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Vitamin D Deficiency in Iraqi Women with Hashimoto Thyroiditis

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ABSTRACT

One kind of autoimmune thyroid disease is Hashimoto's thyroiditis (HT), which is more frequent in women than in males. The purpose of our study was to demonstrate any possible variations in vitamin D levels between ladies with HT and healthy women.

METHODS: Fifty healthy Individuals (HI) and fifty HT patients made up the research group of 100 volunteers. Anti-thyroid peroxidase antibody (TPO-Ab) and anti-thyroglobulin antibody (Tg-Ab) levels were used to diagnose HT. The amounts of thyroid-stimulating hormone (TSH), free thyroxin (fT4), free triiodothyronine (fT3) and Vitamin D (Vit-D) were also assessed.

RESULTS: In comparison to the HI, the patients' levels of anti-TPO, anti-TG and TSH were considerably greater, with an overall decrease in vitamin D levels in the three categories Vit-D < 20 (Deficiency), Vit-D 20–30 (Insufficiency) and Vit-D > 30 (Sufficiency). Furthermore, there was a significant increase in anti-TPO levels in patients compared to HI in all categories. This study also found a significant positive association between the anti-TPO and TSH levels in HT patients whose serum vitamin D level was more than 30 and a negative correlation between the levels of TSH and fT3 in HT patients whose serum vitamin D level was less than 20.

CONCLUSIONS: A lower 25(OH)D level is seen in HT patients, and TSH is a separate risk factor for HT. Additionally, a significant increase in anti-TPO levels was observed overall and in the categories (deficient, insufficient, and sufficient) in women with HT.

Keywords: Hashimoto's thyroiditis, Anti-thyroid peroxidase, Anti-thyroglobulin, Thyroid-stimulating hormone, Vitamin D (25(OH)D)

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نقص فيتامين د لدى النساء العراقيات المصابات بالتهاب الغدة الدرقية هاشيموتو

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الملخص

أحد أنواع أمراض الغدة الدرقية المناعية الذاتية هو التهاب الغدة الدرقية هاشيموتو (HT)، وهو أكثر شيوعًا لدى النساء منه لدى الرجال، هدفت دراستنا إلى إظهار الاختلافات المحتملة في مستويات فيتامين د بين النساء المصابات ب HT والنساء الأصحاء.

طرق العمل: شكل خمسون فردًا سليمًا (HI) وخمسون مريضًا مصابا بالتهاب الغدة الدرقية هاشيموتو (HT) مجموعة بحثية من 100 متطوع. استُخدمت مستويات الأجسام المضادة لبيروكسيديز الغدة الدرقية (TPO-Ab) والأجسام المضادة للثيروجلوبولين (Tg-Ab) لتشخيص التهاب الغدة الدرقية هاشيموتو (HT)، كما تم أيضًا تقييم مستويات هرمون تحفيز الغدة الدرقية (TSH)، والثيروكسين الحر (fT4)، وثلاثي يودوثيرونين الحر (fT3)، وفيتامين د (Vit-D).

النتائج: بالمقارنة مع الافراد الاصحاء HI، كانت مستويات الأجسام المضادة للغدة الدرقية (anti-TPO و anti-TG) وTSH لدى المرضى اعلى بكثير، مع انخفاض عام في مستويات فيتامين د في الفئات الثلاث: فيتامين د < 20 (نقص)، وفيتامين د 20–30 (عدم كفاية)، وفيتامين د > 30 (كفاية). علاوة على ذلك، كانت هناك فروقات معنوية عالية في مستويات Anti-TPO لدى المرضى HT مقارنة ب مجموعة الضبط HI وفي جميع الفئات. وجدت هذه الدراسة أيضًا ارتباطًا إيجابيًا مهمًا بين مستويات Anti-TPO وTSH لدى مرضى HT الذين كان مستوى فيتامين د في مصلهم أكثر من 30 وارتباطًا سلبيًا بين مستويات TSH وfT3 لدى مرضى HT الذين كان مستوى فيتامين د في مصلهم أقل من 20.

الاستنتاجات: لوحظ انخفاض في مستوى 25(OH)D لدى مرضى HT، ويعد هرمون TSH عامل خطر مستقل للإصابة بـ HT. بالاضافة الى ذلك، كانت هناك فروقات معنوية كبيرة في مستويات Anti-TPO لدى النساء المصابات بـ HT بشكل عام وفي جميع الفئات (نقص، قصور، وكفاية).

INTRODUCTION

Hashimoto's thyroiditis (HT) is a kind of autoimmune thyroid disease (AITD) that is typified by organ-specific autoimmune illness, as evidenced by the death of thyrocytes and infiltration of lymphocytes. It is more frequent in women than in males [1,2]. Also known as autoimmune thyroiditis or chronic lymphocytic thyroiditis, this condition is brought on by immune cells attacking thyroid cells and is characterized by an increased thyroid volume, parenchymal lymphocyte infiltration, and thyroid gland-specific antibodies[3]. At the moment, hypothyroidism is mostly caused by HT[4, 5]. Vitamin D (Vit-D) is a fat-soluble vitamin that comes in two forms: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) [6]. The vitamin D receptor (VDR), which is found in the cell nucleus and activates genes that respond to vitamin D, is responsible for the effects of Vit-D. In addition to altering intracellular calcium levels [7], additional evidence points to vitamin D's potential role in a number of autoimmune disorders as immune cells have been shown to contain VDR [8]. Vit-D controls the inhibition of T-cell proliferation, which ultimately results in a decrease in the quantity of antigen-presenting cells [9]. It has a major impact on immune system modulation, boosting the innate

immune response and inhibiting the adaptive immune system, causing a Type 1 T helper (Th1) to T helper type 2 (Th2) shift, preventing dendritic cell (DC) differentiation and maturation, and skewing immune system cells toward a more tolerogenic status [(10)]. Serum 25(OH)D levels are classified as either sufficient or inadequate depending on whether they are equal to or higher than (30 ng/mL) (sufficiency), between (20 and 29.9 ng/mL) (insufficiency), or less than (20 ng/mL) (deficiency)[(11)]. The goals of this study were to determine whether there were any variations in Vit-D levels between women with HT and healthy women. It also aimed to determine whether there was any relationship between the levels of thyroid-stimulating hormone (TSH) released by the anterior pituitary, thyroid hormones [free triiodothyronine and free thyroxin] released by the thyroid gland, autoantibodies [Anti-thyroid peroxidase antibody (TPO-Ab) and anti-thyroglobulin antibody (Tg-Ab)] with Vit-D concentration in Kirkuk City.

MATERIAL AND METHODS

Study Design and Participants

The study group included 100 subjects whose ages ranged between (20-60 years). The group was divided into two subgroups: (50 healthy women) and (50 HT women). All patients were recruited for nearly eight months from January 2024 to August 2024 at the Azadi Teaching Hospital / Kirkuk and some Medical clinics, especially the Ochi Medical Complex. The Exclusion criteria in this study were: (Children, Men, Pregnant females, who were not from Iraq, Patients and control groups using the drug Vitamin D.

Samples collection

Four ml of venous blood samples were collected from selected patients and the control subjects. Every blood sample was given time to coagulate, then centrifuged for (15 minutes), then serum was separated, aliquoted and put into Eppendorf tubes till the analysis is done. Patients and the control group provided personal and clinical information through the use of a standardized questionnaire. Then assessed: Thyroid Antibodies [TPO-Ab and Tg-Ab], TSH, Thyroid Hormones [fT3and fT4], and 25-hydroxyvitamin D [25(OH)D] levels by using [Cobas e 411 analyzer series (Hitachi/Japan)] in accordance with the manufacturer's guidelines (German-born Roche). The ranges listed below were regarded as typical: Anti-TPO Normal Range (> 35), Anti-TG Normal Range (> 120), TSH Normal Range (0.27 - 4.3 µIU/ml), fT4 Normal Range (0.93 - 1.71 ng/dl), fT3 Normal Range (3.1 - 6.8 pmol/L). The study was approved by the ethical review board of (Azadi Teaching Hospital / Kirkuk). Informed verbal consents were obtained from participants, before blood samples from patients and following their permission.

Statistical analysis

Data entry was performed using an Excel spreadsheet then the statistical analysis was performed by the SPSS version 23 and Chi-square, Pearson correlation tests were used to compare the category data. P. values of 0.05 were used as a cut-off point for the significance of statistical tests.

RESULTS

The age range of the women recruited in this study was (20 to 60 years), the HT women having a mean age of (39.98 ± 11.185 years) and healthy women having a mean age of (39.82 ± 11.26-years). As seen in Figs. (1) and (2), the examination of the responses to the questionnaire revealed that the great majority of the female with HT respondents were married and resided in the city center (90 %). Additionally, (76 %) of them had a family history (FH) of the illness, (62 %) of them were experiencing psychological stress, and (42 %) had high levels of education.

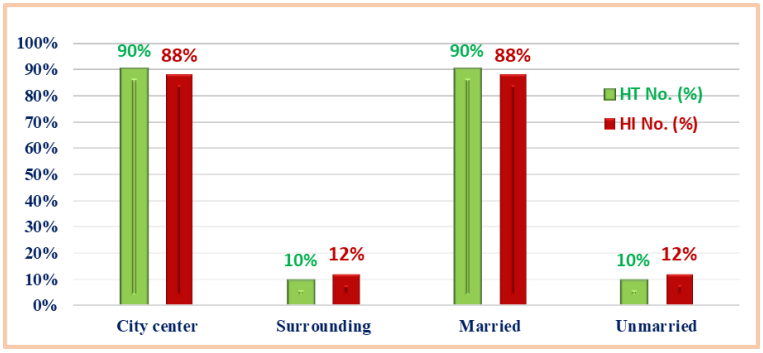

Fig. 1: Baseline socio-demographic characteristics of Hashimoto's thyroiditis (HT) and Healthy individuals (HI)

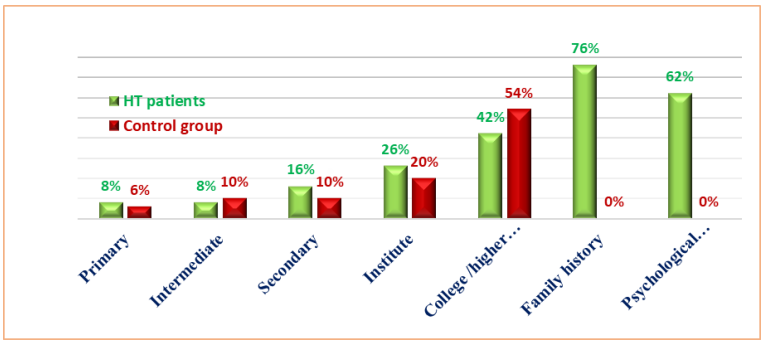

Fig. 2: Educational level, family history, and psychological state stress of study samples

By studying the changes in the variables resulting from Hashimoto's disease compared to healthy individuals, it was discovered that the patients' levels of TSH and antibodies (anti-TPO and anti-TG) were substantially higher ($p < 0.05$) than those of the healthy persons, (12.00 ± 18.560 µIU/mL vs. 2.31 ± 1.22 µIU/mL), (272.389 ± 177.799 IU/mL vs. 17.275 ± 6.751 IU/mL) and (207.769 ± 196.110 IU/mL vs. 38.947 ± 32.277 IU/mL), respectively in HT women compared with healthy women. Furthermore, fT3 and fT4 levels were significantly decreased ($p = 0.001$) in patients with HT than HI (2.889 ± 0.971 pmol/L vs. 4.610 ± 1.069 pmol/L) and (0.876 ± 0.220 Ng/dl vs. 1.258 ± 0.240 Ng/dl). Notably, there was a significant decrease in mean concentration (20.442 ± 12..669 ng/mL) of sera Vit-D levels among HT patients compared to their mean concentration (25.10 ± 6.02 ng/mL) in sera of the control group ($P = 0.021$). Fig (3).

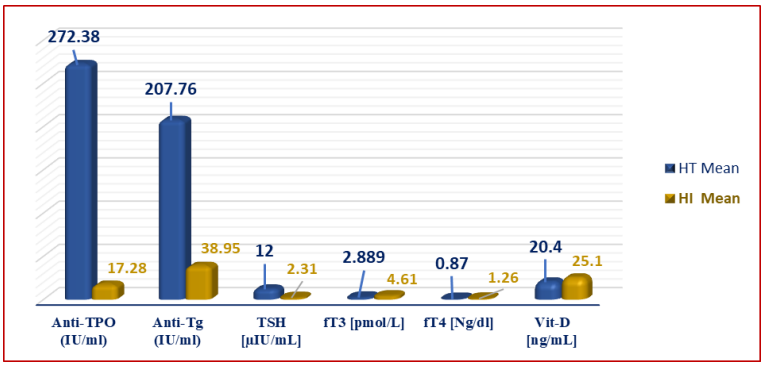

Fig. 3: The research participants' distribution based on the average levels of fT3, fT4 anti-TPO, ant-Tg, TSH, and Vit- D of study samples

When we studied the levels of thyroid antibodies, TSH and thyroid hormones in participants of the study in statuses of (Vit-D < 20), (Vit-D 20-30) and (Vit-D > 30), we found that in both statuses of (Vit-

D < 20) and (Vit-D 20-30) there was a highly significant increase in (Anti-TG, anti-TPO and TSH) of patients with HT compared to HI p = (0.057, 0.0003, and 0.007) and (0.034, 0.0002 and 0.026), respectively. Also, the fT3 decreased significantly in patients with HT compared to the HI (p =0.017 and 0.0003), respectively. Whereas, there was no significant difference seen in the levels of FT4. On the other hand, in range Vit-D [ng/mL] > 30 (Sufficiency) we can see the high significance increase of all Laboratory parameters (Anti-Tg, Anti-TPO, TSH and fT3) (p < 0.05) as shown in Table (1).

Table 1: The level of vitamin D with the levels of thyroid antibodies, TSH, and thyroid hormones participants of the study

parameters	No. (%)	HT (n = 50) (Mean ± SD)	No. (%)	HI (n = 50) (Mean ± SD)	P value
Vit-D [ng/mL] < 20 (Deficiency)					
Anti-Tg (IU/mL)	27(54 %)	337.0 ± 26.1	6(12 %)	41.0 ± 6.72	0.057 *
Anti-TPO (IU/mL)		242.00 ± 78.2		14.76 ± 4.95	0.0003**
TSH [µIU/ml]		12.5 ± 2.7		1.77 ± 0.43	0.007**
fT3 [pmol/L]		2.774 ± 0.914		4.66 ± 1.34	0.017**
fT4 [ng/dl]		1.37 ± 1.94		1.180 ± 0.215	0.628ns
Vit-D [ng/mL]		12.39 ± 4.68		15.40 ± 4.91	0.214ns
Vit-D [ng/mL] 20-30 (Insufficiency)					
Anti-Tg (IU/mL)	16(32 %)	225.0 ± 30.2	34(68 %)	49.5 ± 6.4	0.034*
Anti-TPO (IU/mL)		28.80 ± 3.40		18.00 ± 6.98	0.0002**
TSH [µIU/ml]		12.7 ± 3.51		2.36 ± 1.18	0.026*
fT3 [pmol/L]		3.002 ± 0.907		4.543 ± 0.990	0.0003**
fT4 [ng/dl]		2.32 ± 1.110		1.240 ± 0.265	0.185ns
Vit-D [ng/mL]		23.95 ± 2.74		24.49 ± 3.08	0.534ns
Vit-D [ng/mL] > 30 (Sufficiency)					
Anti-Tg (IU/mL)	7(14 %)	440.0 ± 41.7	10(20 %)	52.5 ± 14.3	0.050*
Anti-TPO (IU/mL)		352.0 ± 53.2		16.32 ± 6.97	0.001**
TSH [µIU/ml]		8.53 ±3.83		2.45±1.27	0.007**
fT3 [pmol/L]		3.07 ± 1.38		4.83 ± 1.25	0.019**
fT4 [ng/dl]		1.930 ± 0.594		1.375 ± 0.182	0.594 ns
Vit-D [ng/mL]		32.98 ± 4.03		43.50 ± 6.91	0.039*

When studying the correlations between the studied variables for patients in the three statuses of vitamin D, the result showed a significant positive association (r = 0.749, P value = 0.053) between the anti-TPO and TSH levels in HT patients whose serum vitamin D level was more than 30 in Fig (4). This study also discovered a negative association (r = -0.398) (p = 0.040) between the level of TSH and fT3 in HT patients whose serum vitamin D level was less than 20. Fig (5).

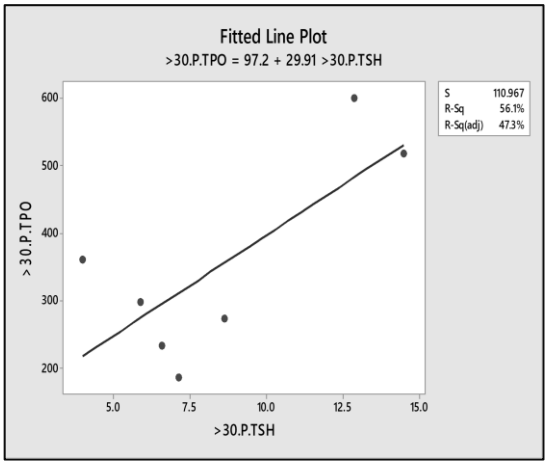

Fig. 4: Correlation between TSH and anti-TPO levels in HT patients with serum vit.D levels more than 30

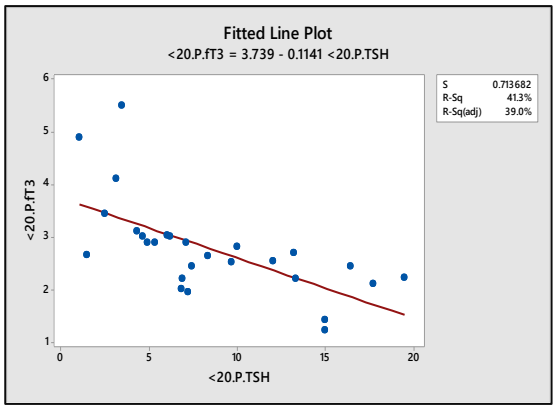

Fig. 5: Correlation between TSH and fT3 levels in HT patients with serum Vit-D less than 20

DISCUSSION

Immune system regulation is one of vitamin D's significant extra skeletal effects. A lack of vitamin D has been linked to autoimmune diseases, such as Hashimoto's thyroiditis, [12]. In our study, we found lower levels of vitamin D in HT patients compared with healthy women as seen in Fig (3). Similar results were obtained by Bozkurt et al. who also demonstrated that vit-D deficiency severity correlated with the duration of HT, antibody levels and thyroid volume [13]. Many researchers suggest that Vit-D can contribute to the inhibition of the immune process in Hashimoto's disease through four potential mechanisms: 1) Prevention of dendritic cell (DC) [DC-dependent T-cell activation], 2) Effect on B-cells and plasma cells, 3) Ratio restoration of the T helper 17 cells (Th17) /regulatory T cells (Tregs), and 4) Down-regulation of human leukocyte antigen (HLA) class II gene expression in the thyroid gland[14]. In our study, women with HT showed lower levels of vit- D in all states Vit-D (Deficiency), Vit-D (Insufficiency) and Vit-D > 30 (Sufficiency) compared to women without HT as seen in Table (1), which may be due to Vit-D having a significant effect on the immune system as VDRs are present in numerous cells, including (T and B cells), antigen-presenting cells (APCs) and dendritic cells (DCs) indicating that vitamin D plays an important role in regulating both innate and adaptive immune systems[15,16]. Accordingly, a lack of vitamin D may weaken the immune system, trigger inappropriate immunological reactions, and ultimately result in illnesses such as autoimmune disorders[9,17-19]. Additionally, Vit-D prevents the development and differentiation of DCs, which is particularly significant when autoimmune and the suppression of self-tolerance are involved. Thus, vitamin D would control T lymphocyte inflammatory activity and cell-mediated immune responses, so limiting autoimmune reactions that are overly severe [20] and several studies proven that the 1,25(OH)2D3-VDR complex can inhibit the expression of many pro-inflammatory cytokines from DCs that activate T lymphocytes such as Interleukins (IL-2, 5, 6, 12, 17, 23) Tumor necrosis factor (TNF), Interferon (INF-), Chemokine (C-C motif) ligand 5 (CCL5, and Chemokine (C-C motif) ligand 7 CCL17), while enhancing the expression of IL-8 and IL-10. Then may lead to the improvement of HT by shifting from the Th1 profile towards Th2, decrease of [cytokine-mediated immune response (CMIR)] and pathological Th17 responses [20, 21]. Anti-TPO and anti-Tg were shown to be connected with vitamin D insufficiency, indicating that vitamin D may be involved in individuals with HT [22-25]. Our results recorded that patients with lower Vit D level, had substantially greater levels of thyroid antibodies (anti-TPO, anti-TG) and TSH than healthy women. Furthermore, the parameters mentioned above showed a significant increase in the serum levels of anti-TPO, anti-TG and TSH for three statuses of vitamin D (Vit-D < 20 (Deficiency), Vit-D 20-30 (Insufficiency), and Vit-D > 30 (Sufficiency) in HT women, as seen in Table (1), Similarly, Riseh et al. noted significant increased in the level of TSH ($P = 0.032$) and anti-TG ($p < 0.001$) as well as anti-TPO ($p < 0.001$) [26]. This may be revealed to the role of B cells in the pathogenesis of HT mainly by producing autantibodies (anti-TPO and anti-Tg) which are thyroid self-antigens, these autoantibodies contribute to the apoptosis of thyroid follicular cells in the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC) [27].

Furthermore, Vit-D has been proven to exert inhibitory effects on plasma cell generation, then may be turn, contribute to decreased immunoglobulin production [28] Notably, some studies have suggested that insufficient 25(OH)D concentrations are correlated with increased B-cell differentiation, proliferation, and antibody titers in AIDs, such as HT and SLE [29]. Numerous research (case-control or cross-sectional studies) have revealed a probable relationship between vitamin D insufficiency and an increased risk of HT development [30-32]. The level of TSH and anti-TPO exhibited a strong positive association as shown in Fig. (4). Likewise, a noteworthy positive connection (r = 0.134, P value = 0.036) was seen between the anti-TPO level and the TSH level [33]. This investigation discovered a strong negative association between the levels of TSH and fT3 in individuals with blood Vit-D < 20 as seen in Fig (5). The present result agreed with Al-Rabia's findings, there are substantial inverse relationships (r = -0.289) between TSH and T3 hormone levels[34]. It is known that TSH stimulates the secretion of thyroid hormones through negative feedback. When the concentration of thyroid hormones fT3 and fT4 decreases, the concentration of TSH increases, as in hypothyroidism[35] we concluded that in all three categories presented in Table (1), free T4 results were not statistically significant. Our results is consistent with the study by Ke et al. reported no correlation between low levels of vitamin D in GD and HT and free T4 and TSH[33]. Another study by Cvek et al. results showed a weak significant negative correlation between Vit- D levels and TSH in all HT patients (r =−0.113) [36]. Vit- D inhibits the differentiation of naive T- cells into T helper 17 cells therefore the levels of Tregs increase, which restores the Th17/Treg ratio in the body[37]. Several studies confirmed the important role of increased Th17/Treg ratio in the pathogenesis of various AIDs, including HT [38]. Th17 cells express mainly pro-inflammatory activity, which contributes to the development of inflammation and autoimmune disorders, whereas Tregs modulate the immune system and maintain tolerance to self-antigens which prevents autoimmunity[39]. The study by [40] showed that the follicular thyroid cells of HT patients may express MHC class II molecules, for presenting antigens to CD4+ T cells. 1,25(OH)D can reduce MHC II expression, thus preventing T-cell activation and pro-inflammatory cytokine response[40]. Most studies observed significant associations between vitamin D deficiency and TSH values in HT patients or weak negative correlations between vitamin D levels and TSH [11, 34]. Furthermore, Low Vit- D levels have also been implicated as a risk factor in thyroid disorders [41] and other autoimmune diseases such as rheumatoid arthritis (RA) as reported in Nagi's study [42] and systemic lupus erythematosus (SLE) syndrome [43] and diabetes mellitus[44,45]. Since Vit-D has immunomodulatory effects, its deficiency is a risk factor and indicator of these diseases [42, 43].

CONCLUSION

A lower 25(OH)D level is seen in patients with HT, and TSH is a separate risk factor for HT. In addition, there was a high significance increase in Anti-TPO levels in general and in the three status (Vit-D < 20), (Vit-D 20–30), and (Vit-D > 30).

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Author contribution: Authors contributed equally in the study.

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