# Evaluation of some minerals status in patients with thyroid glands disorders

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***Abstract:***

*Objective: The hormones which were secreting by thyroid gland play a role in regulation of many biological processes, therefore, the disorder in production of these hormones lead to changes in many metabolic and catabolic processes. The aim of this study is to evaluate the status of some minerals, and trace elements in patients with thyroid disorders (hyperthyroidism, hypothyroidism, and treated thyroid cancer).*

*Subjects &protocol: This study includes (125) healthy controls and (125) patients with thyroid disorders were distributed into three groups. The first group includes hyperthyroidism patients, the second includes hypothyroidism patients. Each of these groups include (50) patients newly diagnosed, While the third group includes (25) patients with treated thyroid cancer by surgery. Hormonal assay was done by gamma counter, while minerals and trace elements were determined by spectrophotometer and Combisys II set.*

*Results: Significant increase in serum (Cu) levels of hyperthyroidism patients and significant decrease in hypothyroidism and thyroid cancer patients when compared with normal group 2-. Significant decrease in serum Zn levels of hyperthyroidism patients and significant increase of Zn levels in hypothyroidism and thyroid cancer patients when compared the previous groups with normal group. 3- This study showed significant decrease in serum Fe in all groups of thyroid disorders when compared with normal group. 4- Li levels were significantly decreased in all groups of thyroid disorders patients when compared with normal group. 5- Some data (Fe) levels of thyroidectomy group showed no significant difference when compared with hypothyroidism patients.*

*Conclusion: This study illustrated the role of thyroid disorders in anabolic and catabolic processes of the minerals and trace elements metabolism. To our knowledge (by midline studies, and internet till 2004) this is the first study concerned with the determination of Li level in serum of patients with thyroid disorders in Iraq.*

**Key words:** Minerals, Thyroid Gland Disorders.

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**Introduction:**

There are three main types of clinical thyroid diseases [1]:

1. Secretary malfunction: hyper- or hypothyroidism
2. Swelling of the entire gland: diffuse goiter
3. Solitary masses: benign or malignant.

**Secretary malfunction:**

Hyperthyroidism (Thyrotoxicosis): It is second most prevalent endocrine disorder after diabetes mellitus [2]. Hyperthyroidism is the clinical syndrome resulting from production by sustained high plasma concentration of thyroid hormones; the overall result is an increased metabolic rate [3]. Hyperthyroidism may result from three main pathological lesions [4]:

- Grave's disease: Toxic multinodular goiter and Toxic multinodular goiter.
- Hypothyroidism (Myxoedema): It is clinical syndrome occurs when there is deficiency in the circulating levels of thyroid hormones [4].
- Recently is found that cases of congenital hypothyroidism had inherited 2 mutated genes thyroid oxidase 2 (THOX2) genes, or one of these genes [5].

**Swelling of the entire gland (Simple or non toxic goiter):-**

It is any thyroid gland enlargement not associated with hyper and hypothyroidism and does not result from inflammation or neoplasia [6].

In nontoxic goiter, inadequate thyroid hormone synthesis leads to TSH stimulation with resultant enlargement of thyroid gland [7]. Simple goiter is the most common disease of thyroid gland, and it is more common in females [8].

**Solitary Thyroid Nodule**:-

There are either benign or malignant. Benign thyroid nodules are the more common than malignance. Thyroid cancer has been shown to be a genetic disease [9, 10].

## Mineral elements and thyroid disorders

**Macro Elements**:

*Iron (Fe):* Iron containing enzymes such as peroxidase, catalase, and cytochrome (Fe-S and Fe-Cu) centers which are electron carriers in the respiratory chain [11]. Iron is capable of reduction /oxidation activity, therefore, in recent years, iron has been investigated as a prooxidant, which contributes to lipid peroxidation, atherosclerosis, deoxyribonucleic acid (DNA) damage, carcinogenesis, and neurodegenerative diseases [12,13]. Iron is essential for thyroid hormones synthesis by thyroperoxidase, the activity of this enzyme is dependent on the association with a heme (the ferriprotoporphyrin IX or a closely related porphyrin) [14]. Thyroperroxidase oxidizes iodide and incorporates the last into thyroid hormones [15].

Anemia (typically macrocytic, non megaloblastic) is one of clinical features of hypothyroidism. Luong K.V. in 2001 had reported a lower serum iron levels in hyperthyroidism [16].

***Copper (Cu):*** Copper is one of the essential elements in the body [17]. Divalent Cu forms complexes with proteins, many of which are enzymes such as cytochrome oxidase, ferroxidase (ceruloplasmin), superoxide dismutase (SOD), dopamine β – hydroxylase, spermine oxidase, tyrosinase, uricase, benzylamine oxidase, diamine oxidase, tryptophan 3,3 –di-oxygenase, and lysine oxidase,it also has the ability to induce the synthesis of metallothionein [11].Verma et al. in 1990 [18] reported that copper shares in synthesis of thyroid hormones by supply hydrogen peroxide by superoxide dismutase (SOD) – a copper containing enzyme and superoxide anion radicals ($O^-$). Serum copper increases in hyperthyroidism [19]. The interrelationships between copper deficiency and hypothyroidism state are existed concurrently, deficiency in one of them lead to reduce the other [20].

***Zinc (Zn):*** Zinc is an intracellular cation. It is next to iron and the second most abundant of the trace metals in human [21]. Thyroid hormone receptor complex binds to DNA via zinc fingers (the stable complexes of zinc) causing thyroid hormones action [22]. There is a contrariety about serum Zn levels in hyperthyroidism state, as Tsou C.T. (1993) reported a decreased serum Zn [23], while Aihara et al. (1984) found that there was no significant alteration compared to that in the controls [19].

About hypothyroidism, serum Zn levels were elevated, while Low concentration of zinc in the thyroid cancer tissue was reported [24].

**Non- Essential Elements**:

***Lithium (Li):*** Lithium is a small monovalent cation and it is distributed in extracellular and intracellular spaces and closely related to sodium in its properties [25]. Lithium increases intrathyronines iodine content, inhibits the coupling of iodotyrosine residues to form $T_4$, $T_3$, and inhibits secretion of $T_4$, $T_3$ [26].

The incidence of goiter in Li – treated patients is about 50%, while 20-30% of lithium – treated patients with goiter also have hypothyroidism [27].

Aim of the study:

1. To measure changes in minerals and trace elements levels (Fe, Cu, Zn, and $Li^+$) in serum of patients with thyroid disorders (hyperthyroidism, hypothyroidism, treated thyroid cancer).
2. To compare the results with each other and with healthy subjects.
3. To specify which elements in term of concentration is more affected by the underlying pathology of the patients.

**Materials & Methods:**

*Patients Selection*: This study had enrolled (250) subjects (144 females and 106 males) with age range between (18-80) years, and the mean age (41.45) years. One hundred twenty five served as control group and (125) patients with various thyroid disorders as follows:

- Group (1): 50 patients with hyperthyroidism.
- Group (2): 50 patients with hypothyroidism.
- Group (3): 25 patients with thyroid cancer, who were treated by surgery without receiving radioactive iodine 131.

All patients of group (1) and (2) are newly diagnosed and did not receive any treatment, while patients of group (3) withholds the thyroxin one month ago. Moreover, volunteers who had any other diseases or taken any drugs (that might affect our data measurements) were excluded from this study.

**Results:**

**Trace Elements:**

***Serum Iron (Fe):*** Table (1) demonstrates significant reduction in serum Fe level of patients with hyperthyroidism (14.125 ± 3.609, P < 0.0001) when compared with healthy (control) group (20.004 ± 2.594).Similarly, there was significant decrease in serum Fe level of patients with hypothyroidism and thyroid cancer (11.466 ± 2.885), (10.604 ± 3.069) respectively, when compared to healthy (control) group (P< 0.0001). In addition, significantly lower serum Fe levels were noticed in patients with hypothyroidism and thyroid cancer when compared to hyperthyroidism group (P < 0.0001).

***Serum Copper (Cu):***Table (2) shows significant increase in serum Cu level of patients with hyperthyroidism (25.981 ± 5.593, P < 0.0001) when compared with healthy (control) group (19.388 ± 3.084).While, significant reduction in serum Cu level of patients with hypothyroidism and thyroid cancer (13.799 ± 2.278), (17.387 ± 7.844) respectively when compared to healthy (control) group (P < 0.0001, P < 0.033 in series).In addition, significant low serum Cu levels were noticed in patients with hypothyroidism and thyroid cancer when compared with hyperthyroidism patients (P < 0.0001).Significantly reduced level of serum Cu was found in patients with hypothyroidism when compared with thyroid cancer group (P < 0.004).

***Serum Zinc (Zn):***Table (3) shows significantly reduced serum Zn level of patients with hyperthyroidism (12.252 ± 2.453, P < 0.0001) when compared to healthy (control) group (14.662 ± 2.218).There was a significant increase in serum Zn level of patients with hypothyroidism and thyroid cancer (20.765 ± 4.094), (16.615 ± 3.657) respectively when compared to healthy (control) group (P < 0.0001), (P<0.001) respectively.

Highly significantly increased serum Zn levels were noticed in patients with hypothyroidism and thyroid cancer when compared to hyperthyroidism group (P< 0.0001).Significant increase of serum Zn level was also observed in patients with hypothyroidism when compared with thyroid cancer patients (P<0.0001).

**Non-Essential Elements:**

***Serum Lithium (Li):***Table (4) shows significant decrease in serum Li level of patients with hyperthyroidism (0.278 ± 0.076, P < 0.0001) when compared with healthy (control) group (0.599 ± 0.237).Similarly, there was significant lower serum Li level of patients with hypothyroidism and thyroid cancer (0.383 ± 0.102), (0.310 ± 0.026) respectively when compared with healthy (control) group (P < 0.0001).In addition, significant elevation of serum Li levels was noticed in patients with hypothyroidism and thyroid cancer when compared with hyperthyroidism patients (P < 0.0001, P< 0.05 in series). Significant increase in serum Li level was noticed in patients with hypothyroidism when compared to thyroid cancer group (P < 0.001).

**Discussion:**

- **Effect of Thyroid Disorders on Trace Elements:**

***Iron (Fe):*** Significant reduction in serum iron levels was found in patients with hyperthyroidism when compared with normal group (Table (1)).

This result was correlated by many studies but they have different explanation. Ingbar et al. (1987) reported that the cellular demand for oxygen in those thyrotoxic patients to be increased [28], so tissue hypoxia may result in triggering the production of erythropoietin that increases iron turnover, so thyrotoxic patients may develop anemia as a result of the decreased survival of the red blood cells [29].Significant decrease in serum iron levels were recognized in sera of myxedema patients when compared with normal group (Table (1)). Anemia in this group is usually due to iron and vitamin $B_{12}$ deficiency [7].Generally, macrophages transfer iron (most comes from the destruction of old erythrocytes) to plasma transferrin, which then carries it to the bone marrow for hemoglobin synthesis, macrophages also maintain a storage pool of iron when red cell destruction exceeds the rate of production, iron accumulates within macrophages and the storage pool expands, and when the balance shifts toward red cell production, macrophage releases additional iron from their store [30]. Malignancy interferes with the release of iron from macrophages and may cause a drop in red cell production despite the presence of adequate Fe reserves [31]. This reason and in addition to thyroid hormones deficiency due to thyroidectomy lead to iron deficiency in patients with thyroidectomy, therefore, this study was found a significant decrease of serum Fe for patients with thyroid cancer when compared with normal group (Table (1)).

This result is in agreement with Zaichick et al. (1995) [32].

***Copper (Cu)****:* The elevated copper levels in serum of patients with hyperthyroidism when compared with control group (Table (2)) could be related to the increase cerulopasmin levels [19], which is in agreement with Sugawara et al. (1988) who found that the SOD activity in thyroid tissues with hyperthyroidism was higher than normal, thus the increased activity of SOD in thyrotoxic patients could be related to the increase serum Cu levels [33]. There are limited numbers of studies for serum copper in hypothyroidism. In this study we found a significant reduction of serum copper in patients with hypothyroidism when compared with normal group (Table (2)).Copper homeostasis is influenced by estrogen, which induced the synthesis of ceruloplasmin [34]. Estrogen is decreasing in hypothyroidism for two reasons, the first is a higher prolactin level, and the other is that thyroid hormones receptors interact with estrogen by specific bounds [35]. Therefore, the decrease of Cu may by related to these changes in hypothyroidism. In this study we found significant reduction in serum copper of patients with thyroid cancer when compared with normal group (Table (2)) which is in agreement with Hasegawa et al (2003) who suggested that the decreased expression levels of SOD in thyroid cancer group is due to the possibility that cancer cells are more likely to suffer damage by oxygen free radicals than normal thyroids cells or differentiated tumor cells [36].

***Zinc (Zn):*** As demonstrated in table (3) serum Zn levels were found to be decreased significantly in patient with hyperthyroidism when compared with normal subjects. As the large fraction of Zn in serum is known to be bound to albumin (80%) [30], thus lowered Zn levels might accompany low albumin levels in hyperthyroidism. The increase in loss via urine could be attributed to the increased levels of serum amino acids due to catabolic effect of thyroid hormone; these ultrafilterable molecules can form complexes with this metal which can easily pass glomeruli [19]. Zinc in serum of hypothyroidism patients showed significant increase when compared with control group (Table (3)). This increase was supported by Tosu et al (1993) who reported that in hypothyroidism, the excretion of Zn is low because of the slowing circulation rate [23]. The serum Zn of patients with thyroid cancer was significantly high when compared with control group (Table (3)), this finding is in agreement with Kucharzewski et al. (2003) who suggested this may result from the carcinogenic process [24], which includes a damage to the cancer cell by oxygen free radical more than normal thyroid cells [36].

- **Effect of Thyroid Disorders on Non – Essential Elements:**

***Lithium (Li):*** To our knowledge (by medline studies till 2004), this is the first study concerned with the determination of

Li level in serum of patients with thyroid disorders before treatment, because many studies have measured serum Li concentration after treatment especially hyperthyroidism [37,31].Lithium is closely related to sodium in its properties [25]. Therefore, we found in this study significant low serum Li level in thyrotoxic patients when compared with normal group (Table (4)), and it might be due to decrease of $Na^+$-$Li^+$ countertransport(CTT) value during hyperthyroidism [38].Low Na concentration in hypothyroidism and thyroid cancer groups (as mentioned before) may lead to low Li value as we found in this study ( significant decrease in serum Li level of hypothyroidism and thyroid cancer groups when compared with normal subjects ) (Table (4)).

**Conclusions:**

1. This study illustrated the main effects of thyroid hormones on minerals and trace elements metabolism during thyroid disorders.
2. To specify which elements in term of concentration is more affected by the underlying pathology of the patients.
3. The levels of (Fe) in thyroidectomy showed no significant difference when compared with hypothyroidism group.
4. Significant increase in serum (Cu) levels of hyperthyroidism patients and significant decrease in hypothyroidism and thyroid cancer patients were found when compared with normal group. But the reverse was shown in serum Zn levels.
5. Iron deficiency was found to be associated with all the thyroid disorders in this study.
6. Serum Li level was decreased in all groups of thyroid disorders in this study.

**Table (1):** comparison of serum Fe (µmol/L) in control, hyperthyroidism, hypothyroidism, and thyroid cancer patients

| **Serum Fe (µmol/L)** | **Healthy Individual (control)** | **Hyperthyroid** | **Hypothyroid** | **Thyroid cancer** |
|---|---|---|---|---|
| **Samples size (n)** | 125 | 50 | 50 | 25 |
| **Mean ± SD** | 20.004±2.594 | 14.125±3.609 | 11.466±2.885 | 10.604±3.069 |
| **SEM** | 0.232 | 0.510 | 0.408 | 0.613 |
| **P - value** | | * < 0.0001 | * <0.0001<br>** <0.0001 | * <0.0001<br>** <0.0001<br>*** NS |

**Table (2):** comparison of serum Cu (µmol/L) in control, hyperthyroidism, hypothyroidism, and thyroid cancer patients

| Serum Cu (µmol/L) | Healthy Individual (control) | Hyperthyroid | Hypothyroid | Thyroid cancer |
|---|---|---|---|---|
| **samples size (n)** | 125 | 50 | 50 | 25 |
| **Mean ± SD** | 19.388±3.084 | 25.981±5.593 | 13.799±2.278 | 17.387±7.844 |
| **SEM** | 0.275 | 0.790 | 0.322 | 1.568 |
| **P - value** | | * <0.0001 | * <0.0001<br>** <0.0001 | * <0.033<br>** <0.0001<br>*** <0.004 |

**Table (3):** comparison of serum Zn (µmol/L) in control, hyperthyroidism, hypothyroidism, and thyroid cancer patients

| Serum Zn (µmol/L) | Healthy Individual (control) | Hyperthyroid | Hypothyroid | Thyroid cancer |
|---|---|---|---|---|
| **Samples size (n)** | 125 | 50 | 50 | 25 |
| **Mean ± SD** | 14.662±2.218 | 12.252±2.453 | 20.765±4.094 | 16.615±3.657 |
| **SEM** | 0.198 | 0.346 | 0.579 | 0.731 |
| **P - value** | | * <0.0001 | * <0.0001<br>** <0.0001 | * <0.001<br>** <0.0001<br>*** <0.0001 |

**Table (4):** comparison of serum Li (mmol/L) in control, hyperthyroidism, hypothyroidism, and thyroid cancer patients

| Serum Li (mmol/L) | Healthy Individual (control) | Hyperthyroid | Hypothyroid | Thyroid cancer |
|---|---|---|---|---|
| **Samples size (n)** | 125 | 50 | 50 | 25 |
| **Mean ± SD** | 0.599±0.237 | 0.278±0.076 | 0.383±0.102 | 0.310±0.026 |
| **SEM** | 0.021 | 0.010 | 0.014 | 0.005 |
| **P - value** | | * <0.0001 | * <0.0001<br>** <0.0001 | * <0.0001<br>** <0.05<br>*** <0.001 |

* For comparison with control/** For comparison with hyperthyroidis/*** For comparison with hypothyroidism/NS: no significance

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