# Vitamin D Status and Autoimmune Disease (Hashimoto's Thyroiditis) in Saudi Arabian Women

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## ABSTRACT

Recently, the role of vitamin D on autoimmune disorders has been investigated by several researchers. Hashimoto's thyroiditis (HT) chronic inflammation is one of autoimmune disorders, caused by environmental and genetic factors that may lead to produce antibodies from immune system that attacked thyroid gland, however; causes are not yet completely understood.

Objective: To examine the 25 hydroxy vitamin D (25(OH) D3) status in Saudi Arabian females with HT Saudi female.

Subjects and Methods: A cross-sectional study was recruited 50 female patients diagnosed by HT aged 20 and above, from King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Patients were on specific routine of LT4 medication for a minimum 6 months. Blood samples were collected to measure the levels of 25(OH) D3, thyroid stimulation hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and calcium.

Results: Biochemical data revealed that mean values for vitamin D among the three vitamin D categories were significant ($P<0.05$). There was insignificant relationship between vitamin D and TSH, as well as between vitamin D and FT3 ($r=0.147$, $r=0.148$, $P>0.05$) respectively. In addition, there was insignificant negative correlation between calcium level and TSH, and FT3 ($r= -0.121$, $r=-0.264$, $P>0.05$), respectively. Although there was a significant relationship between BMI categories and vitamin D levels, the study observed that majority of obese patients had high percentage of vitamin D deficiency.

Conclusion: There was no association between 25(OH) D levels and HT among Saudi Arabian women. However, significant difference was found between vitamin D status in patients having insufficient and sufficient level ($P < 0.05$).

**Key Words:** Hashimoto's Thyroiditis (HT), Vitamin D, Calcium, Hypothyroid Disease.

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## INTRODUCTION

Hashimoto's thyroiditis (HT) one of the most common endocrine disorders, is caused by the interaction between environmental and genetic factors, which until now is not fully understood [1]. Vitamin D deficiency is one of the main epidemic health problem [2], and in Saudi Arabia more than 92% of population suffer from it and more obvious in females especially in earlier age groups than males [3]. Vitamin D is a secosteroid hormone and can be synthesized by 7-Dehydrocholesterol in the skin and converted to active form by 2 hydrolyzed to active form 1.25-dihydroxyvitamin D [1.25(OH)2D3] [1]. This active form has many biological important effects on bone metabolism, cell differentiation and immune regulation [4]. Epidemiological researches have associated vitamin D insufficiency with autoimmune diseases such as systemic autoimmune thyroiditis, rheumatoid arthritis, and lupus erythematous [5,6]. Clinical trials have revealed that vitamin D deficiency has demonstrating an increase incidence of HT [7, 8]. Some studies suggest that vitamin D supplementation inhibit the autoimmune reaction, which results in a reduction in the levels of thyroid autoantibodies [9, 10]. Therefore, the purpose of the study was to assess vitamin D status among HT Saudi female.

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## SUBJECTS AND METHODS

The study was done in King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Research protocol was approved by the Ethical Research Committee in King Abdulaziz University Hospital. The procedure was carefully clarified to all participants, and written consent was obtained signed from all subjects.

### Study design

A cross-sectional study was conducted in 50 Saudi female participants, diagnosed with hypothyroidism, or selected upon routine screening at the endocrinology outpatient clinic in King Abdulaziz University Hospital, Jeddah, Saudi Arabia from September 2015 to November 2016.

### Inclusion criteria

Females age ≥20 years, with hypothyroidism, taking LT4 medication for at least six months, with no history of liver or renal disorders, thyroid disease or surgery, primary hyperparathyroidism, any medication history that involved taking calcium or vitamin D supplements were enrolled in the study.

## METHODS

General information was collected including age, health status, social status, and educational level. Also, height and weight were measured for each patient to calculate body mass index (BMI). Subjects were classified as obese if BMI was ≥ 30, overweight if BMI was (25-29.9), normal if BMI was (18.50-24.9) and underweight if BMI was <18.50. Color analyzer was measured to each participant as light, normal, reddish and dark. Skin color was determined depended on how much pigmentation in their skin by using standardized color charts [11]. Patients were requested to fast for 8 hours before collecting blood samples to examine selected biochemical tests.

### Biochemical analysis

### Estimation of thyroid function test

The levels of serum TSH (reference range, 0.27-4.2 mIU/L), free $T_3$ ($FT_3$) (reference range, 2.8–7 pmol/L), free $T_4$ ($FT_4$) (reference range, 12–22 pmol/L) were examined by using the automated immunechemiluminescent assay (ICMA) kits (Abbott, IL, USA).

### Estimation of serum 25 (OH) D3

All sera of subjects were determined for 25(OH) D3 levels by ECLA using a commercial kits (Roche). Vitamin D status was well-defined as deficiency with serum level of 25(OH) $D_3$ of ≤30 nmol/L and insufficiency as a serum level between >30 nmol/L and <50 nmol/L and normal >50 nmol/L.

### Determination of serum calcium

Serum calcium level was determined by using the automated immunochemiluminescent assay (ICMA) kits (Abbott, IL, USA). The reference range (2.12–2.52 mmol/L).

### Statistical analysis

The results of the study analyzed by using SPSS program version (24.0). Various statistical models performed statistical analysis. The descriptive statistics used to compute means and variances. Chi-square test performed to find out the relationship between categorical variables among studied hypothyroidism women, as well as, it utilized analysis of variance Kruskal-Wallis test to measure the changes between groups. Pearson correlation coefficient test measured to detect the relationships between both of vitamin D level and TSH, FT3, FT4 and calcium levels, with P-value ≤ 0.05 was considered as a significant level.

## RESULTS

### General physiognomies of hypothyroidism patients

Table (1) showed general characteristics of the hypothrodisum patients included in the current study. The study revealed that, the majority of hypothrodisum participants are in the age categories between 20-29 and 30-39 Y with percent (30 and 34%) respectively. Concerning BMI, about half 46 % of patient (n=23) are obese with BMI >30 kg/$m^2$, 20 % are overweight (n=10). Regarding education level, 44 % of the hypothrodisum patients (n=22) finished the university or master, while only 26 % of them finished secondary (n=13). Social status data revealed that, the majority of hypothrodisum patients in the study are married 64% (n=32). Regarding health status, 92 % of the hypothyroidism patients (n=46) did not complain from any kind of diseases. Lastly, 40% from patients had normal facial skin color, while 38% had reddish color.

### Vitamin D classification among hypothyroidism patients

Results in Table (2) showed the classification of hypothyroidism patients according to vitamin D level. It showed that 18 patients (36%) had deficiency of vitamin D with the mean values of (18.24 ± 6.42nmol/L), 11 patients (22%) had insufficiency of vitamin D with the mean values of (40.21 ± 5.58nmol/L), while 42% (21 patients) had sufficient vitamin D with the mean values of (72.53 ± 24.36 nmol/L). Data demonstrated that there was a significant difference between numbers of patients having insufficient and sufficient vitamin D (P< 0.05).

### Biochemical indices of hypothyroidism patients

Table (3) illustrated the result of serum biochemical analysis for hypothyroidism patients; calcium, TSH, vitamin D, FT3 and FT4 levels. The results indicated that, calcium, FT3 and FT4 levels are normal (2.20 ±0.11mmol/L, 3.86 ±0.84Pmol/L and 12.07 ±2.43Pmol/L) respectively. On the other hand, TSH level for patients are elevated (14.21± 19.36 nmol/L). Vitamin D of hypothyroidism patients was low (45.87± 29.24 nmol/L), when compared to the reference range (50-80 nmol/L).

### Relationship between vitamin D classifications and facial skin color

Table (4) showed the correlation between vitamin D classifications and facial skin color categories. As shown, there was no significant relationship between facial skin color categories and vitamin D levels. Higher percentage of reddish facial skin color patients observed in vitamin D deficiency group (44.4%); while, normal facial skin color has been higher in percentage in vitamin D insufficient and sufficient groups with (45.5%and 47.6%), respectively.



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### Relationship between vitamin D concentration and anthropometric measurements

Table (5) demonstrated the association between vitamin D concentration and anthropometric measurements of hypothyroidism patients. As shown, there were insignificant differences between vitamin D groups in regards to the height (P>0.05). However statistically significant differences (P<0.05) between vitamin D groups were observed in related to weight and BMI, where weight and BMI were highest in deficiency level of vitamin D.

**Table 1.** General characteristics of the hypothyroidism patients

| Parameters | | N | % |
|---|---|---|---|
| **Age (Years)** | 20 - 29 | 15 | 30 |
| | 30 - 39 | 17 | 34 |
| | 40 - 49 | 12 | 24 |
| | >50 | 6 | 12 |
| **Educational Level** | Illiterate | 2 | 4 |
| | Elementary | 7 | 14 |
| | Intermediate | 6 | 12 |
| | Secondary | 13 | 26 |
| | University and above | 22 | 44 |
| **Marital status** | Single | 12 | 24 |
| | Married | 32 | 64 |
| | Widower | 2 | 4 |
| | Absolute | 4 | 8 |
| **Disease status** | No | 46 | 92 |
| | Yes Hypertension (N=1) High blood cholesterol (N=3) | 4 | 8 |
| **BMI** | 29.73 ± 8.59* | | |
| | Under weight (<18.5) | 2 | 4 |
| | Normal (18.5 - 24.9) | 16 | 32 |
| | Overweight (25 - 29.9) | 10 | 20 |
| | Obese (>30) | 22 | 44 |
| **Facial Skin Color** | Light | 9 | 18 |
| | Normal | 20 | 40 |
| | Reddish | 19 | 38 |
| | Dark | 2 | 4 |

Data are represented as number and percent (N=50).* Mean ± SD.

**Table 2.** Distribution of hypothyroidism patients according to vitamin D classification

| Vitamin D Classification | N (%) | Mean ± SD | Mean Rank* | Chi-Square | df | P-value |
|---|---|---|---|---|---|---|
| **Deficiency** (≤30 nmol/L) | 18 (36) | 18.24±6.42 | 9.50 | 42.607 | 2 | 0.000 |
| **Insufficiency** (30 to <50 nmol/L) | 11 (22) | 40.21±5.58 | 24.00 | | | |
| **Sufficiency** (≥50 nmol/L) | 21 (42) | 72.53±24.36 | 40.00 | | | |

Data are represented as number and percent (N=50). Kruskal Wallis Test. P-value < 0.05

**Table 3.** Serum biochemical analysis for hypothyroidism patients

| Biochemical indices | Mean ± SD | Reference value |
|---|---|---|
| **TSH** (mlU/L) | 14.21 ±19.63 | 0.27 - 4.2 |
| **FT3** (pmol/L) | 3.86 ± 0.84 | 2.8 - 7 |
| **FT4** (pmol/L) | 12.07 ± 2.43 | 12 - 22 |
| **Vitamin D**(nmol/L) | 45.87 ±29.24 | 50 - 80 |
| **Calcium** (mmol/L) | 2.20 ± 0.11 | 2.12 – 2.52 |

**TSH:** Thyroid stimulating hormone, **FT3:** Free triiodothyronine, **FT4***:* Free thyroxine

Data are represented as number and percent (N=50).

**Table 4.** Association between vitamin D classifications and facial skin color

| Vitamin D and Skin Color | | Light | Normal | Reddish | Dark | Total | Chi-Square | P-value |
|---|---|---|---|---|---|---|---|---|
| Deficiency (<30 nmol/L) | N | 4 | 5 | 8 | 1 | 18 | 2.30 | 0.89 |
| | % | 22.2 | 27.8 | 44.4 | 5.6 | 100 | | |
| Insufficiency (30 to <50 nmol/L) | N | 2 | 5 | 4 | 0 | 11 | | |
| | % | 18.2 | 45.5 | 36.4 | 0 | 100 | | |
| Sufficiency (>50 nmol/L) | N | 3 | 10 | 7 | 1 | 21 | | |
| | % | 14.3 | 47.6 | 33.3 | 4.8 | 100 | | |

Data are represented as number and percent (N=50).

**Table 5.** Correlation between vitamin D and anthropometric measurements

| Anthropometric indices | Mean ±SD | Vitamin D classification | N | Mean Rank | Chi-Square | P- value |
|---|---|---|---|---|---|---|
| Height (Cm) | 156.32 ±8.12 | Deficiency | 18 | 28.08 | 1.398 | 0.497 |
| | | Insufficiency | 11 | 21.50 | | |
| | | Sufficiency | 21 | 25.38 | | |
| Weight (Kg) | 72.50 ± 20.42 | Deficiency | 18 | 32.97 | 9.645 | 0.008 |
| | | Insufficiency | 11 | 15.95 | | |
| | | Sufficiency | 21 | 24.10 | | |
| BMI (Kg/cm2) | 29.73 ± 8.59 | Deficiency | 18 | 31.56 | 7.443 | 0.024 |
| | | Insufficiency | 11 | 16.36 | | |
| | | Sufficiency | 21 | 25.10 | | |

Data are represented as number and percent (N=50). Kruskal Wallis Test.

## Correlation between vitamin D classifications and TSH, FT3, FT4, and calcium

Table (6) showed the correlation between vitamin D concentration and TSH, FT3, FT4, and calcium of hypothyroidism patients. As shown, there was insignificant differences between vitamin D groups with regards to the TSH, FT3, FT4, and calcium (P > 0.05).

## Pearson correlation coefficient between biochemical indices

Table (7) showed the correlation coefficient between both of vitamin D, TSH, FT3, FT4 and calcium levels. As shown there are a positive correlation between FT4 and FT3 level (r= 0.384, p= 0.006), means as long as FT3 level increase will FT4 level increase too, and vice versa. On the other hand, TSH level was negatively and significant (P<0.05) correlated with both FT4 (r= - 0.402) and FT3 (r = - 0.282), means as long as TSH level increase will lead to decrease of FT3 and FT4. According to calcium level correlation with TSH, FT3, FT4, and vitamin D, results showed insignificant correlation (P>0.05) between calcium level and TSH and FT3 (r= -0.121, r = -0.264, respectively). While there was positive correlation but not significant between calcium level and vitamin D status (r=0.22, P>0.05). It seems that there is no association between calcium level and FT4, since r = 0.008 and P>0.05. Finally, regarding the relationship between vitamin D and all other parameters, it was illustrated that correlation between vitamin D level and TSH level was insignificant (r=0.147, P>0.05); while, it was negative with FT3 level (r=0.148, P>0.05), and finally having almost no correlation with FT4 level (r=0.061, P>0.05).

**Table 6.** Relationship between vitamin D and TSH, FT3, FT4 and calcium

| Parameters | Mean ±SD | Vitamin D classification | N | Mean Rank | Chi-Square | P-value |
|---|---|---|---|---|---|---|
| TSH (mlU/L) | 14.21 ± 19.63 | Deficiency | 18 | 24.86 | 0.077 | 0.96 |
| | | Insufficiency | 11 | 25.32 | | |
| | | Sufficiency | 21 | 26.14 | | |
| FT3 (pmol/L) | 3.86 ± 0.84 | Deficiency | 18 | 28.33 | 1.213 | 0.55 |
| | | Insufficiency | 11 | 25.27 | | |
| | | Sufficiency | 21 | 23.19 | | |
| FT4 (pmol/L) | 12.07 ±2.43 | Deficiency | 18 | 24.19 | 0.897 | 0.64 |
| | | Insufficiency | 11 | 23.32 | | |
| | | Sufficiency | 21 | 27.76 | | |
| Calcium (mmol/L) | 2.20 ±0.11 | Deficiency | 18 | 26.44 | 0.279 | 0.87 |
| | | Insufficiency | 11 | 23.55 | | |
| | | Sufficiency | 21 | 25.71 | | |

Data are represented as number and percent (N=50). Kruskal Wallis Test

**Table 7.** Pearson Correlation Coefficient between biochemical indices

| Biochemical indices | | TSH | FT3 | FT4 | Vitamin D |
|---|---|---|---|---|---|
| TSH (mlU/L) | r | 1 | | | |
| | P-value | | | | |
| FT3 (pmol/L) | r | -0.282* | 1 | | |
| | P-value | 0.047 | | | |
| FT4 (pmol/L) | r | -0.402** | 0.384** | 1 | |
| | P-value | 0.004 | 0.006 | | |
| Vitamin D (mmol/L) | r | 0.147 | -0.148 | 0.061 | 1 |
| | P-value | 0.310 | 0.304 | 0.675 | |
| Calcium (mmol/L) | r | -0.121 | -0.264 | 0.008 | 0.220 |
| | P-value | 0.404 | 0.064 | 0.959 | 0.125 |

* Correlation is significant P< 0.05 level (2-tailed).
** Correlation is significant P< 0.01 level (2-tailed).

## DISCUSSION

Vitamin D insufficiency recently associated with various illnesses such as cancer, obesity and osteoporosis. Interestingly, the biological activity of vitamin D is to regulate calcium and phosphorus metabolism. Although, researches showed in the past 30 years that vitamin D plays a vital role in immune-modulatory and in the pathogenesis of autoimmune diseases. Hashimoto's thyroiditis is one of the most autoimmune diseases affecting more than 5% of people [7,8]. Hypothyroidism is a common disease in the general population, most of which as consequences of HT with a tendency to increase with age. Moreover, it was 8 to 15 times higher in female than male. The main purpose of the current cross-sectional study was assessing vitamin D status in HT Saudi females.

In current study, our participants were in the most appropriate age of HT because this disease was common in age between 25 to 50 years [12,13]. We hypothesized that lower serum 25(OH)$D_3$ status in HT patients. As expected, it showed incidence of vitamin D deficiency (serum 25(OH)D levels <30 nmol/L) among the patients in this study, the mean value was (45.87 ± 29.24 nmol/L). However, not all the HT patients suffer from vitamin D deficiency. There have been numerous studies indicating high incidence of vitamin D insufficiency among Saudi people perhaps due to inadequate exposure to sensible sunlight or females are wearing black outer cloak, which may reduce the benefit of sensible sunlight [14, 15]. In contrast, several studies revealed no relation between HT and vitamin D deficiency [7,16]. The correlation of vitamin D with autoimmune thyroid disease (AITD) was confirmed by Kivityet al. [17] who found that the occurrence of anti-thyroid antibodies and irregular thyroid functions was more prevalent in vitamin D deficient subjects. In addition, vitamin D level was linked to the cell-destroying activity of the innate immune system [18]. However, available data remain controversial.

Calcium level was observed with mean 2.20 ± 0.11(mmol/L). According to calcium level correlation with TSH and FT3, results showed insignificant correlation (P>0.05) between calcium level and TSH and FT3 (r= -0.121 and r= -0.264, respectively). While, there was positive correlation but not significant as well between calcium level and vitamin D level was observed (r=0.22, P>0.05). It seems that there is no relationship between calcium level and FT4, since r= 0.008 and P>0.05.

Vitamin D is of great importance because of its role in calcium homeostasis, as well as in reducing the risk of fractures and osteomalacia. In addition to its classic skeletomuscular functions, vitamin D was identified as a factor involved in both innate and adaptive immunity [19]. It has been proved that vitamin D plays significant roles in the pathogenesis of autoimmune diseases and has potent effects in immune-modulatory [20]. Vitamin D insufficiency diagnosed of the patients with thyroid diseases compared to the healthy control. The prevalence of vitamin D deficiency was higher in patients with autoimmune diseases, particularly in those with HT [17].

In our study women with hypothyroidism had TSH value very high (14.21±19.63 mIU/L) when compared with the range of reference values (0.27-4.2 mIU/L). While FT3 and FT4 levels were within the normal range. In pearson correlation, there was a significant negative (P<0.05) association between TSH and both FT4 and FT3. Thyroid diseases are one of the most common endocrine abnormalities [21,22]. There were decreased thyroid hormones and increased TSH levels in HT patients [23].

Numerous studies have confirmed that serum 25(OH)$D_3$ to be inversely related with body mass index. In this study about half 46% of patient are obese with BMI >30 kg/$m^2$ (44%). The mean value of BMI for group with deficiency of vitamin D was significantly higher than insufficiency and sufficiency groups (P<0.05) with mean values 31.56±2.34. The obtained results may be related to high leptin levels that play a role in the hypothyroidism patients of obesity and also increase susceptibility to thyroid autoimmunity and subsequent hypothyroidism [24]. It is proposed that low circulation of serum 25(OH)$D_3$ could affect hypothalamus region of the brain which induces the appetite and decrease in energy consumption [25].

In conclusion, our results indicated that there was no correlation between vitamin D and TSH in HT of the Saudi female. However, significant correlation between vitamin D and BMI was found. Further studies are needed with larger number of subjects to clarify this association especially regarding to vitamin D receptor agonists on the effects autoimmune thyroid diseases.

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