STATUS OF SERUM ZINC LEVELS IN FEMALES WITH THYROID DYSFUNCTION

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ABSTRACT

Background: Low serum zinc levels have been connected to thyroid function in more than one way, but to date there is still arguments about the association between zinc deficiency and thyroid disease, particularly in females. The aim of this study was to assess status of serum zinc levels in a sample of females with thyroid dysfunction in comparison with those of normal thyroid function and to ascertain its association with thyroid hormone levels.

Patients and Methods: A case control study was conducted on 225 females referred to the Endocrine Unit for definitive diagnosis of thyroid dysfunction and 100 females with normal thyroid function, serves as a control group.

Results: The results revealed that the serum zinc levels were significantly lower in Hypothyroid females (62.2±16.3µg/dl) as compared to hyperthyroid (80.5±13.9µg/dl) and controls (86.2±13.2 µg/dl) with p=0.001. The prevalence of severe zinc deficiency (<50 µg/dl) was found to be significantly higher in hypothyroid females (25.0%) as compared to hyperthyroid females (3.0%), p-value of 0.01, whereas none of the controls had severe zinc deficiency. In the hypothyroid group, positive correlations of zinc were observed with FreeT3 and FreeT4 (p=0.007, p<0.001, respectively) and a negative correlation was observed with thyroid stimulating hormone (TSH), p<0.001. In the overall studied subjects, negative correlation was also found for zinc with TSH (p< 0.001). We did not observe a significant correlation of FT3, FT4 and TSH with zinc in controls or in hyperthyroid group.

Conclusions: Decreased serum zinc levels may lead to hypothyroidism in females. Efforts to increase zinc status in this group may help correct abnormal levels of thyroid hormones.

Keywords: Zinc levels, Thyroid dysfunction, Serum of female.

Zinc is an essential element involved in many basic biochemical reactions in thyroid1. It is an essential part of an enzyme 1, 5-deiodinase, which converts thyroxine (T4) into a functional triiodothyronine (T3). If zinc is low or missing from the body, T3 cannot be made2. Many studies have described a marked relationship between serum zinc levels and the thyroid hormones3. Moreover, zinc deficiency may be a risk factor for the hypothyroidism, a condition that is highly prevalent in the Iraqi women4. Nevertheless, the effect of zinc

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on thyroid hormone levels are still not clear and to date there is still arguments about the association between zinc deficiency and thyroid disease, particularly in females\textsuperscript{5,6}. Attempts to assess the relationship between status of serum zinc levels and thyroid dysfunction in our population are limited. We undertook this study to investigate serum zinc levels in females with hypothyroidism and hyperthyroidism and to ascertain its relationship with thyroid hormones.

**MATERIALS AND METHODS**

This study was conducted at Azadi Teaching Hospital, Duhok, Kurdistan Region (Iraq); during the period from February to November 2018. The study was formally approved by the research ethics committee; Directorate of Health of Duhok and the institutional Review Board of Duhok College of Medicine. The non-probability convenience sampling technique was used. It was a case control study, in which a group of females with thyroid dysfunction was compared with a control group of normal thyroid function females to find out the relationship between serum zinc levels and thyroid hormone profiles (FreeT3, FreeT4 and thyroid stimulating hormone, TSH). Serum was obtained randomly from blood samples of 325 females; 225 with thyroid dysfunction (ages 25-70 years of age) and age matched normal thyroid females (n=100) referred to the Endocrine Unit of Azadi Teaching Hospital for definitive diagnosis of thyroid diseases. The diagnosis of hypothyroidism and hyperthyroidism were made first clinically and confirmed biochemically using FT3, FT4 and TSH. The hypothyroid group was those with elevated TSH concentration (> 10 IU/L) in the presence of low concentration of FT4 and/or FT3, while the hyperthyroid group was with suppressed or undetectable TSH concentration(<0.05 IU/L) in the presence of elevated FT4 and/or FT3 concentration. Enrollees who had normal clinical examination as well as normal thyroid function test and with no history of thyroid illness were included as normal thyroid function females (control group). Serum zinc measurement was obtained, and females with serum zinc level between 50 and 70 µg/dl considered with mild-moderate zinc deficiency, and severe deficiency for levels<50 µg/dl. Zinc levels were measured by flame atomic absorption spectrophotometer (Perkin Elmer) using a standard procedure. Serum FT3, FT4 and TSH were performed using commercially available standardized electrochemiuminescence immunoassay (ECLIA) method (Cobas 6000, Roche-Hitachi, Germany)). All data were analyzed using the statistical package for Social Sciences (SPSS) version 21(USA). Independent t-test was used to assess differences in serum analyte among groups. Categorical variables were analyzed by Chi-square test. Pearson’s correlation coefficient was used to describe the association between serum zinc and thyroid hormones. Power analysis was performed for zinc and thyroid hormones with values exceeding 0.90. P-value <0.05 was considered as statistically significant.
RESULTS

Table 1 illustrates the baseline characteristics of the studied females. Overall, hypothyroid females comprised 56.4% (n=127) and hyperthyroid females 43.5% (n=98). The mean serum zinc level was significantly lower in hypothyroid females compared to hyperthyroid and control females.

Table 1. Baseline Characteristics of the Studied Females

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n=100)</th>
<th>Hypothyroid (n=127)</th>
<th>Hyperthyroid (n=98)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.2±13.5</td>
<td>36.7±15.0</td>
<td>36.3±11.6</td>
<td>0.57</td>
</tr>
<tr>
<td>TSH (IU/L)</td>
<td>2.09±4.1</td>
<td>29.8±35.3</td>
<td>0.02±0.04</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>4.5±0.6</td>
<td>4.2±1.4</td>
<td>12.1±10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>14.8±2.5</td>
<td>10.1±4.9</td>
<td>36.1±24.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zinc (µg/dl)</td>
<td>86.2±13.2</td>
<td>62.2±16.3</td>
<td>80.5±13.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2 illustrates the percentage of females with serum zinc levels. Of the three hundred twenty five females, 35(10.5%) had severe zinc deficiency (<50 µg/dl). Of the severe zinc deficiency females, 32(25.2%) were with hypothyroidism, and hyperthyroidism comprise 3(3.0%). Sub-clinical hypothyroidism was present in 48 of the females. The prevalence of females with sub-clinical hypothyroidism according to the current guidelines ranged from 10.4% of females with severe zinc deficiency to 39.6% with mild-moderate zinc deficiency (serum zinc between 50-70ug/dl).

Table 2. Percentage of females with serum zinc levels.

<table>
<thead>
<tr>
<th>Serum zinc (µg/dl)</th>
<th>Overall (n=325)</th>
<th>Control (n=100)</th>
<th>Hypothyroid (n=127)</th>
<th>Hyperthyroid (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50, n (%)</td>
<td>35(10.8)</td>
<td>0(0.0)</td>
<td>32(25.0)</td>
<td>3(3.0)</td>
</tr>
<tr>
<td>50-70, n (%)</td>
<td>75(23.1)</td>
<td>13(13.0)</td>
<td>47(37.0)</td>
<td>15(15.3)</td>
</tr>
<tr>
<td>&gt;70, n (%)</td>
<td>215(66.1)</td>
<td>87(87.0)</td>
<td>48(38.0)</td>
<td>80(81.7)</td>
</tr>
</tbody>
</table>

Table 3 illustrates the relationship between serum zinc and thyroid hormones in hypothyroid and hyperthyroid females. In the hypothyroid group, zinc correlated positively with FT3 and FT4 (p=0.007; p<0.001, respectively) and a negative correlation was observed with TSH (p<0.001). In the overall studied subjects, negative correlation was also found for

Table 3. Correlation coefficient between serum zinc and free T3, free T4 and TSH

<table>
<thead>
<tr>
<th>Thyroid Hormone</th>
<th>Overall r p</th>
<th>Control r p</th>
<th>Hypothyroid r p</th>
<th>Hyperthyroid r p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT3</td>
<td>0.01 0.862</td>
<td>0.07 0.440</td>
<td>0.35 0.007</td>
<td>0.03 0.720</td>
</tr>
<tr>
<td>FT4</td>
<td>1.00 0.070</td>
<td>0.08 0.390</td>
<td>0.44 &lt;0.001</td>
<td>0.11 0.280</td>
</tr>
<tr>
<td>TSH</td>
<td>-0.46 &lt;0.001</td>
<td>-0.07 0.480</td>
<td>-0.56 &lt;0.001</td>
<td>0.06 0.650</td>
</tr>
</tbody>
</table>
zinc with TSH ($p<0.001$). We did not observe a significant correlation of FT3, FT4 and TSH with zinc in controls or in hyperthyroid group.

Figures 1 and 2 shows a positive correlation between serum zinc levels and both free T3 and Free T4 in hypothyroid females ($r=0.35$ and $r=0.44$, respectively).

Figures 3 and figure 4 shows a negative correlation between serum zinc levels and TSH in hypothyroid females and in the overall studied females ($r=-0.56$ and $r=-0.46$, respectively).

**DISCUSSION**
Zinc is one of the essential micronutrients that play a significant role in the metalloenzyme process of the body. Zinc is involved in protein and nucleic acid synthesis, as well as in various metabolic and cellular functions. Some Studies showed that zinc deficiency leads decrease in T3 level. In addition, a potential link between nutritional zinc deficiency and hypothyroidism has been suggested by de Lima et al and Baltaci et al. In our study we investigated females with and without thyroid dysfunction and we found a significant positive correlation between FT3 and FT4 with serum zinc levels in hypothyroid group, but no such correlations in the hyperthyroid and normal thyroid group. Moreover, there
were significant differences in the mean serum zinc levels among the groups. It was observed that, mean serum zinc was lower in hypothyroidism females than in hyperthyroidism and healthy control females. The same manner was observed for prevalence of zinc deficiency when compared among the three groups. The current results are in agreement with finding from previous study\(^\text{10}\), who found that T3 and T4 were significantly lower and TSH significantly higher in zinc deficiency patients and they demonstrated that T3 levels have been increased with zinc supplementation\(^\text{11}\).

The present study also showed that zinc level correlated negatively with TSH in the hypothyroidism females. We found that 25% of females with hypothyroidism and that about 3% of the females with hyperthyroidism had severe zinc deficiency (<50 \(\mu\)g/dl). Such a high prevalence of low zinc status is worth mentioning. The potential link between zinc and thyroid metabolism is based on the hypothesis that T3 receptors, like other nuclear receptors, include nuclear zinc-binding proteins\(^\text{12}\). Therefore, zinc is thought to be an integral part of nuclear receptor proteins, stabilizing them in a conformation required for binding to target genes\(^\text{13}\). Moreover, zinc is also required for the activity of the enzyme 1, 5-deiodinase, which converts biologically inactive T4 to biologically active T3\(^\text{14,15}\). The fact that zinc levels are lower in hypothyroidism females, it is important to note that stronger association between hypothyroidism and zinc values have been reported for women compared with men\(^\text{16}\).

Our study confer a high proportion (62\%) of females with hypothyroidism, but not normal thyroid females (13\%) or females with hyperthyroidism (18.3\%), had serum zinc levels (<70 \(\mu\)g/dl). These may suggest an important mechanism through which zinc can influence higher risk of hypothyroidism in our population. Indeed, several Iraqi studies reported that nutritional zinc deficiency is prevalent in our population, particularly females at child bearing age\(^\text{17,18}\). This appears to be a new finding as previous study by Mocayo et al\(^\text{19}\) reported that neither zinc nor selenium correlated with thyroid function in benign thyroid disease.

The lack of correlations between serum zinc level and thyroid hormones in hyperthyroid females seems to be similar to the results of other studies\(^\text{20,21}\), but in contrast to others\(^\text{22,23}\). This discrepancy of our results as compared to those of other studies may be related partly to the nutritional zinc status. However, several factors are known to make a negative impact on zinc status, particularly in females. Of these pregnancy and lactation are the factors which cause the most marked negative effects on serum zinc levels\(^\text{24,25}\). The current study has shown a similarity in serum zinc levels among hyperthyroid females and normal thyroid females, although none of the studied females were pregnant. Another probable explanation is that TSH has significant influence in the variation of zinc concentration in normal and changed human thyroid tissues\(^\text{26}\).

The results confirm that zinc deficiency may play a role in thyroid function. We have shown positive correlations between FT3 and FT4 with zinc and negative correlation between TSH and zinc in hypothyroid females. Efforts to increase
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zinc status in patients with hypothyroidism may help to normalized thyroid hormone levels.

ACKNOWLEDGEMENT
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REFERENCES
پیشی‌کش: گرندان دنا ویه نرمی نازیک دی که خوینی دا ب کارین سایروده رژین فه ب پتر زه کی.

نامه: نارامین زهام کوئینی نیوه هامسانگاندا باره رژیستانی زینک د سیروما خوینی دا ل دفوان نافرذین رازه د سایروده رژین دا ههین، بین ساردنان ییکا رژیتان نینکوشدنی کری ل نمکوشخانات نازاریدی یا تیازکه‌ر ل پاره‌گه‌ه دهوك.

ریکینگ‌کوئینی: فکیلیم ل سر 225 نافرذین هاکه‌سین بین ناماده‌بون‌ه ل ییکا رژیتان نینكرودینی بو دست‌بستن‌اندازه‌ه د کنیم‌ا کارئی سایروده رژین دا و 100 نافرذین دی کو سایروده رژینا وان ناسی کارده‌که و مک کووما کونترولی پان بندما.

ناتنیم: ناخنامان دیابرسی کو نئسنیکی د سیروما خوینی دا یا کم بو یزنونی دی دار لدف نافرذین ناریشه د سایروده رژین دا ههین (62.2±16.3ماکروگرام/دیسیلیتر) ب هامبکرکن دگل نافرذین ناریشه د زینک دیاکی سایروده رژین دا ههین (80.5±13.1ماکروگرام/دیسیلیتر) و نافرذین ساختم (86.2±13.1ماکروگرام/دیسیلیتر). (ص=0.001)

هاتیقاها کو کم‌بیونکا دوزار د نئسنیکی دا یا ههین (50ماکروگرام/دیسیلیتر) کو دیته‌ بلندترین نافرذین ناریشه د سایروده رژین دا ههین (25%) ب هامبکرکن نگل نافرذین ناریشه د زینک دیاکی سایروده رژین دا ههین (3.0%) د هماما دم د چ بارین کیم‌بیونکا دوزار د نئسنیکی د سایروده رژین دا ههین نبه‌ون.

د کوما ناریشه د سایروده رژین دا ههین دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دا TSH,P=0.010FT3,P=0.007,FT4,P=0.001 و دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دا TSH,P=0.001FT3,P=0.007,FT4,P=0.001 ههی، هامبکرکن و دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دگل 1 ههی، و دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دگل 1.0 ههی، و هامبکرکن سایروده رژین دا ههین.

د کوما ساختم و ناریشه د TSH,FT3,FT4 زینک دگل 0.010 و 0.007,0.001 نئسنیکی یا زینکی دگل 1 ههی، و دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دگل 1.0 ههی، و هامبکرکن سایروده رژین دا ههین.

ناتنیم: ناخنامان دیابرسی یا پیوپمونیکا نئسنیکی یا زینکی دا دیبه دگل دیازه نیکی که کارئی ناماده‌بون‌ه د نافرذین دا دیازه نیکی دی که کارئی یازدکفتن د سایروده رژین دا نافرذین دا. زینکندنی زینکی د ینه کومی دا دی بیته هاریکبار بو راست‌که‌که نئسنیکی سایروده رژین.
الخلاصة

حالة مستويات مصل الزنك في الإناث المصابات بخلل في الغدة الدرقية

الخلفية والأهداف: لقد تم ربط مستويات الخارضين المنخفضة في الدم بوظائف الغدة الدرقية في أكثر من طريقة واحدة. الهدف من الدراسة الحالية هو تقييم حالة مستويات الخارضين في مصل الدم لدى الإناث اللواتي يعانيين من خلل في وظائف الغدة الدرقية وتأكيد العلاقة مع هورمونات الغدة الدرقية.

المواضيع وطرق البحث: تم جمع الدراسة على 225 حالة من الإناث اللواتي حضرن وحدة الغدد الصماء للتشخيص النهائي من الخلل في وظيفة الغدة الدرقية و100 من الإناث مع وظيفة الغدة الدرقية العادية بمثابة المجموعة الضابطة.

النتائج: أظهرت النتائج ان مستويات الخارضين في مصل الدم كانت أقل بشكل ملحوظ في الإناث المصابين بخمول الغدة الدرقية (62±16 ميكروغرام/ديسيليرتر) بالمقارنة مع الإناث المصابين بزيادة نشاط الغدة الدرقية (80.5±13 ميكروغرام/ديسيليرتر) والإناث الإصحاء (86.2±13 ميكروغرام/ديسيليرتر) (P=0.001). تم العثور على انتشار تقص الخارضين الشديد (>50 ميكروغرام/ديسيليرتر) لدى أكبر كثيرة لدى الإناث المصابين بخمول في الغدة الدرقية (25%) بالمقارنة مع الإناث المصابين بزيادة نشاط الغدة الدرقية (3.0%), بينما لم تكن هناك أي حالة تقص شديد للخارضين بين مجموعه الإصحاء.

في المجموعة الخمول في الغدة الدرقية لوحظ ارتباط أيجابي من الخارضين مع هورمون الغدة النخامية. ولم تكن هناك ارتباط كبير بين الخارضين وكل من TSH, FT3, FT4 في مجموعة الإصحاء ومجموعه زيادة نشاط الغدة.

الاستنتاجات: انخفاض مستويات الزنك في الدم قد يؤدي إلى قصور الغدة الدرقية عند الإناث. قد تساعده الجهد المبذول لزيادة حالة الزنك في هذه المجموعة على تصحيح مستويات غذاء طبيعية من هورمونات الغدة الدرقية.