

## ORIGINAL RESEARCH

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# Assessment of vitamin D level in Hashimoto thyroiditis in Turkish population

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### Abstract

The aim of this study was to assess vitamin D serum levels in autoimmune thyroid disease, Hashimoto thyroiditis in the Turkish population. The subjects with Hashimoto thyroiditis (HT, n=67, mean age 45.1±10.9, F/M=61/6), control subjects (mean age 42.1±15.7, n=29, F/M=26/3) were recruited for the study. Thyroid function tests, thyroid antibodies (AntiTg, AntiTPO, TSHRAb), ultrasound features, demographic and antropometric variables were recorded. Vitamin D level was not different between the HT and the control groups (53.1±24.7 nmol/L and 54.1±19.8 nmol/L, as mean, respectively, p = 0.482). In the HT group, 35.8% of subjects had vitamin D insufficiency, only 16.4% of subjects with HT were vitamin D sufficient. There was no significant difference between the HT and the control groups according to the vitamin D classification status (p = 0.666). Vitamin D levels were significantly higher in the subjects who were taking replacement compared to subjects who were not (58.7 ± 26.0 vs. 46.0 ± 23.3, as mean, respectively, p = 0.033). There was no significant correlation between vitamin D levels and TgAb and TPOAb levels in HT group (p = 0.754 r = -0.039, p = 0.134 r = -0.290, respectively). In both HT and control groups, vitamin D levels were significantly correlated only with the fT4 levels (p <0.001 r = 0.485, p = 0.02 r = 0.428, respectively). Vitamin D level was not different significantly between HT and control groups. Further studies are needed to enlighten the relationship between HT and vitamin D.

**Keywords:** Vitamin D, Hashimoto thyroiditis, Thyroid function tests

### Introduction

Vitamin D is a pro-hormone which is converted to 25-hydroxy vitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). It functions by binding to vitamin D receptors (VDRs). Vitamin D produced in the skin has also non-skeletal effects on autoimmune diseases, cardiovascular diseases, infectious diseases, cancers beside skeletal effects [1-3]. Epidemiological studies showed association between vitamin D deficiency and some autoimmune diseases like type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus [3].

Pathogenesis of Hashimoto thyroiditis (HT) is multi-factorial in which there are genetic, environmental and immune factors. In recent years, vitamin D was thought as a contributing factor for autoimmune thyroid disease development. In HT, there is a shift in the balance between type 1 T helper (Th1) and type 2 T helper (Th2) immune response in favor of Th1-cell-mediated autoimmune

reaction resulting in thyrocyte destruction [4]. 1,25(OH)<sub>2</sub>D vitamin inhibits Th1 cell proliferation [5]. While some studies in the literature have shown the association between vitamin D deficiency and thyroid autoimmunity [6-10], several other studies have not shown this association [5,10]. So, literature data has conflicting results about the association between vitamin D deficiency and HT. Our aim was to investigate vitamin D levels in patients with HT in Turkish population and correlation of vitamin D levels with thyroid function and thyroid autoantibodies.

### Material and Methods

The subjects with HT (n=67, mean age 45.1±10.9, F/M=61/6) and control subjects matched with age and sex (mean age 42.1±15.7, n=29, F/M=26/3) were recruited for the study during October-November 2016. Local ethical approval was obtained from Ege University Ethics Committee. All subjects had given oral and written informed consent for the study.

The subjects whose ages were between 18-75 were taken for the study. Hashimoto thyroiditis (HT) was diagnosed according to the presence of antibody positivity for thyroglobulin antibody (TgAb) and/or for thyroid-peroxidase antibody (TPOAb) or both of them.

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The control group consisted of the subjects who didn't have HT and were negative for TgAb and TPOAb. All subjects have normal thyroid function tests. Besides thyroid antibodies (TgAb, TPOAb) and thyroid function tests, ultrasound features, thyroid volume, anthropometric variables were also recorded. Thyrotropin stimulation hormone (TSH) was accepted as normal for the reference range of 0.35-5.5  $\mu$ IU/mL. TgAb was positive above 60 IU/mL, TPOAb was positive above 60 IU/mL. The reference range for free thyroxine (fT4) was 0.89-1.76 ng/dL and for free triiodothyronine (fT3) was 2.3-4.2 pg/mL. Thyroid function and thyroid autoantibodies were evaluated with chemiluminescence immunoassays.

Exclusion criteria were as follows: any malabsorptive disease causing vitamin D deficiency, chronic renal failure, chronic hepatic failure, usage of oral contraceptives and antiepileptic medications, vitamin D replacement.

The serum 25(OH)D concentration was determined by using commercial chemiluminescence immunoassays (Roche diagnostics). Vitamin D was accepted as sufficient if the vitamin D level was  $\geq 75$  nmol/L. Vitamin D deficiency was defined as vitamin D  $\leq 50$  nmol/L, insufficiency was defined if vitamin D level was between 51-74 nmol/L.

Statistical analysis was performed by using IBM Statistical Package of Social Science (SPSS Inc, USA) version 21.0 for Mac. Shapiro-Wilk test was used to check the normality assumption of the continuous variables. Student's t test or Mann-Whitney U test was used for comparison of two independent groups. Categorical variables were compared by the Chi-square test. Correlation analyses were performed using Spearman's correlation coefficient. A p-value of less than 0.05 was accepted as statistically significant.

## Results

Vitamin D level was not different between the HT and the control groups as shown in Table 1 (53.1 $\pm$ 24.7 nmol/L and 54.1 $\pm$ 19.8 nmol/L, as mean, respectively, p=0.482). The groups were not different regarding fT3 and fT4 levels (p = 0.133 and p = 0.410, respectively). TSH level was significantly higher in the HT group compared to the control group (2.5  $\pm$  1.7 vs. 1.6  $\pm$  1.0, as mean, respectively, p = 0.024). TgAb and TPOAb levels were significantly higher in the HT group (73 IU/mL and 339 IU/mL, as median, respectively) (Table 1).

In the HT group, 35.8% of subjects had vitamin D insufficiency, 47.8% of subjects had vitamin D deficiency. Only 16.4% of subjects with HT were vitamin D sufficient. In the control group, 20.7% of subjects were vitamin D sufficient, 41.4% of subjects had vitamin D insufficiency, 37.9% of the subjects had vitamin D deficiency. There was no significant difference between the HT and the control groups according to the vitamin D classification status (p = 0.666). Significant difference was also not observed between the HT and the control groups regarding vitamin D classification status according to gender (p = 0.269) (Table 2).

When all the subjects in the study group were categorized according to vitamin D levels as vitamin D level  $\leq 50$  nmol/L and  $>50$  nmol/L, fT4 level was significantly higher in the subjects whose vitamin D level was  $>50$  nmol/L compared to subjects whose vitamin D level was  $\leq 50$  nmol/L (Table 3). TgAb and TPOAb levels were

higher in the subjects with vitamin D level  $\leq 50$  nmol/L although this difference didn't reach statistical significance (p = 0.050 and p = 0.325, respectively).

When the subjects with HT were grouped according to the levothyroxine replacement status as shown in Table 4, vitamin D levels were significantly higher in the subjects taking replacement compared to subjects not taking (58.7  $\pm$  26.0 vs. 46.0  $\pm$  23.3, as mean, respectively, p = 0.033).

There was no significant correlation between vitamin D levels and TgAb and TPOAb levels in HT group (p = 0.754 r = -0.039, p = 0.134 r = -0.290, respectively). No correlation between vitamin D and either TgAb or TPOAb levels was observed in the control group (Table 5). In both HT and control groups, vitamin D levels were significantly correlated only with the fT4 levels (p<0.001 r = 0.485, p=0.02 r = 0.428, respectively).

**Table 1.** Demographic and laboratory variables in the Hashimoto thyroiditis and the control groups

| Variables                | HT              | Control         | p value* |
|--------------------------|-----------------|-----------------|----------|
| Age                      | 45.1 $\pm$ 10.9 | 42.1 $\pm$ 15.7 | 0.322    |
| Gender (F/M)             | 61/6            | 26/3            | 0.830    |
| BMI (kg/m <sup>2</sup> ) | 29.7 $\pm$ 6.4  | 29.2 $\pm$ 5.1  | 0.702    |
| fT3 (pg/mL)              | 2.9 $\pm$ 0.3   | 3.1 $\pm$ 0.4   | 0.133    |
| fT4 (ng/dL)              | 1.1 $\pm$ 0.1   | 1.1 $\pm$ 0.2   | 0.410    |
| TSH ( $\mu$ IU/mL)       | 2.5 $\pm$ 1.7   | 1.6 $\pm$ 1.0   | 0.024*   |
| TgAb (IU/mL)             | 73 (14-501)     | 14(14-20.6)     | 0.000*   |
| TPOAb (IU/mL)            | 339 (27-1301)   | 49 (27-59)      | 0.000*   |
| Vitamin D (nmol/L)       | 53.1 $\pm$ 24.7 | 54.1 $\pm$ 19.8 | 0.482    |

BMI, body mass index; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyrotroph stimulating hormone; TgAb, thyroglobulin antibody; TPOAb, thyroidperoxidase antibody.

**Table 2.** Percent frequencies of vitamin D classification in the Hashimoto thyroiditis and the control groups according to the gender

| Vitamin D classification                | HT          |            | Control     |            |
|-----------------------------------------|-------------|------------|-------------|------------|
|                                         | Female      | Male       | Female      | Male       |
| Sufficient<br>( Vitamin D ≥75 nmol/L)   | 9<br>14.8%  | 2<br>33.3% | 5<br>19.2%  | 1<br>33.3% |
| Insufficient<br>(Vitamin D 51-74 mol/L) | 31<br>50.8% | 1<br>16.7% | 10<br>38.5% | 1<br>33.3% |
| Total                                   | 100%        | 100%       | 100%        | 100%       |
| p value                                 | 0.240       |            | 0.848       |            |
| p value total                           | 0.269       |            |             |            |

HT. Hashimoto thyroiditis

HT, Hashimoto thyroiditis

**Table 3.** Demographic and laboratory variables in subjects with vitamin D  $\leq 50$  nmol/L and vitamin D  $>50$  nmol/L

| Variables                | Vitamin D<br>$\leq 50$ nmol/L<br>n=42 | Vitamin D<br>$>50$ nmol/L<br>n=54 | p value* |
|--------------------------|---------------------------------------|-----------------------------------|----------|
| Age                      | 41.8 $\pm$ 11.9                       | 46.0 $\pm$ 12.7                   | 0.102    |
| BMI (kg/m <sup>2</sup> ) | 30.6 $\pm$ 6.4                        | 28.8 $\pm$ 5.6                    | 0.236    |
| fT3 (pg/mL)              | 3.05 $\pm$ 0.46                       | 3.03 $\pm$ 0.38                   | 0.757    |
| fT4 (ng/dL)              | 1.04 $\pm$ 0.19                       | 1.19 $\pm$ 0.17                   | <0.001*  |
| TSH ( $\mu$ IU/mL)       | 2.29 $\pm$ 1.56                       | 1.99 $\pm$ 1.56                   | 0.296    |
| TgAb (IU/mL)             | 40.9 (14-501)                         | 17.0 (14-501)                     | 0.050    |
| TPOAb (IU/mL)            | 114.6 (27-1301)                       | 59.4 (27-1301)                    | 0.325    |
| Thyroid volume           | 11.5 $\pm$ 10.4                       | 11.0 $\pm$ 8.4                    | 0.756    |
| HT (%)                   | 74.4                                  | 66.0                              | 0.374    |
| Vitamin D (nmol/L)       | 31.2 $\pm$ 8.7                        | 71.2 $\pm$ 18.9                   | <0.001*  |

BMI, body mass index; fT3, free triiodothyronine; fT4, free thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; HT, Hashimoto thyroiditis. p<0.05 was accepted as statistically significant

**Table 4.** Demographic and laboratory variables in subjects with Hashimoto thyroiditis according to levothyroxine replacement status

| Variables                | HT<br>Levothyroxine<br>replacement<br>present | HT<br>Levothyroxine<br>replacement<br>absent | p value* |
|--------------------------|-----------------------------------------------|----------------------------------------------|----------|
|                          |                                               |                                              |          |
| Age                      | 47.4± 9.7                                     | 42.5 ±11.6                                   | 0.066    |
| BMI (kg/m <sup>2</sup> ) | 29.6± 6.2                                     | 29.9± 6.7                                    | 0.370    |
| ft3 (pg/mL)              | 2.87± 0.33                                    | 3.14± .0.43                                  | 0.010*   |
| ft4 (ng/dL)              | 1.17± 0.17                                    | 1.10± 0.17                                   | 0.078    |
| TSH (μIU/mL)             | 2.49± 1.88                                    | 2.23± 1.52                                   | 0.807    |
| TgAb (IU/mL)             | 90.8 (14-501)                                 | 20.7 (14-501)                                | 0.020*   |
| TPOAb (IU/mL)            | 631.4 (27-1301)                               | 112.4 (27-1301)                              | 0.090    |
| Thyroid volume           | 8.2± 3.6                                      | 13.7± 11.9                                   | 0.065    |
| Vitamin D (nmol/L)       | 58.7± 26.0                                    | 46.0± 23.3                                   | 0.033*   |

BMI, body mass index; ft3, free triiodothyronine; ft4, free thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.  
p<0.05 was accepted as statistically significant

**Table 5.** Spearman correlation analysis for vitamin D in the Hashimoto thyroiditis and the control groups

| Independent variables | HT group |         | Control group |        |
|-----------------------|----------|---------|---------------|--------|
|                       | r        | p       | r             | p      |
| Age                   | 0.205    | 0.096   | 0.212         | 0.270  |
| BMI                   | -0.197   | 0.110   | 0.096         | 0.621  |
| ft3                   | 0.089    | 0.471   | -0.156        | 0.448  |
| ft4                   | 0.485    | <0.001* | 0.428         | 0.020* |
| TSH                   | 0.021    | 0.866   | -0.270        | 0.156  |
| TgAb                  | -0.039   | 0.754   | -0.290        | 0.134  |
| TPOAb                 | -0.033   | 0.789   | -0.123        | 0.534  |
| Thyroid volume        | 0.025    | 0.844   | 0.199         | 0.309  |

Spearman correlation analysis was used. r stands for correlation coefficient.

\* p <0.05 was considered significant. HT, Hashimoto thyroiditis; BMI, body mass index; ft3, free triiodothyronine; ft4, free thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

## Discussion

Our study showed that vitamin D levels were not significantly different in HT group compared to the control group. There was no correlation between vitamin D levels and antithyroid antibodies. Vitamin D levels were significantly higher in the HT subjects taking levothyroxine replacement compared to HT subjects who are not taking.

Kivity et al. [6] showed that vitamin D deficiency was higher in autoimmune thyroid patients (both HT and Graves' disease) and association between vitamin D deficiency and antithyroid antibodies and thyroid function tests. Bozkurt et al. [7], figured out that vitamin D levels were lower in chronic HT patients taking thyroxine replacement than newly diagnosed HT patients without thyroxine replacement and than the control subjects. They showed that vitamin D levels were positively correlated with thyroid volume and negatively correlated with TPOAb and TgAb levels. Female subjects with HT had lower vitamin D levels compared to the male HT patients in the study of Bozkurt et al. [7]. We have not found any significant difference between the HT and the control groups as far as vitamin D levels are concerned. Moreover, vitamin D levels were not different between the HT and the control groups regarding the gender in our study. Bozkurt et al. [7] hypothesized that levothyroxine may change the metabolism of vitamin D based on the finding referring to low vitamin D levels in HT subjects who

were taking levothyroxine compared to the new onset HT subjects without levothyroxine replacement. On the other hand, we showed that vitamin D levels were higher in HT subjects who were taking levothyroxine replacement compared to HT subjects who were not. Besides, ft4 levels were significantly higher in the subjects who had vitamin D levels greater than 50 nmol/l compared to ones with vitamin D levels with ≤50 nmol/L. In opposition to the suggestion of Bozkurt et al. [7], we may speculate that serum T4 may be influencing the absorption of vitamin D level in a positive way. Vitamin D deficiency may be occurring as a consequence of the disease process. Another study showing association between vitamin D deficiency and HT by Kim et al. [11] depicted that HT subjects with overt hypothyroidism had a significantly higher rate of vitamin D insufficiency compared with euthyroid and subclinically hypothyroid and the control subjects who had no autoimmune thyroid disease. They suggested the association between vitamin D deficiency and thyrocyte damage leading to thyroxine replacement.

On the contrary to those studies, Yasmeh et al. [12] showed that vitamin D levels were not different in the HT group compared to control group. They observed that female subjects with HT had a higher rate of vitamin D sufficiency and lower rate of vitamin D insufficiency compared to the control female subjects as opposed to the other studies carried out in Hungary and Turkey [6,7,9]. In the study of Yasmeh [12], vitamin D levels didn't differ between male HT and male control subjects. According to those results, sex could be a confounding factor affecting vitamin D levels in HT but in our study vitamin D insufficiency and deficiency didn't differ between the HT and the control groups when sex was taken into statistical analysis. In the study of Tamer et al. [9], 92% of the HT cases had vitamin D insufficiency, while the control group had 63% vitamin D insufficiency which was statistically significant. In the HT group, there was no significant difference regarding to vitamin D levels in HT subjects with overt hypothyroidism, subclinical hypothyroidism and euthyroidism. Yasmeh et al. [12] mentioned that vitamin D sufficiency rate was high in their HT group. In the other studies showing association between vitamin D deficiency and HT, the rate of vitamin D deficiency was higher. Yasmeh et al. [12] suggested that having higher rate of vitamin D sufficiency in their study may be leading to more accurate statistical results.

Another study from Turkey showed that vitamin D levels were 19.4 ng/mL in the HT group and were 22.5. ng/mL in the control group pointing to the significant difference [13]. Unal et al. [13] also figured out that vitamin D levels were inversely correlated with TgAb and TPOAb levels.

Small number of subjects and being cross-sectional study were limitations of our study. Since we recruited the study subjects in the October and November, it could be thought that seasonal variation had been ruled out.

## Conclusion

To the best of our knowledge, our study was the first one in the literature regarding to Turkish population showing that HT was not associated with vitamin D deficiency. There was no significant difference for vitamin D levels between the HT and the control group. There was no correlation of vitamin D levels with thyroid antibodies. It is not clear whether there is association with vitamin

D insufficiency and HT. Since vitamin D deficiency is common for most of the countries, findings regarding the association could be just a coincidence. Further studies are needed to clarify the relationship of vitamin D with the development of HT.

#### Competing interests

*The authors declare that they have no competing interest*

#### Financial Disclosure

*The financial support for this study was provided by the investigators themselves.*

#### Ethical approval

*Before the study, permissions were obtained from local ethical committee.*

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