

# The relationship between vitamin D level and thyroid antibodies in primary hypothyroidism

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## Background

Vitamin D deficiency is a global health problem. Its deficiency has been reported to be associated with different autoimmune diseases. The aim of this study was to evaluate the relationship between vitamin D level and thyroid antibodies in primary hypothyroidism.

## Patients and methods

A total number of 90 individuals were enrolled in this study. They were divided into the following groups: group I included 60 naïve patients with hypothyroidism representing the case group, and this group was further subdivided into 30 patients with autoimmune thyroid disease (AITD) and 30 patients without autoimmune thyroid disease. Group II included 30 apparently healthy participants matched for age and sex representing a control group. All participants underwent a detailed clinical examination and laboratory tests including, 25 (OH) vitamin D, thyroid function tests (thyroid-stimulating hormone, free triiodothyronine, and free thyroxine), and thyroid autoantibodies assessment, including anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies.

## Results

Serum levels of 25 (OH) vitamin D recorded a highly significant difference between the studied groups (13.08±3.58 ng/ml in group I vs. 20.67±13.33 ng/ml in group II;  $P<0.01$ ). Moreover, there was a highly significant difference between patients with AITD and patients without AITD (12.6±5.5 ng/ml vs. 14.5±7.3 ng/ml, respectively;  $P<0.01$ ), and vitamin D deficiency was more frequent in patients with AITD (43.3%), rather than 23.3% in patients without AITD. There was a significant negative correlation between serum 25 (OH) vitamin D and thyroid-stimulating hormone, anti-thyroid peroxidase antibodies, and anti-thyroglobulin ( $r=-0.459$ ,  $-0.582$ , and  $-0.324$ , respectively;  $P<0.05$ ), whereas a significant positive correlation between serum 25 (OH) vitamin D and both of free triiodothyronine and free thyroxine ( $r=0.368$  and  $0.598$ , respectively;  $P<0.05$ ).

## Conclusion

Vitamin D deficiency is associated with AITD, and further studies are needed to determine its role in management of primary hypothyroidism.

## Keywords:

autoimmune thyroid disease, primary hypothyroidism, vitamin D

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## Introduction

Vitamin D deficiency is a global health problem [1]. There is increasing interest in the role of vitamin D deficiency in a number of chronic health problems including autoimmune diseases [2,3]. The demonstration of vitamin D receptor in monocytes, dendritic cells, and activated T cells indicates significant interaction between vitamin D and immune system [4,5].

As an immune modulator, vitamin D reduces activation of the acquired immune system. Hence, vitamin D deficiency has been shown to be associated with autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and

type 1 diabetes, and that vitamin D supplementation prevents the onset and/or development of these autoimmune diseases [6]. Hashimoto thyroiditis (HT) is an autoimmune progressive inflammatory disorder of the thyroid gland. A dense lymphocytic infiltration of the gland is involved in the pathogenesis of HT. The incidence of this disease is 2% with a peak in women 30–50 years old [7].

Genetic and environmental factors are considered the main triggers of the disease. Vitamin D also inhibits

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generation of cytokine, which plays an important role in developing autoimmune thyroiditis [8]. Some studies were performed to elucidate the association between vitamin D deficiency and HT. However, the results of these studies are insufficient for clear information [9–12]. The aim of this study was to evaluate the relation between vitamin D level and thyroid antibodies in primary hypothyroidism.

### Patients and methods

A total number of 90 individuals were enrolled in this case-control study, selected from the outpatient clinic of Endocrinology Department of Ain Shams University Hospitals during the autumn months of 2017. Participants were divided into the following groups: group I included 60 naïve patients with hypothyroidism representing the case group, and this group was further subdivided according to retrospective selection into 30 patients with autoimmune thyroid disease (AITD), HT and 30 patients without autoimmune thyroid disease. Group II included 30 apparently healthy participants matched for age and sex, representing a control group.

Participants with a history of other autoimmune disease, thyroidectomy, and chronic diarrhea or patients with a history suggestive of malabsorption, diabetes, malignancy, and chronic renal or liver diseases were excluded. Furthermore, participants who took vitamin or calcium supplements and medications that may interfere with serum levels of 25 (OH) vitamin D (e.g., antiepileptics, steroids, methotrexate, isoniazid, thiazides, antacids, calcium channel blockers, and anticonvulsants) were not included in this study.

This study was conducted after approval from the Institutional Ethics Committee. All participants gave informed consent.

All enrolled individuals were subjected to complete history taking emphasizing on symptoms of hypothyroidism, use of medications as well as exclusion of other systems disorders. Anthropometric parameters were obtained while the participant was standing erect and barefoot. Height and weight were determined using standardized conventional methods. BMI was calculated as weight (kg) divided by height (m) squared. Systolic blood pressure and diastolic blood pressure were measured with a mercury sphygmomanometer with the patient in the sitting position.

### Laboratory measurements

After fasting overnight for 10–12 h, blood samples were collected for the following measurements: 25 (OH)

vitamin D, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), ionized calcium, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Test procedure for the determination of 25 (OH) vitamin D in human serum by ELISA kit (DRG International Inc., Mountain Avenue, Springfield, USA) is a solid-phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding. Serum 25 (OH) vitamin D concentrations of less than 10 ng/ml (<25 nmol/l) were defined as vitamin D deficiency and from 10 to 29 ng/ml (25–72.5 nmol/l) as insufficiency. A value of 25(OH) vitamin D concentration from 30 to 100 ng/ml (75–250 nmol/l) was considered as normal vitamin D level, whereas greater than 100 ng/ml (>250 nmol/l) as toxicity [13].

Ionized calcium, creatinine, AST, and ALT were analyzed on Beckman Coulter Synchron LX 20 (Massachusetts, USA) using commercially available kits.

Thyroid function tests (FT3, FT4, and TSH) were performed in Chemical Pathology Unit, Ain Shams University Hospitals, on ELISA Reader Stat Fax – 2100 using enzyme immunoassay kits supplied by DRG International Inc. The normal ranges of serum hormone concentrations were as follows: FT3=1.2–4.4 pg/dl, FT4=0.8–2 ng/dl, and TSH=0.5–5 mIU/l.

Estimation of anti-thyroid peroxidase antibodies (anti-TPO) was done using Elecsys 2010 Immunoassay autoanalyzer (Roche Diagnostics, Hague Rd Indianapolis, USA) by electrochemiluminescence immunoassay. Normal range is 0–35 IU/ml. So, values greater than 35 IU/ml are considered positive.

Estimation of anti-thyroglobulin antibodies (anti-TG) was done using the DRG-anti-thyroglobulin ELISA kit (DRG International Inc.). Normal range is 0–100 U/ml. So, values greater than 100 U/ml were considered positive.

Participants with elevated anti-TPO and/or anti-TG serum levels underwent thyroid ultrasound to confirm the diagnosis of AITD. Thyroid ultrasonography was performed using high-frequency linear probe 5–12 MHz of ATL HDI 500 Machine (DOTmed. com Inc. Broadway, New York, USA). Elevated serum levels of thyroid autoantibodies, together with characteristic ultrasonographic features (diffuse parenchymal hypoechogenicity and/or heterogeneous echogenic pattern of thyroid gland) were used for diagnosis of AITD.

### Statistical analysis

Statistical package for the social science program, version 15, was used for an analysis of data. Data were summarized using mean±SD for quantitative and numbers and percentages for categorical variables. Student's *t* test was used to compare the difference between the two groups.  $\chi^2$  test was used to compare qualitative data. An analysis of variance test was done in comparison between more than two groups. Correlation between variables of interest was performed using Pearson's correlation. The significance of the test was determined according to the *P* value to be as follows: not significant if *P* value more than 0.05, significant if *P* value less than 0.05, and highly significant if *P* value less than 0.01.

### Results

This study enrolled 90 participants who were subdivided into two groups: group I included 60 patients recently diagnosed with hypothyroidism, where 30 patients of them were found to have AITD (evidenced by autoimmune features, elevated anti-TPO, and/or anti-TG serum levels, together with ultrasonographic features) and 30 showed no evidence of autoimmunity, and group II included 30 apparently healthy participants representing a control group. The clinical and biochemical characteristics of the study groups are listed in Table 1.

Age and sex distribution showed no statistical difference ( $P>0.05$ ) between the groups. Moreover, the mean values of creatinine, AST, and ALT showed no significant statistical difference between groups

( $P>0.05$ ). However, BMI was significantly increased in the patients group compared with the control group, with  $29.54\pm 6.34$  kg/m<sup>2</sup> in group I vs.  $26.03\pm 5.74$  kg/m<sup>2</sup> in group II ( $P<0.05$ ).

Serum levels of 25 (OH) vitamin D recorded a highly significant difference between the studied groups ( $13.08\pm 3.58$  ng/ml in group I vs.  $20.67\pm 13.33$  ng/ml in group II,  $P<0.01$ ). Moreover, ionized calcium levels were significantly lower in the patient group than in the controls ( $1.03\pm 0.12$  mmo/l vs.  $1.21\pm 0.10$  mmo/l, respectively;  $P<0.01$ ), as illustrated in Table 1.

Regarding vitamin D sufficiency, it was revealed that 25 (OH) vitamin D was deficient in 33.3% and insufficient in 66.7% of the patient group, whereas it was not sufficient in any of the patients. On the contrary, 25 (OH) vitamin D was deficient in only 6.7%, insufficient in 73.3%, and sufficient in 20% of control group ( $P<0.01$ ).

On comparing patients with AITD with those without AITD, and each of them with the control group (as shown in Table 2), there was a significant difference in sex between patients with AITD and those without AITD. Female patients were more presented in the former subgroup (93.3% of patients with AITD vs. 73.3% of patients without AITD,  $P<0.05$ ). Moreover, there was a highly significant difference between patients with AITD and patients without AITD regarding BMI ( $27.45\pm 4.98$  kg/m<sup>2</sup> in patients with AITD vs.  $31.64\pm 6.91$  kg/m<sup>2</sup> in patients without AITD,  $P<0.01$ ), TSH ( $6.73\pm 4.91$  mU/l in patients

**Table 1 Comparison between the study groups regarding the clinical and biochemical characteristics**

Variants	Group I=patients (N=60) (mean±SD)	Group II=control (N=30) (mean±SD)	Independent <i>t</i> test	
			<i>t</i> / $\chi^2$ <sup>a</sup>	<i>P</i> value
Age (years)	40.50±11.80	43.93±11.68	-1.306	0.195
Sex F/M [ <i>n</i> (%)]	50 (83.30)/10 (16.70)	25 (83.3)/5 (16.7)	0.000 <sup>a</sup>	1.000
BMI (kg/m <sup>2</sup> )	29.54±6.34	26.03±5.74	2.554	0.012
TSH (mU/l)	8.72±7.22	2.49±0.96	4.697	0.000
FT3 (pg/dl)	1.54±0.67	2.12±0.80	-3.650	0.000
FT4 (ng/dl)	0.67±0.47	1.05±0.31	-3.987	0.000
Serum creatinine (mg/dl)	1.07±0.55	0.93±0.26	1.310	0.194
AST (mg/dl)	25.57±10.51	24.30±12.52	0.505	0.615
ALT (mg/dl)	18.90±14.15	15.80±11.84	1.032	0.305
Ionized calcium (mmo/l)	1.03±0.12	1.21±0.10	-7.079	0.000
25 (OH) vitamin D (ng/ml)	13.08±3.58	20.67±13.33	-5.229	0.000
Vitamin D sufficiency [ <i>n</i> (%)]				
Deficient	20 (33.30)	2 (6.7)		
Insufficient	40 (66.70)	22 (73.3)	17.947 <sup>a</sup>	0.000
Sufficient	0 (0.00)	6 (20.0)		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; F/M, female/male; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone. <sup>a</sup> $\chi^2$  test. *P* value more than 0.05 is not significant. *P* value less than 0.05 is significant. *P* value less than 0.01 is highly significant.

**Table 2 Comparison between patients with autoimmune thyroid disease, patients without autoimmune thyroid disease, and control group**

Variants	Patients group (mean±SD)		Control group (N=30) (mean±SD)	One-way ANOVA test		Post-hoc analysis by LSD		
	With autoimmune hypothyroidism (N=30)	Without autoimmune hypothyroidism (N=30)		$F/\chi^2$ a	P value	$P_1$	$P_2$	$P_3$
Age (years)	48.83±9.19	51.1±11.50	43.93±11.68	9.188	0.125	0.215	0.327	0.427
Sex F/M [n (%)]	28 (93.3)/2 (6.7)	22 (73.3)/8 (26.7)	25 (83.3)/5 (16.7)	4.320 <sup>a</sup>	0.115	0.038	0.228	0.347
BMI (kg/m <sup>2</sup> )	27.45±4.98	31.64±6.91	26.03±5.74	7.250	0.001	0.007	0.359	0.000
TSH (mU/l)	6.73±4.91	10.72±8.58	2.49±0.96	15.467	0.000	0.008	0.005	0.000
FT3 (pg/dl)	1.26±0.60	1.80±0.62	2.12±0.80	12.416	0.000	0.087	0.002	0.000
FT4 (ng/dl)	0.71±0.37	0.63±0.56	1.05±0.31	8.201	0.001	0.449	0.003	0.000
Serum creatinine (mg/dl)	1.06±0.52	1.07±0.58	0.93±0.26	0.851	0.430	0.935	0.280	0.246
AST (mg/dl)	29.97±11.45	21.17±7.33	24.30±12.52	5.241	0.007	0.002	0.043	0.259
ALT (mg/dl)	20.13±19.31	17.67±5.60	15.80±11.84	0.781	0.461	0.480	0.216	0.593
Ionized calcium (mmo/l)	0.96±0.12	1.10±0.06	1.21±0.10	51.019	0.000	0.000	0.000	0.000
25 (OH) vitamin D (ng/ml)	12.6±5.5	14.5±7.3	20.67±13.33	14.387	0.001	0.000	0.001	0.000
Vitamin D sufficiency [n (%)]								
Deficient	13 (43.3)	7 (23.3)	2 (6.7)					
Insufficient	17 (56.7)	23 (76.7)	22 (73.3)	21.273a	0.001	0.001	0.001	0.012
Sufficient	0 (0.0)	0 (0.0)	6 (20.0)					

AITD, autoimmune thyroid disease; ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; BMI, body mass index; F/M, female/male; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone. <sup>a</sup> $\chi^2$  test.  $P_1$ , patients with AITD versus patients without AITD.  $P_2$ , patients with AITD versus control group.  $P_3$ , patients without AITD versus control group.  $P$  value more than 0.05 is not significant.  $P$  value less than 0.05 is significant.  $P$  value less than 0.01 is highly significant.

with AITD vs. 10.72±8.58 mU/l in patients without AITD,  $P<0.01$ ) and ionized calcium (0.96±0.12 mmo/l in patients with AITD vs. 1.10±0.06 mmo/l in patients without AITD).

Regarding 25 (OH) vitamin D level, there was a highly significant difference between patients with AITD and patients without AITD (12.6±5.5 vs. 14.5±7.3 ng/ml, respectively,  $P<0.01$ ), as well as between patients with AITD and control group (12.6±5.5 vs. 20.67±13.33 ng/ml, respectively,  $P<0.01$ ), and between patients without AITD and control group (14.5±7.3 vs. 20.67±13.33 ng/ml, respectively,  $P<0.01$ ) (Fig. 1). Moreover, vitamin D deficiency was more frequent in patients with AITD (43.3%) versus in patients without AITD (23.3%).

Within patients group (Table 3), highly significant positive correlations were recorded between serum 25 (OH) vitamin D and each of FT3 ( $r=0.368$ ,  $P<0.01$ ) and serum ionized calcium levels ( $r=0.574$ ,  $P<0.01$ ). Moreover, there was a significant positive correlation between serum 25 (OH) vitamin D and FT4 ( $r=0.598$ ,  $P<0.05$ ). On the contrary, there was a significant negative correlation between serum 25 (OH) vitamin D and TSH ( $r=-0.459$ ,  $P<0.01$ ), anti-TPO ( $r=-0.582$ ,  $P<0.01$ ), and anti-TG ( $r=-0.324$ ,  $P<0.05$ ).

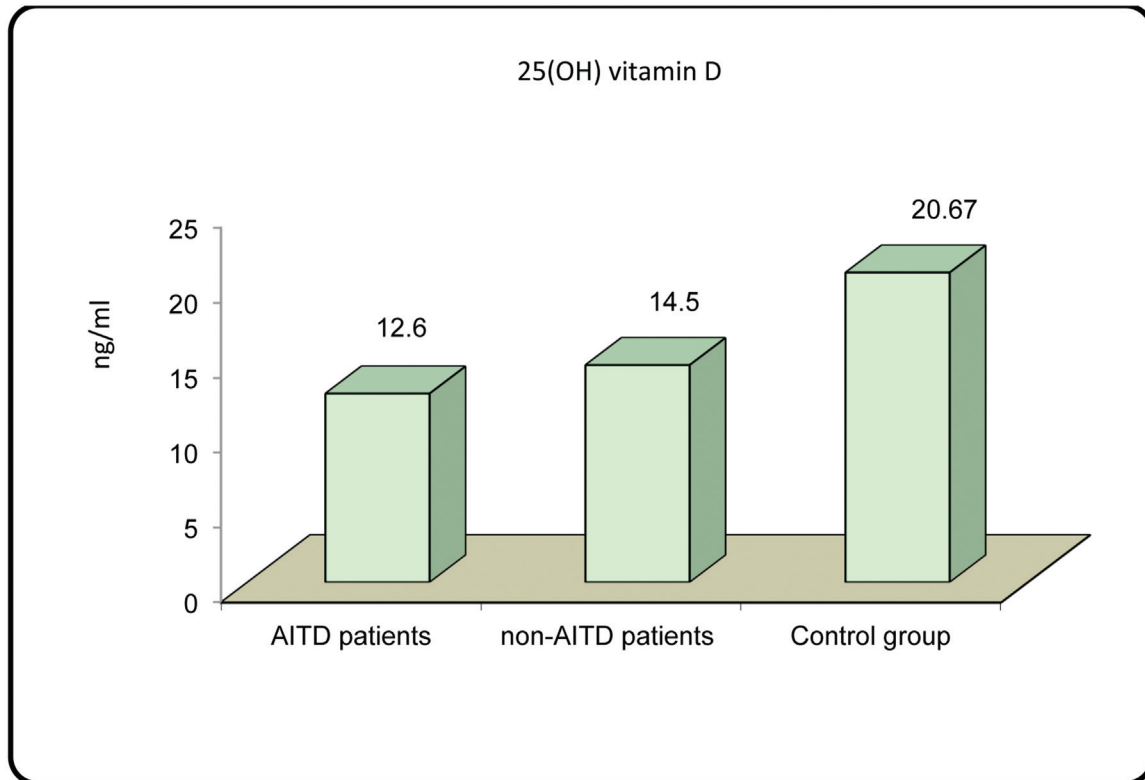
Receiver operating characteristic analysis was performed to find out the cutoff value for vitamin D (Fig. 2). In receiver operating characteristic curve analysis, the cutoff value for vitamin D between the control group and patients was less than or equal to 13, and 80.00% sensitivity and 76.67% specificity (area under the curve, 0.822) were observed.

## Discussion

Vitamin D has been suggested to be active as an immunomodulator in autoimmune diseases such as HT. The goal of the present study was to investigate the vitamin D status in Egyptian patients with HT and to evaluate the relation between vitamin D level and thyroid antibodies in primary hypothyroidism. Few studies have been conducted to find any significant association between the levels of vitamin D and hypothyroidism and to determine whether vitamin D deficiency is involved in the pathogenesis of hypothyroidism or is a consequence of the disease.

In our study, there was a high significant difference regarding vitamin D level among the studied groups; vitamin D level was 13.08±3.58 ng/ml in patients with hypothyroidism versus 20.67±13.33 ng/ml in control group. Regarding vitamin D status, it was deficient in 33.3% and insufficient in 66.7% in patients with

Figure 1



Comparison between patients with AITD, patients without AITD, and control group regarding 25 (OH) vitamin D level. AITD, autoimmune thyroid disease.

**Table 3 Correlation between 25 (OH) vitamin D and other variables in patients group**

	25 (OH)D (ng/ml)	
	Patients group	
	<i>r</i>	<i>P</i> value
Age (years)	0.256	0.458
BMI (kg/m <sup>2</sup> )	0.063	0.631
TSH (mU/l)	-0.459	0.000
FT3 (pg/dl)	0.368	0.007
FT4 (ng/dl)	0.598	0.002
Anti-TPO (IU/ml)	-0.582	0.003
Anti-TG (IU/ml)	-0.324	0.022
Serum creatinine (mg/dl)	-0.277	0.032
AST (mg/dl)	0.099	0.451
ALT (mg/dl)	0.184	0.159
Ionized calcium (mmol/l)	0.574	0.000

ALT, alanine aminotransferase; anti-TG, anti-thyroglobulin antibodies; anti-TPO, anti-thyroid peroxidase antibodies; AST, aspartate aminotransferase; BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone. *P* value more than 0.05 is not significant. *P* value less than 0.05 is significant. *P* value less than 0.01 is highly significant.

hypothyroidism, whereas it was deficient in 6.7% and insufficient in 73.3% in control group.

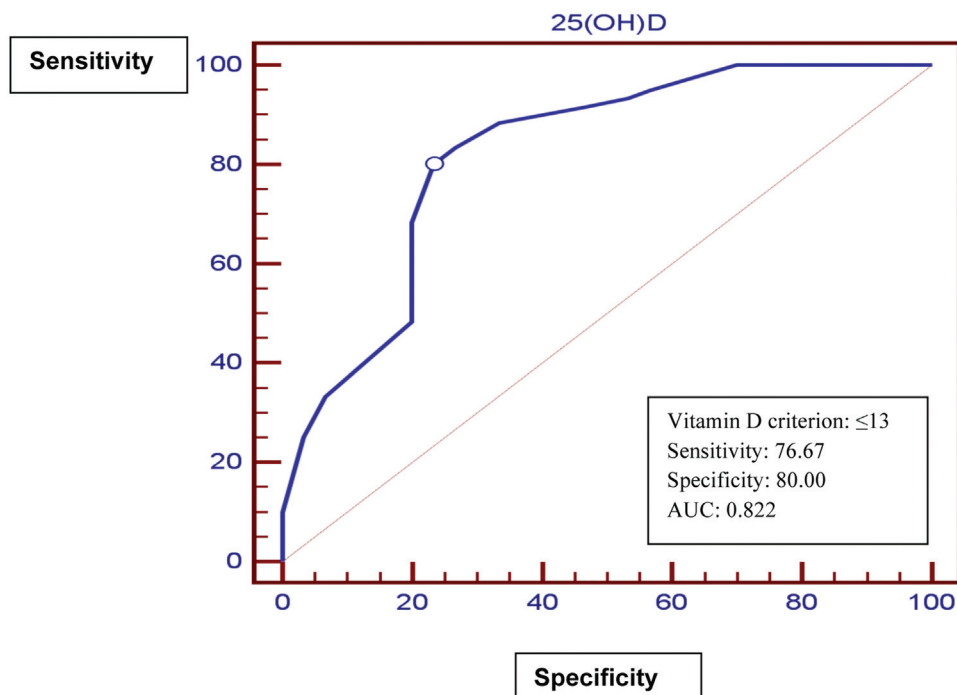
This is in agreement with Friedman who explained the low levels of vitamin D in patients with

hypothyroidism by two mechanisms. First, it may be owing to poor absorption of vitamin D from the intestine. Second, the body may not activate vitamin D properly. Importantly, both vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors. A different gene in the vitamin D receptor was shown to predispose people to AITD including Graves' disease and HT [13].

Also, Kivity and colleagues reported that the prevalence of vitamin D deficiency [25 (OH) vitamin D level <25 nmol/l] was significantly higher in 50 patients with AITD compared with 98 healthy individuals (72 vs. 30.6%, respectively,  $P < 0.001$ ). Vitamin D deficiency was also found to be correlated with the presence of anti-thyroid antibodies ( $P = 0.01$ ), suggesting the involvement of vitamin D in the pathogenesis of AITD [4].

Moreover, we found that 43.3% of patients with AITD had vitamin D deficiency, whereas only 23.3% of patients without AITD had vitamin D deficiency ( $P = 0.001$ ). And, 56.7% of patients with AITD were vitamin D insufficient in comparison with 76.7% of patients without AITD. However, serum TSH level was higher in patients without AITD ( $10.72 \pm 8.58$  mU/l) than in patients with AITD ( $6.73 \pm 4.91$  mU/l) ( $P = 0.01$ ). This may suggest that vitamin D

Figure 2



ROC analysis and cutoff value for vitamin D. ROC, receiver operating characteristic.

deficiency is more closely related to thyroid antibodies rather than thyroid function.

This comes in agreement with Shin *et al.* [14] who reported that patients with elevated anti-thyroid antibodies had lower levels of serum 25 (OH) vitamin D<sub>3</sub> than others with no elevation ( $P < 0.001$ ). Moreover, Colak *et al.* [15] reported that 94.4% of patients with HT had vitamin D deficiency. Likewise, Tamer *et al.* [10] demonstrated that the prevalence of vitamin D insufficiency [25 (OH) vitamin D level  $< 75$  nmol/l] in 161 HT cases was significantly higher than in 162 healthy controls (92 vs. 63%, respectively,  $P < 0.0001$ ).

However, Yasmeh *et al.* [16] have found no association with anti-TPO positivity as well as weak inverse correlation between 25 (OH) vitamin D and anti-TPO levels, which comes in contrast to our results. Moreover, Ergur *et al.* [17] have found high prevalence of vitamin D deficiency in Turkish population regardless of HT, and they reported the frequency of severe vitamin D deficiency as 27% among reproductive age women.

Our study showed a high significant negative correlation between serum 25 (OH) vitamin D and TSH ( $r = -0.459$ ,  $P = 0.000$ ), as well as a significant positive correlations with FT3 ( $r = 0.368$ ,  $P = 0.004$ ), FT4 ( $r = 0.598$ ,  $P = 0.032$ ) and serum ionized calcium ( $r = 0.574$ ,  $P = 0.000$ ).

This result comes in agreement with Mansournia *et al.* [18], who found a significant inverse association between serum 25 (OH) vitamin D levels and TSH in HT. Moreover, Al-Hakeim, in Saudi Arabia, mainly Qassim region, observed that vitamin D and serum calcium levels were significantly lower in hypothyroid patients. Moreover, they recorded a significant positive correlation between serum 25 (OH) vitamin D and serum FT3 ( $r = 0.564$ ,  $P = 0.001$ ) [19].

In addition, Metwalley *et al.* [20] have shown that vitamin D deficiency rate was higher in AIT group (71.4%) than that in control group (21.4%) ( $P < 0.001$ ). The mean level of 25 (OH) vitamin D was significantly lower in AIT group compared with the control group (16.2 versus 33.9 nmol/l,  $P < 0.001$ ). There was a negative correlation between 25 (OH) vitamin D and BMI, anti-TPO, anti-TG, and TSH ( $r = -0.676$ ,  $-0.533$ ,  $-0.487$ ,  $-0.445$ , respectively) in their study on Egyptian children with AITDs and age- and sex-matched controls.

In addition, Muscogiuri *et al.* [21] studied 168 elderly participants (mean age of 82 years) and showed a significantly higher prevalence of AITD in participants with vitamin D deficiency [25 (OH) vitamin D level  $< 50$  nmol/l] ( $P = 0.002$ ) and a significant correlation between 25 (OH) vitamin D and anti-TPO levels ( $r = -0.27$ ,  $P = 0.03$ ).

On the contrary, Saler *et al.* [22] observed that HT is not associated with vitamin D deficiency in Turkish women and found that 25 (OH) vitamin D concentrations were not associated with thyroid autoantibodies ( $P>0.05$ ).

The controversial and varying results of the studies are partly owing to interassay and interlaboratory variability in the measurements of 25 (OH) vitamin D, seasonal variations in blood sampling of 25 (OH) vitamin D, differences in the selection of patients, dietary vitamin D intake, exposure to sunlight, and the different cutoff levels used to define vitamin D deficiency or insufficiency.

## Conclusion

Significantly lower levels of vitamin D were documented in patients with AITD. Deficiency of vitamin D was linked to the presence of thyroid autoantibodies and abnormal thyroid functions. Further studies are required to determine whether vitamin D deficiency is the causal factor or the consequence of primary hypothyroidism, and to provide insight into the efficacy and safety of vitamin D as a therapeutic tool for AITD.

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## Conflicts of interest

There are no conflicts of interest.

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