Correlation between vitamin D3 (cholecalciferol) and thyroid diseases in Iraqi patients

Reem M. Obaid 1*, Farah Tareq Yaseen2 and Alia Kadhim Salim3

1. Ph.D. in Physiology (Endocrinology) from college of science, University of Baghdad, a lecturer in a medical Laboratory Techniques Department, Al-Farabi University College, Baghdad- Al-Doura, Iraq.

2. Farah Tareq Yaseen, MS.c. in Zoology from college of science, University of Baghdad, a lecturer in a medical Laboratory Techniques Department, Al-Farabi University College, Baghdad- Al-Doura, Iraq.

3. Alia Kadhim Salim, Ph.D. in Medical paracytology From college of veterinary medicine, University of Baghdad, a lecturer in a medical Laboratory Techniques Department, Al-Farabi University College, Baghdad- Al-Doura, Iraq.

*Corresponding Author: E-mail: reem_m2478@yahoo.com (Reem)

Abstract:
Vitamin D is a type of fat-soluble vitamins that is responsible for increasing intestinal absorption of calcium, magnesium, and phosphate. Synthesis of D3 occurs in the lower layers of the skin through a chemical reaction that is dependent on sun exposure. Low levels of vitamin D have also been associated with autoimmune thyroid diseases (AITD) such as Hashimoto Thyroiditis (HT) and Grave’s Disease (GD). We aimed in our study to examine the relationship between thyroid diseases and vitamin D3 levels and to clarify the relationship between sex, age and weight with vitamin D3 in Iraqi patients. The study included 100 individuals (50 men and 50 women) age ranged from (10-80) years old, body weight of 21-98 Kg. They are divided into three groups: control group (group with normal T4 level), high T4 level group and low T4 level group. D3, T3, T4 and Thyroid Stimulating Hormone (TSH) were measured for all patients.

Our results showed that the Mean ± SE of D3 in control group was higher than that of low and high T4 patients, no significant negative correlation coefficient between age, body weight and D3, a significant negative correlation coefficient between TSH, T3 and D3(P≤0.01), but a positive correlation coefficient between D3 and T4. We concluded that Iraqi patients with hypothyroidism suffering from deficiency in vitamin D3. Moreover D3 deficiency associated with age, body weight and sex.

Keywords: cholecalciferol, ergocalciferol, Graves’s disease, Hashimoto thyroiditis, autoimmune thyroid disease

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1. Introduction:
Vitamin D is a type of fat-soluble vitamins that responsible for increasing intestinal absorption of calcium, magnesium, and phosphate. The most important compounds in this group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Synthesis of D3 occurs in the lower layers of the skin through a chemical reaction that is dependent on sun exposure [1]. D3 and D2 can be ingested from the diet and from supplements. Only a few foods, such as fatty fish, contain high amounts of vitamin D. Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk [2].
The structural difference between vitamin D$_2$ and vitamin D$_3$ is the side chain of D$_2$ contains a double bond between carbons 22 and 23, and a methyl group on carbon 24. Vitamin D also affects the immune system, and vitamin D receptors (VDRs) are expressed in several white blood cells, including monocytes and activated T and B cells. Severe vitamin D deficiency in children causes rickets, a softening and weakening of bones, which is a rare disease in the developed world [3]. Vitamin D deficiency is found worldwide in the elderly and remains common in children and adults [4]. Maternal vitamin D deficiency may cause overt bone disease from before birth and impairment of bone quality after birth [5]. Osteomalacia is a disease in adults that results from vitamin D deficiency. Although the effects of osteomalacia are thought to contribute to chronic musculoskeletal pain [6]. Dark-skinned people living in temperate climates have been shown to have low vitamin D levels [7]. Dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis [8,9]. Supplementation with higher doses of vitamin D, in those older than 65 years, may decrease the risk for many diseases [10]. AITD, including HT and G.D., are the most common organ-specific autoimmune disorders [11]. These AITDs are polygenic diseases resulting from a combination of genetic predisposition (thyroid-specific genes and immune-modulating genes) and environmental triggers (iodine, selenium, drugs, irradiation, smoking, infections, stress, etc.), characterized by lymphocytic infiltration into the thyroid gland and production of thyroid-specific autoantibodies [12].

Aims of the study:
We aimed to examine the relationship between thyroid diseases and vitamin D3 levels and to clarify the relationship between sex, age and weight with vitamin D3 in Iraqi patients.

2. Materials and Methods:

2.1. The experimental groups:

The study included 100 individuals (50 men and 50 women) age ranged from (10-80) years old, body weight of 21-98 Kg. They were divided into three groups: control group (group with normal T4 level), high T4 level group and low T4 level group.

2.2. Laboratory investigations:

2.2.1. Measuring of T3, T4 and TSH hormones in the serum by using TOSOH AIA 360 full automated (Japan), depending on Florescent enzyme immunoassay technology (FEIAT).

2.2.2. Measuring of D3 vitamin in the serum:

The test performed by using Roche Cobas e411 a product of Roche Company (Us FDA approved).

2.3. Statistical analysis:

The Statistical Analysis System- SAS (2012) program [13] was used to detect the effect of difference factors in study parameters. Least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significant compare between means. Estimate of correlation coefficient between variables in this study.

3. Results:

Table (1) showed that the Mean ± SE of D3 in control group was higher than that of low and high T4 patients. There is no significant differences in Mean ± SE of D3 between control group and high T4 patients, a significant difference between (control, high T4) groups and low T4 patients at (P≤0.05).

Table 1: Comparison between different groups in D3 level

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SE of D3 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23.20 ± 2.13 a</td>
</tr>
<tr>
<td>Low T4</td>
<td>10.37 ± 2.21 b</td>
</tr>
</tbody>
</table>

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In table (2), the Mean ± SE of TSH in low T4 group was significantly differs from Mean ± SE of TSH in both control and high T4 groups at (P≤0.01), the LSD value was 1.727. There is a no significant difference in Mean ± SE of T3 between three groups. A significant difference in the Mean ± SE of T4 between three groups (P≤0.01), the LSD value was 22.276.

**Table 2: Comparison between different groups in hormones level**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SE</th>
<th>TSH (mIU/ml)</th>
<th>T3 (ng/ml)</th>
<th>T4 (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.066 ± 0.22 b</td>
<td>1.420 ± 0.17 a</td>
<td>82.96 ± 2.80 b</td>
<td></td>
</tr>
<tr>
<td>Low T4</td>
<td>4.060 ± 1.27 a</td>
<td>1.836 ± 0.54 a</td>
<td>44.43 ± 11.49 c</td>
<td></td>
</tr>
<tr>
<td>High T4</td>
<td>1.560 ± 0.84 b</td>
<td>1.598 ± 0.18 a</td>
<td>134.26 ± 17.22 a</td>
<td></td>
</tr>
<tr>
<td>LSD value</td>
<td>1.727 **</td>
<td>1.064 NS</td>
<td>22.276 **</td>
<td></td>
</tr>
</tbody>
</table>

Means having different letters in same column differ significantly. ** (P≤0.01).

Our results in table (3) showed no significant negative correlation coefficient between age, body weight and D3, a significant negative correlation coefficient between TSH, T3 and D3 (P≤0.01), but a positive correlation coefficient between D3 and T4.

**Table 3: Correlation coefficient between D3 and other variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient –r with D3</th>
<th>Level of Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>-0.45</td>
<td>**</td>
</tr>
<tr>
<td>T3</td>
<td>-0.29</td>
<td>*</td>
</tr>
<tr>
<td>T4</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight</td>
<td>-0.16</td>
<td>NS</td>
</tr>
</tbody>
</table>

** (P≤0.01), NS: Non-Significant.

In table (4), when we study the effect of sex, age and body weight on D3 level, there is a no significant differences in the Mean ± SE of D3 between males and females, no significant difference in the Mean ± SE of D3 between age groups, another no significant difference in the Mean ± SE of D3 was seen between body weight groups.

**Table 4: Effect of sex, age and body weight on D3 level**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Mean ± SE of D3 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20.47 ± 3.36</td>
</tr>
<tr>
<td>Female</td>
<td>22.16 ± 2.16</td>
</tr>
<tr>
<td>LSD value</td>
<td></td>
</tr>
<tr>
<td>Least than 30</td>
<td>22.58 ± 3.93</td>
</tr>
<tr>
<td>30-50</td>
<td>21.56 ± 2.68</td>
</tr>
<tr>
<td>More than 50</td>
<td>21.03 ± 2.90</td>
</tr>
</tbody>
</table>

** (P≤0.01), NS: Non-Significant.
Table 5 showed that there is no significant difference in the Mean ± SE of TSH and T4 between males and females but a significant difference in the Mean ± SE of T3 (LSD= 0.627). A no significant difference in the Mean ± SE of TSH, T3 and between age groups (LSD was 1.283, 0.699, 21.760 respectively), another no significant difference in the Mean ± SE of TSH and T3 between body weight groups, but a significant difference was observed between them in the Mean ± SE of T4.

Table 5: Effect of sex, age and body weight on hormones level

<table>
<thead>
<tr>
<th>Factors</th>
<th>TSH (mIU/ml)</th>
<th>T3 (ng/ml)</th>
<th>T4 (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.49 ± 0.66</td>
<td>1.94 ± 0.46 a</td>
<td>76.93 ± 6.88</td>
</tr>
<tr>
<td>Female</td>
<td>2.12 ± 0.23</td>
<td>1.30 ± 0.06 b</td>
<td>87.40 ± 5.49</td>
</tr>
<tr>
<td>LSD value</td>
<td>1.151 NS</td>
<td>0.627 *</td>
<td>19.518 NS</td>
</tr>
<tr>
<td><strong>Age groups (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 30</td>
<td>2.32 ± 0.39</td>
<td>1.28 ± 0.11</td>
<td>92.81 ± 9.02</td>
</tr>
<tr>
<td>30-50</td>
<td>1.71 ± 0.17</td>
<td>1.25 ± 0.06</td>
<td>82.29 ± 2.61</td>
</tr>
<tr>
<td>More than 50</td>
<td>2.58 ± 0.56</td>
<td>1.84 ± 0.35</td>
<td>79.15 ± 8.75</td>
</tr>
<tr>
<td>LSD value</td>
<td>1.283 NS</td>
<td>0.699 NS</td>
<td>21.760 NS</td>
</tr>
<tr>
<td><strong>Body weight groups (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 40</td>
<td>2.12 ± 0.50</td>
<td>1.25 ± 0.16</td>
<td>101.31 ± 12.4 a</td>
</tr>
<tr>
<td>40-50</td>
<td>1.86 ± 0.28</td>
<td>1.31 ± 0.06</td>
<td>83.71 ± 3.31 ab</td>
</tr>
<tr>
<td>More than 50</td>
<td>2.62 ± 0.49</td>
<td>1.75 ± 0.32</td>
<td>76.95 ± 7.78 b</td>
</tr>
<tr>
<td>LSD value</td>
<td>1.348 NS</td>
<td>0.734 NS</td>
<td>22.859 *</td>
</tr>
</tbody>
</table>

Means having different letters in the same column differ significantly. * (P≤0.05), NS: Non-Significant.

The following figures explain the comparison between different groups in D3, TSH, T3 and T4 levels.
Figure 1: Comparison between different groups in D3

![Comparison between different groups in D3](image1)

Figure 2: Comparison between different groups in TSH

![Comparison between different groups in TSH](image2)
D3 is a steroid (fat soluble) vitamin, produced in the skin [14]. D3 receptors found in most tissues in the body and have many roles especially in the regulation of calcium and phosphorous homeostasis. Recently, many studies suggest that D3 deficiency has an important role in autoimmune diseases, cancers, cardiovascular diseases and mortality [14, 15, 16, 20]. Low levels of vitamin D have also been associated with AITD such as HT and GD [17, 18, 19, 21]. Few studies have been conducted in order to find any significant association between the levels of vitamin D and hypothyroidism and to determine whether vitamin D deficiency involves in the pathogenesis of hypothyroidism or rather a consequence of the disease and those that yielded conflicting results. According to our knowledge, there are some researchers examined the prevalence of vit D deficiency in Iraqi populations but our study was one from few studies aimed to examine the association between Vit D levels with hypo and hyper-thyroidism in Iraq mainly Baghdad city. We therefore undertook this study to evaluate the levels of vitamin D among patients with hypo and hyper-thyroidism compared to healthy controls who did not complain from any thyroid diseases.

Our results revealed a non significant decreased serum vitamin D levels in females than those of male controls and patients that similar to author [22]. In concordance to our results, previous studies have observed that serum vitamin D levels did not differ significantly between males and females [23, 24]. Moreover, Hashemipour et al [25] studied the prevalence of vitamin D in Tehran and found non-significant differences between males and females. Our results are in disagreement with the results of Sedrani,[26] Al-Jurayyan et al,[27] Fida, [28] Naeem et al, [29] stated that vit D serum levels are significantly more decreased in females than males. Although several authors revealed higher serum levels of vitamin D in normal men than in normal women, [30, 31, 32] data has not been available for patients with hypothyroidism. In Iraqi patients, the prevalence of vitamin
D deficiency was non-significantly lower in the elderly persons (more than 50 years old) than in young persons (less than 30 years old) of both sexes.

However, a study from Japan including 200 patients with G.D. found vitamin D deficiency in 40% of women and around 20% of men (p < 0.005) [33]. The differences between these studies may be related to the differences in the selection of patients, dietary vitamin D intake, duration of exposure to sunlight, and seasonal variations. Furthermore, the present study showed that vitamin D serum levels were significantly lower in hypothyroid (low T4) patients compared to the controls (as in table 1). We recorded no significant positive correlation coefficient between vitamin D3 and T4 levels (table 3).

Vitamin D serum levels had negative correlation when compared to TSH levels. These results suggested that there may be a significant association between vitamin D deficiency and hypothyroidism. Our results were in agreement with the previous studies that showed the prevalence of vitamin D insufficiency in Hashimoto’s cases (92%) was significantly higher than that observed in healthy controls (63%, p < 0.0001) [34,35]. The reason for these results (low levels of vitamin D in patients with hypothyroidism) may be due to poor absorption of vitamin D in the intestine, or the body may not activate vitamin D properly. Other articles have demonstrated that patients with G.D. also have low levels of Vitamin D [36]. Because thyroid hormone is a steroid hormone and vitamin D3 is a fat soluble vitamin thus, they are both bind to similar receptors called steroid hormone receptors. Vitamin D inhibits the production of Th1 polarizing cytokine (IL-12), thereby indirectly shifting the polarization of T cells from a Th1 toward a Th2 phenotype. In the CD4+ T cell response, vitamin D directly inhibits the production of Th1 cytokines (IL2 and IFN-c), and enhances Th2 cytokine (IL-4) production [37]. In addition, recent numerous studies have shown the relation of vitamin D and various autoimmune diseases. VDR gene polymorphisms and vitamin D status are associated with different autoimmune diseases [38,39]. Furthermore, vitamin D supplementation prevented the onset and development of several kinds of autoimmune diseases in humans and animal models [37].

Many research have demonstrated a role of vitamin D in G.D.; either vitamin D related gene polymorphisms such as VDR gene and vitamin D binding protein gene are associated with G.D. or vitamin D deficiency modulates Graves’ hyperthyroidism induced by thyrotropin receptor immunization in BALB/c mice or vitamin D analog inhibits inflammatory responses in human thyroid cells and T cells [40, 41].

Conclusion

Our results indicated that Iraqi patients with hypothyroidism suffering from deficiency in vitamin D3. Moreover, the positive correlation between serum vit D with T4 and negative significant correlation with TSH levels. Screening for Vitamin D deficiency recommended for all hypothyroid Iraqi patients to avoid osteoporosis if the deficiency continued.

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References:


