considered. Age and BMI of subjects were successfully matching, represented by a non-significant value ($p>0.05$) between the studied group. It can be noted that the weight of the hyperthyroidism patients is more than the average of hypothyroidism patients, and this is contrary to the scientific evidence, but this can be attributed to the effect of the treatment. In this study, TPO showed a

significant increase in hypo and hyperthyroidism patients, moderately increased levels of TPO Ab maybe give rise to the cause of Hashimoto's disease(an autoimmune disease)in hypothyroidism and Graves' disease (an autoimmune disease) in hyperthyroidism [18,19]

The TPO Ab is responsible for the autoimmune destruction of thyrocytes, either by fixing complement or through cell-mediated cytotoxicity (antibody-mediated cytotoxicity may be a secondary mechanism to thyroid destruction) [20]

It has also been shown that the complement pathway may be directly activated by component C4 binding to TPO itself (Blanchin et al., 2003).

The thyroid gland is stimulated by antibodies that activate the receptor for TSH on the follicular cells of the thyroid. Therefore, these TSH receptor• stimulating antibodies mimic the action of TSH but are distinct from authentic TSH from the anterior pituitary gland. In this case, the patient producing too much thyroid hormone, leading to thyrotoxicosis(Graves' disease). (Han & Goleman, daniel; boyatzis, Richard; Mckee, 2019) Which gives a possible explanation for these findings, that chronic TSH stimulation leads to increased iodide binding because of increased gland peroxidase content, increased iodine trapping, and presumably increased HO generation, hence, increase TPO activity. (Hasan et al., 2011)Serum Cu shows a significant elevation and a significant decrease in serum Zn concentration in hypo- and hyperthyroidism patients against healthy subjects. Copper (Cu) and zinc (Zn) are essential micronutrients and crucial components for the development and maintenance of the immune and antioxidative defence system. Cu and Zn have an impact especially on the cell-mediated immune reactions of both innate and acquired immune defence (Giacconi et al., 2017), but the balance between these two elements appears to be important. A significant reduction in Zn levels among hypothyroid patients agreement with the results of Rezaei et al. and Arora, results. However, Kuriyama et al reported no marked difference in the Zn levels (Rezaei et al., 2019) (Arora, 2018) (Kuriyama et al. 2011)Low levels of Zn are known to retard the synthesis of thyrotropin• releasing hormone (TRH) with a subsequent reduction in thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) (Severo et al.2019). Zn is essential to thyroid function for converting T4 and T3 outside the thyroid glands (Aziz et al. 2016). Although the disruption in thyroid function has been linked to the reduced levels of Zn (Severo et al. 2019), there is evidence that hypothyroidism can induce Zn deficiency (Brando• Neto et al. 2001). Thyroid hormones can also affect the metabolism of Zn; for instance, free T4 concentrations declined significantly after low zinc supplementation and increased during adequate zinc intake (Erdal et al.2008; Kuriyama et al. 2011; Baltaci et al. 2017). A significant reduction in Zn levels in hyperthyroid patients can see in previous studies like Rezaei et al., Abdrabo and Sinha et al., whilst Giray et al., reported no marked difference in the Zn levels (plasma) between patients with thyroid diseases and healthy controls (Giray et al. 2010) (Rezaei et al.,2019) (Abdrabo, 2016)(Sinha et al., 2015)Serum zinc content decreased considerably in hyperthyroidism It was reported that the reduced serum zinc levels had two main reasons: lower zinc absorption and increased urinary zinc excretion this opinion agreement with Baltaci et al. were revealed in a study of 34 hyperthyroid patients. While Chin et al. and Liu et al. suggested that low erythrocyte zinc concentration in hyperthyroidism, caused by inhibition of zinc enzyme carbonic anhydrase-I synthesis in erythrocytes at high concentrations of thyroid hormones. (Baltaci et al., 2019) (Chin et al., 1987)(Liu et al., 2001)

An increased level of copper in hypothyroidism patients compared the healthy subjects can be seen in Khatun et al.'s study. (Khatun et al., 2019) The possible explanation is that the zinc deficiency leads to increased absorption of copper from the intestine, which agreement with AKCAY et al. (AKCAY et al., 1994). Hyperthyroid patients had significantly elevated plasma Cu concentrations according to their controls, and agreement with (Khadem• Ansari et al., 2017) (Sinha et al., 2015), (Y. Liu et al., 2018) found hyperthyroidism may be associated with higher Cu levels. About 90% of Cu is transported in the bloodstream via ceruloplasmin, and the ceruloplasmin increases significantly in hyperthyroid patients (Sinha et al., 2015). Hence, increased ceruloplasmin and slow excretion of Cu from the body can explain elevated Cu levels in hyperthyroidism patients. (Khadem-Ansari et al., 2017)

Conclusion

It can say that thyroid gland dysfunction (hypothyroidism and hyperthyroidism)is associated with changes in heavy metals (Pb, Cd, Cr, Cu and Zn) some of them elevated while other decreases and this is evident through the results obtained from comparing them with healthy subjects, but at the same time, the study cannot able to arrive at the association or coincidence of a specific mineral change with any of two glandular conditions except for the Cd. But the fact of relying on it and examining it as a routine in the case of thyroid dysfunction needs more accurate studies and a larger number of samples.

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