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Interaction of Some Selected Trace Elements with Thyroid Hormones in Patients with Goiter in Ibadan, Nigeria

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Authors' contributions

This work was conducted with collaboration between all authors. Author KSA designed the study, wrote the protocol and approved the final manuscript. Author AAS collected and analyzed the samples and wrote the first draft of the manuscript. Author Adefemi Afolabi read the manuscript draft and supplied valuable missing patient information and author AA supplied the public health dimension and identified appropriate journal for publication. All authors read and approved the final manuscript.

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ABSTRACT

Trace elements influence hormones at different levels of action, including hormone secretion, activity and binding to target tissue. Thyroid hormones also influence the

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metabolism of some essential trace elements. There is paucity of knowledge on the interaction of some trace elements in goiter development in the study environment. This study was carried out to determine the levels of selenium, copper, and zinc and their correlation with free triiodothyronine (fT_3), free thyroxine (fT_4), and Thyroid Stimulating Hormone (TSH) in patients with goiter in Ibadan. Sixty randomly selected participants who agreed to participate by signing the consent form following due explanation of the purpose of the study, were recruited. They comprised of 30 female patients (19 hyperthyroid and 11 euthyroid) attending the Nuclear Medicine and Surgery clinics of the University College Hospital, Ibadan, and 30 apparently healthy women as controls. Serum zinc, copper and selenium were determined by atomic absorption spectrophotometery and fT_3, fT_4 and TSH by ELISA. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) soft version 20.0 and data were expressed as mean and Standard Error of Mean (SEM). Results showed that hyperthyroid goiter patients had significantly lower levels of Selenium (0.9±0.027 vs. 4.00±0.02 µg/dl), Zinc (70.56±1.46 vs. 73.88±2.05 µg/dl) and Copper (85.23±5.09 vs. 123.11±1.80 µg/dl) compared with the controls ($p<0.05$). For euthyroid goiter, a significant positive correlation was found between FT_3 with copper and selenium ($p<0.05$, $r=0.46$), ($p<0.05$, $r=0.80$) respectively; and positive correlation ($p<0.05$, $r=0.46$) between Zinc and TSH in the hyperthyroid group. Diets and/or supplementations rich in Selenium, Copper and Zinc may reduce the development of certain goiters.

Keywords: Trace elements; thyroid hormones; euthyroid goiter and hyperthyroid goiter.

1. INTRODUCTION

The term 'goiter' simply refers to the abnormal enlargement of the thyroid gland. The presence of a goiter however does not necessarily mean that the thyroid gland is malfunctioning [1]. The thyroid gland stores nearly half of the total amount of iodine present in the body and is essential for the formation of thyroid hormones. Inability to produce the thyroid hormones lowers basal metabolism and this leads to the enlargement of the gland in an attempt to increase secretion. Goiter can, however, occur in the presence of hypothyroidism, hyperthyroidism, or normal levels of thyroid hormone.

Goiter is caused by iodine deficiency, autoimmune thyroiditis, excess iodine (Wolff chakoff effect), goitrogens, and Graves' disease while hyperthyroidism can result also from Graves' disease, toxic adenoma, thyroiditis or pituitary adenoma.

Some epidemiological studies have shown that iodine and selenium should be used together when managing thyroid conditions because both iodine excess and iodine deficiency, in the absence of adequate selenium status, may increase oxidative stress in the thyroid gland. The physiological adaptation in an iodine deficient state is an increase in plasma Thyroid Stimulating Hormone (TSH), enabling the body to increase expression of the sodium/iodide Symporter (NIS) in an attempt to trap as much iodine as possible for thyroid hormone synthesis. During thyroid hormone synthesis, thyroid tissue is exposed to increased concentration of hydrogen peroxide (H_2O_2) making it imperative for protective systems to prevent damage to the gland [2]. This tissue protection can be achieved by selenium-dependent products, e.g. the glutathione peroxidase [3]. Serum levels of selenium (Se) are considered to depict the adequacy regarding glutathione peroxidase (GPx) levels and activity [4]. Selenium is mostly utilized for biosynthesis of the unique amino acid

selenocysteine (Sec), which is co-translationally incorporated into selenoproteins, functioning primarily in redox reactions [5]. Selenium is an essential nutrient that act as cofactor in enzymes involved in oxidation–reduction reactions, iodothyronine deiodinase and glutathione peroxidases, [6-7], which are essential for the activity of the deiodinase complex that converts T_4 to T_3. The increased levels of thyroid hormones and the concomitant increased production of hydrogen peroxide by the thyrocytes, give glutathione peroxidase, the required substrate, which may be the cause of selenium depletion in the systemic circulation. Selenium deficiency leads to a reduction of the selenium containing enzyme glutathione peroxidase [8]. Glutathione peroxidase detoxifies H_2O_2 which is abundantly present in the thyroid gland as a substrate for the thyro-peroxidase that catalyzes iodide oxidation and binding to thyroglobulin, and the oxidative coupling of iodotyrosines into iodothyronine. Reduced detoxification of H_2O_2 may lead to thyroid cell death. The consequences of the above include increased risk of goiter, thyroid gland atrophy, and necrosis.

Trace elements are known to influence hormones at levels of their action, influence also include hormonal secretion, and binding to target tissue [9]. Copper and Zinc have also been reported to play important roles in iodine metabolism and thyroid hormone metabolism.

Copper stimulates the production of thyroxine (T_4), and prevents over-absorption of T_4 in the blood cells by controlling the body's calcium levels (calcium being required for the stabilization of cell membranes and reducing cell permeability). The potential link between zinc and thyroid metabolism is based on the hypothesis that T_3 receptors, like other nuclear receptors, include nuclear zinc-binding proteins [10]. Therefore, zinc is thought to be an integral part of nuclear receptor proteins, stabilizing them in a conformation required for binding to target genes [11].

Paucity of knowledge on the interaction of some trace elements in goiter development in the study environment necessitated this study aimed at investigating the relationship between thyroid hormones (T_3, T_4, and TSH) and selenium, copper and zinc) in patients with goiter.

2. MATERIALS AND METHODS

Sixty randomly selected participants were recruited for this study. They were made up of 30 clinically diagnosed female hyperthyroid and euthyroid patients with goiter attending the Nuclear Medicine and Surgery clinics of the University College Hospital, Ibadan, Nigeria, and another 30 apparently female healthy individuals as controls. All participants were recruited after voluntarily agreeing to participate by signing the consent form, following due explanation of the purpose of the study. Their ages ranged between 25 and 65 years and were new patients who had not undergone any treatment. Blood samples were obtained from the subjects in accordance with the guidelines of the Joint Ethical Committee of the College of Medicine and the University College Hospital, Ibadan, Nigeria.

The diagnosis of euthyroid and hyperthyroid goiters were made first clinically and confirmed biochemically using serum free T_3, T_4 and TSH assay. The hyperthyroid test group were those with suppressed or undetectable TSH concentration (<0.05mIU/L) in the presence of elevated fT_4 concentration while the euthyroid test group have normal thyroid function test but had clinically enlarged thyroid gland. The female control participant were not pregnant and were clinically and biochemically euthyroid with no history of thyroid illness. The rejection criteria include pregnancy, thyroid cancer, and any form of clinical or radioiodine treatment.

2.1 Sample Collection

Blood samples were carefully collected from each subject into clean universal bottles, and stoppered avoiding haemolysis. The blood was allowed to clot, centrifuged and serum separated and stored at -20ºC until analyzed for Selenium, Zinc, Copper, and TSH, freeT_3, and freeT_4.

2.2 Analytical Methods

Micro plate immunoenzymometric assay techniques were used for the quantitative measurements of free T_3, T_4 and TSH by the use of DS-EIA-THYROID-KIT (DSI S.r. l. *In vitro* diagnostics Germany) the kit minimum quantitation limit is 0.384 pmol/L for fT_3, 1pmol/L for fT_4 and 0.05mIU/L for TSH. Serum level of selenium, copper and zinc, were measured using flame atomic absorption spectrophotometery (AAS), on Model 200 Atomic Absorption Spectrophotometer, manufactured by Buck Scientific Instrument Manufacturing Company Boston. Digestion of samples was done at 120-150ºC using a mixture (3:2) of conc. nitric acid (69%) and perchloric acid (70%) till complete digestion and white ash was obtained. The ash was then dissolved in 100 µl 5% nitric acid and made up with deionized water up to 5 ml. Before measurements, serum samples were diluted one in two with a 0.1N hydrochloric acid solution, in order to reduce the effect of sample matrix on the flame and to enhance aspiration of the samples. Absorbance values were determined and a calibration curve was constructed by plotting the concentrations of metals (µg/ml) against their absorbances. Metals levels were obtained directly from the standard curve of each metal.

2.3 Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) soft version 20.0. All data were expressed as mean and Standard Error of Mean (SEM). The mean and standard error of mean of the cases (patients with euthyroid and hyperthyroid goiter) and control were calculated. The correlations between variables were performed using the Pearson method. Test of significance for the differences between the means of the two groups was assessed by Student *t*-test. ANOVA was used to compare the 3 groups (euthyroid, hyperthyroid and control). Levene's Test for Equality of Variances was also used. Data were analyzed at 95% confidence interval and *p*-values less than 0.05 were considered statistically significant.

3. RESULTS

A total of 60 female participants were enrolled in this study including, 30 patients (19 with hyperthyroidism and 11euthyroid patients), while 30 apparently healthy ones served as control.

Table 1 shows the mean values of TSH (0.87 mIU/L), fT_3 (4.3 pmol/L), and fT_4 (11.56 pmol/L), all within normal reference range for the control and euthyroid group, the TSH was suppressed (0.43 mIU/ml), fT_3 was slightly raised (9.32 pmol/L) while the fT_4 was also raised, in keeping with the state of hyperthyroidism for the hyperthyroid group. Trace elements differed significantly across the group.

There were significant differences in the levels of TSH, T_3, T_4, Cu, Zn, and Se between the two groups. Euthyroid goiter patients had significantly lower values for thyroid hormones as well as selected trace elements compared with the control group Table 2.

Table 1. Comparison of the mean values of TSH, fT_3, fT_4, copper, selenium and zinc in all the study participants by ANOVA

Variables	Euthyroid goiter (n=11)	Hyperthyroid goiter (n=19)	Control (n=30)	F value	p value
TSH (mIU/L)	0.87±0.36	0.43±0.18	2.44±0.30	16.54	0.000*
fT_3 (pmol/L)	4.3±0.14	9.32±0.5	5.84±0.11	18.05	0.000*
fT_4 (pmol/L)	11.56±0.86	16.40±1.42	9.17±0.47	43.54	0.000*
Copper (µg/dl)	89.57±3.0	85.23±5.09	123.11±1.80	87.9	0.000*
Selenium (µg/dl)	0.7±0.005	0.9±0.027	4.00±0.02	249.7	0.000*
Zinc (µg/dl)	73.88±2.05	70.56±1.46	109.24±0.03	9.30	0.000*

*This * indicates that p value is significant at <0.05*

Table 2. Comparison of the mean values of TSH, T_3, and T4, copper, selenium and zinc in euthyroid and control group

Variables	Euthyroid (n=11)	Control (n=30)	p value
TSH (mIU/L)	0.87±0.36	2.44±0.30	0.006*
fT3 (pmol/L)	4.3±0.14	5.84±0.11	0.049*
fT4 (pmol/L)	11.56±0.86	9.17±0.47	0.015*
Copper (µg/dL)	89.57±3.0	123.11±1.80	0.000*
Selenium (µg/dL)	0.7±0.005	4.00±0.02	0.000*
Zinc (µg/dL)	73.88±2.05	109.24±0.03	0.029*

** indicates that p value is significant at <0.05*

Similarly the patients with hyperthyroid goiter had significantly lower levels of Copper, Selenium and Zinc, compared with the controls as shown in Table 3.

Table 3. Comparison between TSH, fT3, fT4, selenium, copper, zinc in hyperthyroid and control group

Variables	Hyperthyroid (n=19)	Control (n=30)	p value
TSH (mIU/L)	0.43±0.18	2.44±0.30	0.000*
fT3 (pmol/L)	9.32±0.5	5.83±0.11	0.000*
fT4 (pmol/L)	16.40±1.42	9.17±0.47	0.000*
Copper (µg/dL)	85.23±5.09	123.11±1.80	0.000*
Selenium (µg/dL)	0.9±0.027	4.00±0.02	0.000*
Zinc (µg/dL)	70.56±1.46	109.24±0.03	0.000*

There is a positive or direct relationship between copper and T_3 in the euthyroid group and inverse relationship of copper with TSH in the hyperthyroid group. It also shows a positive or direct relationship between selenium and T_3 in the euthyroid group. Table 4 also shows a direct correlation between zinc and TSH in the euthyroid and the hyperthyroid group Table 4.

Table 4. Relationship between copper, selenium, zinc and thyroid hormones in control group compared with the test group (euthyroid and hyperthyroid)

Variables	Control		Euthyroid		Hyperthyroid	
	r	p	R	p	r	p
Copper						
TSH	0.050	0.790	-0.570	0.700	-0.700	0.001*
fT_3	-0.010	0.970	0.780	0.010*	0.040	0.872
fT_4	-0.210	0.261	0.317	0.340	0.204	0.401
Selenium						
TSH	-0.800	0.660	0.562	0.070	0.047	0.840
fT_3	0.120	0.510	0.804	0.004*	-0.144	0.550
fT_4	-0.130	0.490	-0.490	0.126	0.152	0.530
Zinc						
TSH	0.460	0.010*	0.530	0.097	0.050	0.010*
fT3	0.122	0.520	-0.035	0.700	0.030	0.870
fT4	0.170	0.370	-0.126	0.712	-0.340	0.401

*This *indicates significant correlation*

4. DISCUSSION

The present study showed significant decrease in zinc and reduced copper content in the serum of patients with hyperthyroid goiter. Zinc was deficient in the hyperthyroid participants, while Copper was in the low normal reference range. Zinc level also correlated significantly with TSH in the hyperthyroid group, and this result is in agreement with the findings from a previous study [12]. Zinc plays a very important role in the thyroid gland. Thyroid transcription factors which are essential for modulation of gene expression contain zinc at cysteine residues. An earlier study observed that the existence of a potential link between zinc and thyroid metabolism, which is based on the hypothesis that T_3 receptors like other nuclear receptors, include nuclear zinc-binding proteins [13]. It has also been shown by other researchers that serum zinc and albumin were significantly lower in hyperthyroidism patients than in normal individuals [14].

Copper and zinc are important for the activity of the enzyme Superoxide Dismutase (SOD) which has an active site for both elements in its structure. Copper is also an integral component of tyrosinase, an enzyme that is involved in tyrosine metabolism, which is very relevant in thyroid hormone biosynthesis [15]. Serum copper levels have been found to be positively regulated by thyroid hormone, mainly by directing the production of the Cu-transport protein ceruloplasmin [16]. In hyperthyroidism, the increased rate of body metabolism, may lead to the presence of the superoxide radicals that are formed by univalent reduction of oxygen in tissues. Excessive generation of these free radicals and the scavenging action of Cu-Zn superoxide dismutase can possibly lead to depletion of both copper and zinc store. The increased levels of thyroid hormones in hyperthyroidism and the concomitant increased production of hydrogen peroxide by the thyrocytes, gives glutathione peroxidase, the required substrate, which may be the cause of selenium depletion in the blood [17,18]. This further explains the correlation between selenium and T_3. Selenium helps in the modification of thyroid hormone metabolism via conversion of the pro-hormone T_4 to the active T_3 [19]. Therefore deficiency in selenium results in low T_3 levels, as well as increasing the oxidative stress factor in hyperthyroid patients. The possible influence of diet in amelioration of oxidative stress has been highlighted by certain authors [20,21] where it

was observed that insufficient intake of antioxidant vitamins and minerals may reduce the body's capacity to defend itself from the effect of activated oxygen derivatives on cell processes that play a role in the development of cancer and cardiovascular disease.

Selenium in this study was significantly lower in participants with goiter compared to the controls. Selenium is essential for the biosynthesis and function of a small number of selenocysteine-containing selenoproteins implicated in thyroid hormone metabolism and gland function. However, the availability of H_2O_2 and the subsequent peroxidative damage are decreased by selenoenzyme systems in the thyrocytes which may be involved in regulating hormone synthesis. Extracellular glutathione peroxidase is secreted by thyrocytes into the follicular lumen and may regulate the availability of H_2O_2 for thyroid peroxidase at the apical membrane [17]. The intracellular glutathione peroxidases may detoxify H_2O_2 and lipid hydroperoxides within the thyrocytes and protect the gland from oxidative damage.

A positive correlation exists between copper and T_3 in the euthyroid group of this study. Copper is a cofactor for tyrosinase which is required for the biosynthesis of tyrosine; a protein component of thyroglobulin needed for the synthesis of the thyroid hormones. Besides this, copper is also required for the synthesis of phospholipids, that are found in the myelin sheaths that insulates nerves to protect them. Phospholipids are required for the stimulation of TSH; appropriate levels are therefore required to prevent thyroid disorders. Copper also correlated with TSH in the hyperthyroid group in this study, this appears to be a new finding as previous work by Moncayo et al. [21] reported that neither Zn nor Se correlated with thyroid function in benign thyroid disease.

There was a correlation between TSH and zinc in both the control and hyperthyroid patients. The potential link between zinc and thyroid metabolism is based on the hypothesis that T_3 receptors, like other nuclear receptors, include nuclear zinc-binding proteins and its effectiveness could be impaired in relative zinc deficiency.

5. CONCLUSION AND RECOMMENDATION

This study has established that selenium, zinc and, copper are very important in thyroid hormone synthesis and their deficiency is associated with development of goiter. It is possible that diets and/or supplementations rich in selenium, copper and zinc may modulate the development of goiter.

6. LIMITATION OF THE STUDY

A major limitation of this work is the small sample size as well as the non-comparison of the basic anthropometric data between the study subjects and control as well as the lack of male participants.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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