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# Relationship between Some Trace Elements, Lipid profile and Hypothyroidism

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## الخلاصة

هناك العديد من الأسئلة التي مازالت تركز على العلاقة بين العناصر النزرة وهرمونات الغدة الدرقية. لذلك صممت هذه الدراسة لتعيين تراكيز بعض العناصر النزرة (الزنك، النحاس، السيلينيوم، المنغنيز، والمغنيسيوم) وايجاد العلاقات الممكنة بين هذه العناصر وهرمونات الغدة الدرقية في مصل المرضى المصابين بقصور الغدة الدرقية.

شملت الدراسة 50 مريضا و28 شخص سليم كمجموعة سيطرة. تم مطابقتهم مع المرضى بالنسبة للعمر والجنس ومؤشر كتلة الجسم BMI . لم يتم اعطاء مجموعة الدراسة الفيتامينات او المعادن لمدة اسبوعين على الأقل قبل جمع العينات، جُمعت العينات لقياس مستويات العناصر النزرة(الزنك Zn ،النحاس Cu،السيلينيوم Se، المنغنيز Mn، المغنيسيوم Mg) وهرمونات الغدة الدرقية(التايروسين ثلاثي اليود T3، الثايروكسين T4،الهرمون المحفز للغدة الدرقية TSH) والدهون الكلية (الكوليستيرول الكلي TC، الدهنيات الثلاثية TG، البروتين الدهني منخفض الكثافة LDL، البروتين الدهني العالي الكثافة HDL، البروتين الدهني المنخفض الكثافة جداً VLDL). بينت هذه الدراسة ان المرضى المصابين بقصور الغدة الدرقية كانت لديهم زيادة معنوية في مستوى TSH وانخفاض معنوي في مستوى T3ونسبة T3/T4 مما يدل على وجود قصور في نشاط الغدة الدرقية. ايضا كانت مستويات العناصر النزرة لدى المرضى المصابين بقصور الغدة الدرقية (الزنك Zn، النحاس Cu، السيلينيوم Se، المنغنيز Mn، المغنيسيوم Mg) واطئة عند مقارنتها مع مجموعة السيطرة. اضافة الى ذلك، ليس هنالك علاقة بين مستويات Mg, Mn, Cu وكل من مستويات TSH, T4, T3 ؛ بينما كانت هناك علاقة موجبة بين Se-T3 (r=-0.315, P< 0.02) وبين Zn-T3 (r=0.3, P<0.01) وكانت هناك علاقة سالبة بين (Se-TSH) (r=-0.315, P< 0.02) في المرضى المصابين بقصور الغدة الدرقية. ايضا كانت هنالك زيادة معنوية في مستويات الكوليسترول الكلي والدهون الثلاثية والبروتين الدهني منخفض الكثافة لدى المرضى، كذلك كان هناك انخفاض معنوي في مستوى البروتين الدهني مرتفع الكثافة عند المقارنة بين المرضى ومجموعة السيطرة. اظهرت النتائج ان هناك علاقة موجبة بين مستويات TSH وكل من مستويات الدهون (الكوليسترول الكلي، الدهون الثلاثية، والبروتين الدهني واطئ الكثافة). كانت هنالك

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علاقة سالبة بين مستويات المغنيسيوم Mg والدهون (الكوليسترول الكلي، الدهون الثلاثية، والبروتين الدهني منخفض الكثافة).أستُنتج من ذلك وجود تغير في مستويات العناصر النزرة ( Mg, Mn, Cu, Zn, Se) لدى المرضى المصابين بقصور نشاط الغدة الدرقية، وكانت هناك علاقات بين بعض العناصر النزرة (Se, Zn) وهرمونات الغدة الدرقية؛ لكن لم تكن هناك علاقة واضحة بين القسم الاخر من العناصر النزرة (Mg, Mn, Cu) وهرمونات الغدة الدرقية. وذلك يعني ان هناك تداخلات لبعض العناصر النزرة وهرمونات الغدة الدرقية.

**المفاتيح:** قصور الغدة الدرقية، العناصر النزرة، السلينيوم، الزنك، النحاس، المنغنيز، المغنيسيوم.

## Abstract:

There are many questions still remain concerning the relationship between the trace elements and thyroid hormones. Therefore, this study was undertaken to evaluate the concentration levels of some trace elements (zinc, copper, selenium, manganese, magnesium), and to reach the possible correlation between these trace elements and thyroid hormones in hypothyroidism.

The study was included 50 patients with hypothyroidism and 28 healthy volunteers' serves as control group matched with age, sex, and body mass index (BMI). All participant had not taken vitamin or mineral supplements for at least 2 weeks before sampling, blood sampling were drawn to determine the serum trace elements levels (Zn, Cu, Se, Mn, and Mg), thyroid hormone (T3, T4, and TSH), and lipid profile (TC, TG, LDL, HDL, and VLDL). The results indicate that the hypothyroidism patients have significant increase in TSH levels ($P< 0.01$), and significant decrease in T3, T3/T4 levels ($P<0.001$), although, there were decrease in serum trace elements (Se, Zn, Cu, Mn, and Mg) in hypothyroidism patients compared with controls group, ($P< 0.001$ for all serum Se, Zn, Cu, Mn, and $P< 0.01$ for Mg). The results indicate that there was no significant correlation between serum Cu, Mn, Mg and T3, T4, and TSH level; but, there was a significant positive correlation between Se-T3 ($r=0.286$, $P<0.04$), and Zn-T3 ($r=0.3$, $P<0.01$), also there was only a significant negative correlation between serum Se-TSH levels ($r=-0.315$, $P< 0.02$) in hypothyroidism patients. There is significant increase in the mean serum cholesterol (TC), triglycerides (TG), and low density lipoprotein (LDL) in patients compared with normal controls (P 0.01, $P<0.001$, $<0.05$) respectively. Also, there is significant decrease in the mean serum concentration of high density lipoprotein (HDL) in the patients with hypothyroidism than control, and our results showed that there is positive correlation between TSH levels and lipid (cholesterol, triglyceride, and very low density lipoproteins), although, there is negative correlation between Mg concentration and lipid (TC, TG, LDL) levels. We conclude that the trace elements Se, Zn, Cu, Mn, and Mg have altered in hypothyroidism patients; there are correlations between some trace elements (Se, and Zn) and thyroid hormones, but there are no obvious correlations between the other trace

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elements (Cu, Mn, and Mg) status and thyroid hormones. That is means there is an interactions between some trace elements and thyroid hormones levels.

## Introduction:

Hypothyroidism is a clinically entity results from deficiency of thyroid hormones or more rare from their impaired activity on the tissue. In hypothyroidism, the basal metabolic rate is decreased on other processes dependent upon thyroid hormones[1].

The thyroid gland synthesis two major hormones, tri – iodothyronine (T3), which is the main biologically active thyroid hormones, and thyroxin (T4), which is the precursor of the former. Thyroid hormones promote the cellular growth and development[2]. Iodine is used to synthesize thyroid hormone, and in iodine deficiency state, the decrease in thyroid hormones lead to an increase in thyroid stimulating hormone (TSH) resulting in development of goiter[3].

Both some trace elements and thyroid hormones play essential roles in human body[4], trace elements have been shown to influence hormones at several levels, including hormone secretion, activity, and binding to the target tissue[5]. Moreover, hormones have been shown to influence trace element metabolism at several levels, including secretion and transport of trace elements[5,6]. Several mineral and trace elements are essential for normal thyroid hormone metabolism and Co – existing deficiencies of these elements can impair thyroid function[7].

Selenium (Se) is the essential micronutrient and a main component of selenocystein, and it is involved in the catalysis of all known selenoenzymes e.g, iodothyronine deiodinase. The iodothyronine deiodinase are required for the activation and inactivation of the thyroid hormone T4 and T3 respectively [8,9].

The deficiency of zinc, copper, manganese, selenium, and manganese have been observed to affect the endocrine system [5, 29]. Therefore, because of the essential roles of both trace elements and thyroid hormones in the human body, this study has been designated to evaluated serum Se, Zn, Cu, Mn, and Mg in hypothyroidism and to clear the association of these trace elements with thyroid hormone.

## Materials and Methods:

The study was applied on fifty patients (20 males, 30 females) with hypothyroidism, mean aged (51.75± 6.36 years), who were admitted to the National Diabetic Center in Baghdad from September 2008 to March 2009, all the patients received about 100 mg of thyroxin, the mean duration (3.6±0.3) years.

The control subjects included 28 healthy volunteers (11 males, 17 females), mean aged (48.69 ± 12.9 years). All subjects had not taken vitamin or mineral supplements for at least 2weeks before sampling, blood from fasting subjects was drown in the morning into disposable plastic syringes, blood samples were centrifuged at 3000 rpm for 10 min, and serum was obtained and

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stored at – 20 $C^0$, used for estimation serum thyroxin (T4), serum triiodo-thyronine (T3), and serum thyroid stimulating hormone (TSH), trace elements (zinc (Zn), copper (Cu), selenium (Se), manganese (Mn), magnesium (Mg)), and lipid profile (total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL)).

Serum T3 and T4 concentration levels were measured by radioimmunoassay method using (Gamma Counter model) and Radio immuno technique kit. Lipid profile was determined using the bioMérieux, Marcy 1'toile, France). Analyses of serum selenium and manganese samples were carried by using furnace atomic absorption spectrophotometry model (AA670) Shimadzu made. Serum samples were diluted (1:4) for Se, and (1:49) for Mn with deionized water and measured directly at (196 nm, and 279.5 nm) respectively.

Analysis of zinc (Zn), copper (Cu), and magnesium (Mg) seum samples\were carried by using flame atomic absorption spectrophotometery model (AA670) Shimadzu made. Serum samples were diluted (1:2, 1:2, 1:4) with deionized water to zinc, copper, and magnesium respectively and measured the concentration directly at (213.9 nm, and 324.8 nm, and 285.2 nm) respectively.

**Statistical analysis:**

Data were analyzed using computer facility-the available statistical packages of SPSS-11.5 (statistical packages for social sciences-version 11.5). Data were present in simple measures of number, mean±SD. The significance of difference between quantitative variables was tested using student t-test for comparing between two means of independent groups. $P \leq 0.05$ was used as the level of significance. Person correlation coefficient is significant at the 0.05 level.

## Results:

| | **Hypothyroidism** | **Controls** | ***P value*** |
|---|---|---|---|
| **No. of subject** | 50 | 28 | ---- |
| **Age (years)** | 51.75± 6.36 | 48.69 ± 12.9 | $N.S^{\#}$ |
| **Sex (m/f)** | (20/30) | (11/17) | ---- |
| **BMI ($Kg/m^2$)** | 27.85 ± 3.45 | 26.55 ± 5.7 | $N.S^{\#}$ |

**Table-1: Clinical characteristics of study subjects**

Data are mean ± SD, $P \leq 0.05$ was considered significant. $N.S^{\#}$ no significant.

No significant difference in the age means of hypothyroidism patients as compared with control subjects. Moreover, there was no significant difference in the mean of BMI between hypothyroidism and controls.

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| Parameters | Hypothyroidism | Controls | P value |
|---|---|---|---|
| T3 nmol/L | 1.642 ± 0.593 | 2.085 ± 0.318 | <0.001** |
| T4 nmol/L | 119 ± 61.009 | 108 ± 16.933 | N.S# |
| TSH umol/L | 2.374 ± 2.002 | 1.342 ± 0.718 | <0.01** |
| T3/T4 | 0.014 ± 0.005 | 0.019 ± 0.003 | <0.001** |

**Table-2: Thyroid hormones levels of the patients and controls**

Data are mean ± SD, *P≤ 0.05 was considered significant, and **P<0.01 is a highly significant. N.S# no significant.

| Parameters | Hypothyroidism | Controls | P value |
|---|---|---|---|
| Se (ppm) | 0.073 ± 0.006 | 0.097 ± 0.004 | P<0.001** |
| Zn (ppm) | 0.762 ± 0.065 | 1.193 ± 0.084 | P<0.001** |
| Cu (ppm) | 1.078 ± 0.233 | 1.265 ± 0.078 | P<0.001** |
| Mn (ppm) | 0.021 ± 0.009 | 0.04 ± 0.001 | P<0.001** |
| Mg (ppm) | 17.814 ± 0.623 | 18.075 ± 0.199 | P<0.01** |
| Cu/Zn | 1.425 ± 0.329 | 1.062 ± 0.724 | P<0.001** |
| TC (mg/dl) | 220.1 ± 59.75 | 186.3 ± 24.20 | P<0.001** |
| TG (mg/dl) | 152.2 ± 71.98 | 123.6 ± 32.55 | 0.01** |
| HDL | 29.28 ± 3.160 | 55.82 ± 21.84 | P<0.001** |
| LDL | 139.1 ± 28.1 | 117.6 ± 38.2 | <0.05* |
| VLDL | 32.84 ± 22.99 | 26.89 ± 9.370 | N.S |

**Table-3: The mean ± SD to the trace elements, and lipid profile**

Data are mean ± SD, *P≤ 0.05 was considered significant, and **P<0.01 is a highly significant. N.S# no significant.

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| Parameters | Hypothyroidism | |
|---|---|---|
| | R | P |
| T3 – T4 | 0.757** | <0.001 |
| T3 – TSH | - 0.280* | 0.049 |
| T4 – TSH | - 0.377** | 0.007 |
| T3 – T3/T4 | 0.168 | N.S |
| T4 – T3/T4 | - 0.433** | 0.002 |
| TSH – T3/T4 | 0.295* | 0.037 |
| Se – T3 | 0.286 | 0.04 |
| Se – T4 | 0.222 | N.S |
| Se – TSH | - 0.315* | 0.02 |
| Zn – T3 | 0.30* | 0.01 |
| TSH – TC | 0.43** | 0.002 |
| TSH – TG | 0.33* | 0.019 |
| TSH – VLDL | 0.332* | 0.018 |
| Mg – TC | - 0.344* | 0.015 |
| Mg – TG | - 0.332* | 0.019 |
| Mg – LDL | - 0.343* | 0.015 |

**Table-4: The correlation between the parameters in hypothyroidism patients.**
*correlation is significant at the 0.05 level (2-tailed)
**correlation is a highly significant at the 0.01 level (2-tailed)

A significant increase in TSH (P< 0.01), and significant decrease in T3, T3/T4 levels (P<0.001) in hypothyroidism patients, and this is evidence of induced hypothyroidism. But there is slight increase in the mean of T4 level in patients, but is not statistically significant, is found in table-2.

Also, there was significant positive correlation between serum T3 and T4 levels and serum TSH and T3/T4 ration (r = 0.757, P<0.001; r= 0.295 P=0.03) respectively. And there is significant negative correlation between T3 and TSH levels, T4 and TSH, and T4 – T3/T4 ratio are shown in table-4.

The mean concentrations of serum Se, Zn, Cu, Mn, Mg in patients with hypothyroidism was significantly lower than in controls (P< 0.001 for all serum Se, Zn, Cu, Mn, and P< 0.01 for Mg) as shown in table (3). Moreover there was no significant correlation between serum Cu, Mn, Mg and T3, T4, TSH level, there was only negative correlation between serum Se and TSH levels (P 0.02), and positive correlation between Se-T3, Zn-T3 in hypothyroidism patients as shown in table-4.

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Although, there is significant increase in the mean serum cholesterol (TC), triglycerides (TG), and low density lipoprotein (LDL) in patients compared with normal controls (P 0.01, P<0.001, and P<0.05) respectively. Also, there is significant decrease in the mean serum concentration of high density lipoprotein (HDL) in the patients with hypothyroidism than control. But, there are increase in serum very low density lipoproteins VLDL, nevertheless it is not significant in hypothyroidism and controls as shown in table-3.

Moreover, our results showed that there is positive correlation between TSH levels and lipid (cholesterol, triglyceride, and very low density lipoproteins); although, there is negative correlation between Mg concentration and lipid (TC, TG, LDL) levels, as shown in table-4.

## Discussion:

Our results showed significant increase in TSH, and significant decrease in T3 in hypothyroidism patients. Research revealed that the people with TSH value more than 2.0 umol/l have a higher risk of developing overt hypothyroidism[10]. But there is slight increase in the level of T4 level in patients, but is not statistically significant, this increase of serum T4 may due to the patients received about 100mg L-thyroxin.

At the present, measurement of serum concentration levels of zinc level is considered the most reliable means of diagnosing zinc deficiency[11]. It has been proposed the serum copper level were also measure, then the ratio of the serum copper to zinc level (serum copper/zinc ratio) can be used as reference information for diagnosing in thyroid deficiency[11]. In our results there was significant difference in serum Cu/Zn ratio between hypothyroidism patients and control group; this refers to deficiency in Zn levels in hypothyroidism patients.

Alternation in thyroid function has been reported in zinc deficient status [12], on the other hand, hypothyroidism induced zinc deficiency in humans, as well as zinc deficiency causes hypothyroidism [13]. The current study on serum Zn concentrations showed statistically significant decrease in hypothyroidism patients compared with normal control (P<0.001). This result was similar to that reported by Kandhro *et.al*, [14], Alturfn *et.al*, [15], Akcay *et.al*, [16], the reasons may due to thyroxin administration. Dursun *et.al*, [17] found that zinc was significantly decreased in RBC (45%) between experimental adult rats after beginning of thyroxin treatment induced hyperthyroidism and controls groups; or may due to the increase urinary Zn execration[5].

Our results on serum Zn concentrations demonstrated that there was positive correlation with T3 levels; but, there was no significant correlation with T4, and TSH levels. The causes may due to the activity of hepatic type I 5 deiodinase was decreased by 67% by Zn deficiency[18], or might be the T3 receptor is thought to require Zn to adopt its biologically active conformation[19], so the concentration of T3 may decreased when the level of Zn is decreased.

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Our results showed statistically significant decreased in serum Cu levels in patients with hypothyroidism when compared with control group (P <0.001), our result is agreement with Alturfan *et. al,* [15], Akcay *et. Al,* [16]. But, it is disagreement with Aihara *et. al,* [5] which they found that no significant difference in plasma Cu concentrations between control subjects and patients with thyroid disease, except a higher significant difference in patients with hyperthyroidism. The reason of increase serum Cu concentration in hyperthyroidism and decrease in hypothyroid may due to the most plasma Cu (approximately 93%) is bound to ceruloplasmin and small fraction to albumin (6–7%) or is chelated to amino acids (< 1%), which is diffusible[20,21]. Thyroid hormones enhance the synthesis of lysozymal enzymes in muscle and are necessary for the catabolic response to a variety of stimuli in this tissue and increase the concentration of free amino acids in plasma [21,22]. In addition, a general increase in plasma amino acid concentrations in hyperthyroid rats has been reported[23]. These findings may provide one explanation for our data that concentrations of serum Cu was lower in patients with hypothyroidism, we did not investigated plasma ceruloplasmin levels and erythrocytes Cu concentrations.

Although, our results showed that there is no correlation between serums T3, T4, TSH, and copper levels in hypothyroidism patients, these results was disagree with finding reported by Akcay *et. al,* [16]. Aihara *et. al,* [5], in which they reported that plasma Cu concentrations correlated well with T3 and T4 levels in patients with thyroid disease, this difference with our results may due to the chosen all patients with hypo – and hyperthyroid in this comparison.

The thyroid function depends on the essential trace element selenium[24]. A major advance in our understanding of Selenium (Se) role in metabolism began with discovery that type I iodothyronine deiodinase, the enzyme responsible in humans for the most peripheral conversion of thyroxine (T4) to the active form 3,'3,5- triiodothyronine (T3), is a selenoenzymes [25].

The current study showed the mean concentration of serum Se was significantly lower in hypothyroidism patients than control subjects, this finding compatible with other finding reported by Chanoine *et. al,* [26], Kubasove *et. al,*[27], Our results showed no statistically significant correlation between serum Se levels and T4. But there is significant negative correlation between serum Se levels and TSH, and positive correlation between Se levels and T3, the reason might be the Se deficiency inhibiting the synthesis and activity of iodothyronine deiodinase[28].

Manganese (Mn) is an essential trace nutrient that is potentially toxic at high levels of exposure, although, little is known about the relationship between manganese and thyroid hormones. It has been speculated that manganese interferes with thyroid hormone binding, transport, and activity at the tissue level [29].

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Our study demonstrated significantly lower serum Mn in hypothyroidism patients compared with normal control, this result compatible with finding reported by Kubasov *et. al,* [27]. Although, our results showed there is no significant correlation between serums Mn concentration and T3, T4, TSH levels. These results were disagree with Eder's study[30], which they showed that manganese deficiency has been also been observed in animal in a two generation female rats study, diet low in Mn concentration led to impaired growth, increased the activity of hepatic 5 deiodinase, and increase in relative concentrations of T3 in their offspring. However the concentration of T4 and freeT4 remained unchanged[30]. This difference between these results and our results may be due to Eder's study[30] depends on supplementation of diet low in Mn concentration but our results depends only the measure of serum Mn in patients, also, our study occur in human while Eder's study doing on animals rats. Moreover, the differences may due to rats regulate thyroid hormone differently, and studies in rats can not be extrapolated to humans because circulating T3 is produced mainly by deiodination of T4 in the liver in human[31], but comes primarily by release from thyroid in rats[32], the human and rats type I deiodinase enzymes are also different in several aspects, including amino acid sequence, molecular weight[33].

Our results on Mg concentration showed significant decrease of serum Mg levels in hypothyroidism patients compared with normal control. Although, our results showed that there is no correlation between Mg levels and T3, T4, TSH levels. This finding is compatible with findings reported by Jeng *et. al,* [34] with exception of lower concentration of plasma T4 in magnesium deficient, this difference with our results may due to our patients received about 100mg of L-thyroxin, and this may leads to elevated serum T4 in the presence of Mg deficiency. Jeng's results showed that the ability of pituitary gland to respond to thyrotropin releasing hormone (TRH), was not influence by Mg deficient. This may be explaining that the decreases serum Mg is not influence on TSH concentration.

Our results showed that hypothyroidism patients associated with higher cholesterol, triglycerides, LDL, and this exhibit increase level of the atherogenic parameters. This is compatible with other studies established that hypothyroidism causes hypercholesterolemia and lipoproteinemia [35,36].

Magnesium is necessary the activity of lecithin cholesterol acyltransferase (LCAT), and lipoprotein lipase (LPL), which lowers triglyceride levels and raises HDL-cholesterol levels. Moreover, Mg(2+)-ATP is also the controlling factor for the rate-limiting enzyme in the cholesterol biosynthesis, which associated with cholesterol levels[37]. Ryuji and Takashi[38] reported that with increase in Mg-intake, lipid indices such as TC, TG, HDL decreased, although, Rayssiguire, *et. al*, [39] reported that Mg deficiency in rats results in an increase in plasma TG and TC levels, this is compatible with our results shown in table-3, which revealed that negative correlation between Mg levels and TC, TG, and

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LDL levels. That is revealed Mg deficiency the alteration in thyroid activity may be partially responsible for the observed hyperlipidemia. It conclude that the trace elements Se, Zn, Cu, Mn, and Mg have altered in hypothyroidism patients; there are correlations between some trace elements (Se, and Zn) and thyroid hormones, but there are no obvious correlations of some trace elements (Cu, Mn, and Mg) status on thyroid hormones.

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