Estimation of IL-8, IL-38, Vitamin D, TPO Ab, and CRP Levels in Iraqi Hashimoto Thyroiditis Patients

Mayada Noori Iqbal, Jaleel Samanje
College of Health and Medical Technique, Middle Technical University, Baghdad, Iraq

Abstract

Background: Hashimoto's disorder is an autoimmune disease affecting cells of the thyroid gland via the diffusion of the lymphocytes into thyroid cells. Calcitriol is the active form of Vit.D3; there were a strong correlation between low Vit-D levels and development of autoimmune diseases exists and calcitriol supplementation might play a protective role in the pathophysiology of autoimmune diseases. **Objectives:** This study aimed to estimate the levels of interlukin-8 (IL-8), interlukin-38 (IL-38), Vitamin D, thyroid peroxidase (TPO) Ab, and c-reactive protein (CRP) in Iraqi patients suffering from Hashimoto disease. **Materials and Methods:** In this study, 90 individuals (males and females) were enrolled, and divided into two groups: Hashimoto's disorder group (60) patients and the healthy control group (30) persons were checked by the physician with the aid of medical history. The levels of TSH, Vit.D3, anti-TPO Ab, T4, IL-8, and IL-38 were measured for all the study groups. **Results:** A highly significant reduction ($P < 0.001$) was shown in mean levels of Vit D, T4, and IL-38 among the patient's group in comparison with the controls, whereas a significant reduction ($P < 0.05$) was revealed in mean levels of CRP among patients in comparison with the controls. Also, the results showed a highly significant elevation ($P < 0.001$) in mean levels of TSH, IL-8, and anti-TPO antibodies among the Hashimoto disease group in comparison with the controls. **Conclusion:** Hashimoto disease caused highly significant decreases in mean levels of Vit. D, T4, IL-38, and CRP, whereas there was a highly significant increase in the levels of TSH, IL-8, and anti-TPO antibodies.

Keywords: IL-8, anti TPO, Hashimoto disease, IL-38, TSH, Vit D.

Introduction

Hashimoto's disorder is a thyroid cell disorder considered an autoimmune disorder; this disorder is caused by the diffusion of some lymphocytes into thyroid gland cells. It acts to produce autoantibodies that are able to alter and disrupt the role of thyroid gland cells. This disorder can affect people of all ages and women suffer more from it.[1] The most common types of lymphocytes that infiltrate into cells of the thyroid gland are T and CD+ type-1 T-helper cells, and such diffusion lymphocytes can synthesize special autoantibody types like thyroid peroxidase antibodies (TPO-Abs). The autoantibodies show some features on the thyroid gland, for example, thyroid goiter, hypothyroidism, and others.[2] In addition, lymphocytes (T cells and CD+ type-1 T-helper cells) have effects on immune system response between CD+ type-1 and 2 T-helper cells, which help in the development of CD+ type-1 T-helper cells, which play important roles in autoimmune reactions as a mediator in Hashimoto disorder. Hashimoto thyroid disorder progression is already a lag; therefore, this disorder is considered as an asymptomatic disorder at an early stage but able to detect the thyroid gland hypofunctions and TPO antibodies in the blood sample by laboratory investigations.[3] Calcitriol is a steroid compound and is considered an active form of vit.D3; it acts via a specific mediator called vit. D receptor (VDR) in body cells. The calcitriol is synthesized by activation of vit. D3. Vit.D3 enters

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1503_23

Address for correspondence: Dr. Jaleel Samanje, College of Health and Medical Technique, Middle Technical University, Baghdad, Iraq.
E-mail: Jaleel.najah@mtu.edu.iq

Submission: 03-Oct-2023 **Accepted:** 01-Dec-2023 **Published:** 17-Jul-2024

How to cite this article: Iqbal MN, Samanje J. Estimation of IL-8, IL-38, vitamin D, TPO Ab, and CRP levels in Iraqi Hashimoto thyroiditis patients. Med J Babylon 2024;21:425-30.

into the human body via two sources: exogenous from foods as D3 and endogenous from cutaneous or under-skin synthesis by conversion of some cholecalciferol compounds.[4] Cholecalciferol first arrives in the liver, then the kidney metabolizes it via various enzyme activities and becomes an active form known as calcitriol. The major role of calcitriol is the calcification of bones and Ca homeostasis with PO4. The recent results of the study showed other roles for calcitriol at the genetic regulation level because some un-regulation genes can cause various diseases like cancer, metabolic syndrome, and autoimmune disease. Calcitriol acts to regulate gene expression by binding calcitriol with nuclei VDR to target special genes to regulate them.[5]The humoral and cellular immunities play crucial roles in the development of HT disease, despite the exact cause of the disease has not been completely shown yet. Cytokines are thought to be involved in the autoimmune thyroid disease onset because of their activity within both the effector phase and induction of inflammatory and immunological responses. Both intrathyroidal inflammatory cells and thyroid follicular cells were shown to produce a group of cytokines, for example, IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-14, IFN-γ, and TNF-α.[6] The cytokines IL-6, IL-10, IL-17, IL-22, and TNF-α were proven to play essential roles in HT pathogenesis.[7] IL-38 which belongs to the IL-1 family is highly homologous to IL-1 receptor antagonists (IL-1Ra) and IL-36Ra and functions as an anti-inflammatory cytokine. The expression of IL-38 occurs in the heart, placenta, spleen, liver, thymus, and fetal tissues.[8] The levels of IL-38 and autoimmune disorders such as rheumatoid arthritis[9] and systemic lupus erythematosus[10] have been significantly associated. Despite the sufficiency of the present diagnostic criteria of HT, these criteria do not present information on the included immunopathological mechanism. Studies mentioned before suggest that IL-8, IL-38, and Vit.D3 can be regarded as essential biomarkers aiding in understanding this topic and can be correlated with the pathogenesis of diseases. Hence, the aim of our study was the estimate the levels of S. IL-8 and IL-38 among HT patients and correlates them with Vit.D3 status and other clinical characteristic. Interpretation of such correlations can be useful for understanding inflammatory mechanisms in HT.

Materials and Methods

In this study, 90 Iraqi individuals (males and females) were enrolled, and divided into two groups: Hashimoto's disorder group (60) patients, and the healthy control group (30) persons. The study was done in Al-Yarmouk Hospital/Iraq from July to September 2022. Control group included 30 apparently healthy individuals. They were not complaining of any chronic medical diseases with normal clinical examinations. there were no history of thyroid diseases or any chronic illness that may interfere with our results. They were not on vitamin D supplements. American Thyroid Association (ATA) rules and criteria were applied to all participants in the study to confirm the diagnosis of Hashimoto's disorder.[11] After the complete diagnosis, a written approval statement was taken from each participant.

The levels of TSH, Vit.D3, anti-TPO Ab, T4, IL-8, and IL-38 were measured for all the study groups. Venous blood samples were collected from all study groups and centrifuged after clotting to obtain serum samples, which were used for the measurement of the thyroid stimulating hormone (TSH), thyroxine hormone (T4), and anti-thyroid peroxidase antibodies (anti-TPO-Ab) by using the Cobas and Tosoh instruments, whereas the enzyme-linked immunosorbent assay (ELISA) technique (Catalogue No. MBS-269990 and MBS-580159 consecutively, My BioSource) was used for estimation of the levels of interleukin-8, interleukin-38, and Vit. (1,25-dihydroxyvitamin D) according to the manufacturer's instructions.

Ethical approval

This study was consented by Al-Rusafa Health Directorate Ethical Committee (no. 938 of date 14.2.2022).

Statistical analysis

The SPSS software program, version 25.0 was used for data analysis in the study. The *t* test statistical method, mean (±), standard deviation (SD), and *P*-values were applied to explain the different values after comparing between groups according to previously measured parameters. A value of $P \geq 0.05$ was considered statistically significant.

Results

In this study, the participants were divided into wo groups: 60 Hashimoto patients as a case group and 30 healthy individuals as controls. A highly significant reduction ($P < 0.001$) was shown in mean levels of Vit D, T4, and IL-38 among the patient's group (10.46 ± 3.29, 2.69 ± 1.18, 49.12 ± 10.33), respectively, as compared with their mean levels in the control group ($23.21 \pm 4.376.07 \pm 0.89$, 81.31 ± 7.13), respectively, whereas there was a significant decrease ($P < 0.05$) in the mean level of CRP among the case group (0.69 ± 0.18) as compared with its mean level in the control group (0.81 ± 0.23). There was also a highly significant increase ($P < 0.001$) in mean levels of TSH, IL-8, and anti-TPO antibodies among the Hashimoto disease group (7.03 ± 1.61, 9.38 ± 2.99, 62.98 ± 10.69), respectively, as compared with their mean levels in the controls (4.00 ± 1.07, 3.57 ± 0.66, 22.00 ± 5.06), respectively, as shown in Table 1 and Figure 1.

In this study, the sensitivity of TSH, T4, anti-TPO, IL38, IL-8, and Vit D were 94%, 0%, 100%, 0.04%, 100%,

and 0%, respectively, whereas the specificity of the same parameters were 77%, 100%, 100%, 97%, 100%, and100%, respectively, as shown in Table 2 and Figure 2.

Table 1: Comparison of the mean serum values of Vit. D, TSH, T4, anti TPO-Ab, IL-38, IL-8 and CRP between cases (n = 60) and control (n = 30)

Test	Groups	Mean ± SD	*t* test	*P* Value	Significant
VitD (ng/mL)	Case	10.46 ± 3.29	13.81	≤0.001	H.S
	Control	23.21 ± 4.37			
TSH (mIU/mL)	Case	7.03 ± 1.61	10.08	≤0.001	H.S
	Control	4.00 ± 1.07			
T4 (µg/dl)	Case	2.69 ± 1.18	14.45	≤0.001	H.S
	Control	6.07 ± 0.89			
Anti-TPO (U/mL)	Case	62.98 ± 10.69	23.27	≤0.001	H.S
	Control	22.00 ± 5.06			
IL-38 (pg/mL)	Case	49.12 ± 10.33	16.52	≤0.001	H.S
	Control	81.31 ± 7.13			
IL-8 (pg/mL)	Case	9.38 ± 2.99	13.31	≤0.001	H.S
	Control	3.57 ± 0.66			
CRP (pg/mL)	Case	0.69 ± 0.18	2.29	0.026	S
	Control	0.81 ± 0.23			

Regarding the ROC of IL-38, Table 3 shows reverse results, as it was decreased among patients but increased among controls; therefore, the sensitivity of the test decreased below 1, whereas it was specific for healthy individuals because its level was high. This is confirmed because the mean IL-38 value was 81 in the healthy group, whereas the cutoff value of the kit was 89. The results of this study documented there was a highly significant positive correlation of the levels of Vit.D with T4 and IL-38 at (r = 0.745,0. 765, P = 0.000), respectively, whereas Vit.D levels appeared significantly negative correlation IL-8, anti-TPO-Ab, and TSH, whereas there were a highly significant correlation between the levels TSH and the levels of IL-8 and anti-TPO-Ab levels with (r = 0.627,0.567, P = 0.000), respectively. The results of this study also observed there was a highly significant correlation between the levels of T4 and the levels of IL-38 with (r = 0,696, P = 0.000), as shown in Table 3.

Discussion

In our study, highly significant decreases in the levels of Vit D, T4, and IL-38 were found in patient's group in comparison with the controls, whereas a significant reduction in the CRP level among patients when compared

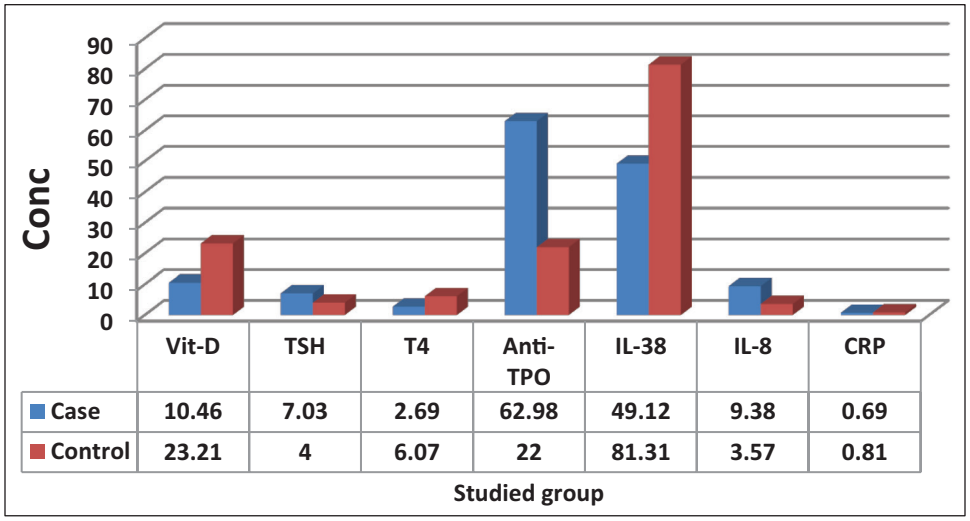

Figure 1: Comparison of the mean serum values of Vit. D, TSH, T4, anti TPO-Ab, between cases (n = 60) and controls (n = 30)

Table 2: ROC for the studied parameters used in this study

Test	Cutoff point	(AUC)	Asymptotic sig.	Asymptotic 95% CI		Sensitivity	Specificity
				LB	UB		
TSH	4.7	.941	.000	.894	.988	94	77
T4	9.3	.008	.000	.000	.021	0	100
Anti-TPO	38.95	1.000	.000	1.000	1.000	100	100
IL-38	89.45	.068	.000	.009	.126	0.04	97
IL-8	5.75	1.000	.000	1.000	1.000	100	100
VitD	31.90	.014	.000	.000	.034	0	100

AUC = area under curve, sig = significant, LB = lower bound, UB = upper bound, CI = confidence interval

with the control group. The results also showed a highly significant increase in the levels of TSH, IL-8, and anti-TPO antibodies among the Hashimoto disease group in comparison with the controls.

In regard to Vit. D, decreased Vit. D levels were reported and related to Hashimoto disease progression in a study done by,[12] which agrees with our finding recently, some studies showed that vitamin D may play a role in elevating the risk of HT disease.[13] Nevertheless, there is controversial information about the roles of vitamin D deficiency in HT pathogenesis such as certain studies that indicate the possible relationship between vitamin D deficiency and HT pathogenesis, and that supplementation of the vitamin can be useful to treat HT.[14]

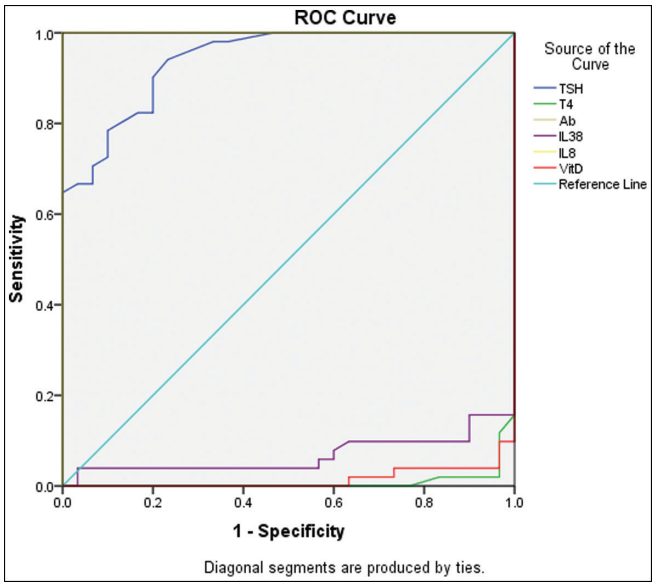

Figure 2: Receiver operating characteristic curve (ROC) for the studied parameters used in this study

Based on these findings, deficiency of vitamin D is thought to be a common problem, although it is more frequent in autoimmune thyroiditis and primary hypothyroidism patients, and this can be attributed to the ability of immunomodulatory ability of the vit. D.[15] Following the VDR discovery in nearly all tissues, new information appeared providing essential perception into the pleiotropic impacts of vitamin D and its possible roles in different extra-skeletal tissue, such as those affecting endocrine diseases (Addison's disease, *Diabetes mellitus*, PCOS as well as autoimmune thyroid disorders).[16]

Furthermore, studies have recently indicated that 1,25(OH)2D modulates both adaptive and innate immune systems. Vitamin D targets immune cells like macrophage, monocyte, dendritic cell, B-lymphocyte, and T-lymphocyte.[17] Production of different cytokines may be promoted by Vit. D deficiency, leading to autoimmune thyroiditis development and usually causes reduced thyroid functions.[15] There is an important role of Vitamin D in endocrine and immune processes, as recently as meta-analysis including 26 observational studies revealed a significant decrease in the levels of 25-hydroxyvitamin D (25(OH)D) in HT patients than the control group.[18] The influence of vitamin D on the immunity of HT patients remains unclear. Certain studies reported a significant

Table 3: Correlation between studied parameters in Hashimoto disease patients

		VitD	TSH	T4	anti TPO-Ab	IL-38	IL-8	CRP
VitD (ng/mL)	R	1	–.578	.745	–.803	.765	–.698	.176
	P-value		.000	.000	.000	.000	.000	.116
	N	81	81	81	81	81	81	81
TSH (mIU/mL)	R	–.578	1	–.578	.627	–.639	.567	–.238
	P-value	.000		.000	.000	.000	.000	.032
	N	81	81	81	81	81	81	81
T4 (µg/dl)	R	.745	–.578	1	–.756	.696	–.634	.206
	P-value	.000	.000		.000	.000	.000	.066
	N	81	81	81	81	81	81	81
Anti TPO-Ab (U/mL)	R	–.803	.627	–.756	1	–.813	.674	–.241
	P-value	.000	.000	.000		.000	.000	.030
	N	81	81	81	81	81	81	81
IL-38 (pg/mL)	R	.765	–.639	.696	–.813	1	–.790	.216
	P-value	.000	.000	.000	.000		.000	.053
	N	81	81	81	81	81	81	81
IL-8 (pg/mL)	R	–.698**	.567**	–.634**	.674**	–.790**	1	–.236*
	P-value	.000	.000	.000	.000	.000		.034
	N	81	81	81	81	81	81	81
CRP (pg/mL)	R	.176	–.238*	.206	–.241*	.216	–.236*	1
	ys	.116	.032	.066	.030	.053	.034	
	N	81	81	81	81	81	81	81

decrease of thyroid autoantibodies following 25(OH) D_3 supplementations to HT patients who are vitamin D deficient, indicating that treatment with vitamin D delays hypothyroidism development.[19] On the contrary, other studies concluded that no significant influence was observed on thyroid autoantibodies following vit. D supplementation in HT patients.[20] We can conclude that in Hashimoto's thyroiditis, the decreased levels of free T4 can be used to predict vit. D inadequacy, indicating that the status of thyroid hormones may play a role in maintaining vitamin D adequacy, and its immunomodulatory role may affect the existence of autoimmune thyroid disorder.[21]

Moreover, the positive relation between vit. D and free T4 levels indicated that sufficient levothyroxine replacement in HT could be an important factor in vitamin D maintenance in adequate concentrations.[22] In agreement with our result, it was found that TPOAb concentration was elevated in patients with HT.[23]The studies showing the impact of vit. D supplementations on thyroid functions mainly involved patients having autoimmune thyroid disorders. Most of these studies showed that vit. D supplementations led to a significant decrease in anti-thyroid antibodies (TPOAbs and TgAbs).[24] AbTPO can be used to predict hypothyroidism, and those who have high titers of serum AbTPO are at higher risks of developing HT. AbTPO antibodies can produce two cytotoxicity types (antibody and complement-dependent cytotoxicities). In fact, these cytotoxicities destroy thyroid tissues, leading to the death of thyroid cells and hypothyroidism.[25] TPO is the main enzyme found in thyroid cell and engaged in the synthesis of iodinated tyrosine, in the coupling of iodinated tyrosine, and other functions.[26] The positivity of TPOAb and TGAb, particularly nearly 100% TPOAb positivity, is one of the essential criteria to diagnose Hashimoto encephalopathy.[27] Nonetheless, it was not recognized whether antithyroid antibodies have direct roles in Hashimoto encephalopathy pathogenicity or simply function as an autoimmune reactivity marker.[28] In the HT patient group, a significantly decreased serum IL-38 level was detected when compared with the control group. The results of[23] also agreed with our findings. The immune cells widely express IL-38, which is a recently identified IL-1F member, and this cytokine plays essential roles in various inflammatory autoimmune disorders, nevertheless, there is a poor understanding of the exact functional and signaling pathways because it was discovered 60 yrs. ago. Similarly to IL-1Ra & IL-36Ra, IL-38 is regarded as an antagonist, that mostly inhibits Th17 cytokine and is correlated to the severity and treatment of the disease, indicating that IL-38 can illustrate a powerful biomarker to predict the development of inflammatory autoimmune disorders and the clinical efficacy of inflammatory autoimmune medication. Since the IL-38 nature in common inflammatory autoimmune disorders is well shown, it was has shown that this cytokine can be used as a biomarker for the development of other inflammatory autoimmune disorders.[29] Significantly decreased levels of IL-38 in HT suggest its related synergistic effects. Because of deficient scientific evidence on IL-38, more purinergic receptors are actively engaged in several cellular and metabolic changes in the disease such as cellular differentiation and proliferation, which are down-regulated in cases of Hashimoto thyroiditis.[30] Results in this study showed decreased S. IL-38 levels in HT and GD in comparison with HC, and this finding is in agreement with IL-38 properties as an anti-inflammatory cytokines. Nevertheless, this result disagreed with other studies regarding increased IL-38 cytokine expression in inflammatory disorders, e.g. RA and SLE. In AITD and other autoimmune disorders, the variable IL-38 levels can be partly due to the different pathogenicity of different diseases. The major features of AITD are autoimmune antibody productions, lymphocytic infiltrations, and thyroid-related hormone dysregulations.[30] In Hashimoto's disorder, there is a significant decrease in IL-38 as an immunological response, which can be attributed to several factors such as the possible increase in serum P2Y1, P2Y2, and P2Y4 antagonists in Hashimoto thyroiditis. The purinergic receptor antagonists including MRS 2179, PPADS and suramin may be produced by different cells for inhibition and minimizing the effects of purinergic receptors. Consequently, IL-38 could act as a major cause for purine receptor inhibition in Hashimoto's disease via the releasing and chemical inhibition of purine receptors that result in the genetic down-regulation of Hashimoto's disorder.[30]

With regard to IL-8, our results agreed with[31] and,[32] which reported that IL-8 is significantly elevated in HT cases in comparison with the healthy control group. In this study, a negative association of pro-inflammatory cytokine concentrations with total concentrations of vit. D was shown in HT cases, i.e. with the reduced concentrations of total vit. D, the levels of inflammatory cytokines start to increase.[33] The levels of pro-inflammatory cytokines: IL-1B, IL-8, IL-10, and TNF-α were shown to increase significantly in Hashimoto disorder patients, who produce anti-thyroid peroxidase antibodies and/or anti-thyroglobulin antibodies in comparison with the age- and sex-matched control group.[31]

This study is compatible with the study of[33] who showed a significantly high level of CRP in hypothyroid patients. We noticed a positive correlation between TSH and CRP values in HT patients. This result indicates that CRP is a beneficial tool to diagnose HT and to assess this disorder.[23] From these studies, our study concluded that elevated inflammatory marker CRP in hypothyroidism may be due to weakening the rate of CRP clearance because of the absence of thyroid hormones. As well, the interaction between IL-1 and IL-6 on TNF-α leads to increased CRP levels in Hypothyroidism.[33]

Conclusion

Our study confirmed that Hashimoto's disease caused highly significant decreases in Vit. D, T4, IL-38, and CRP levels, could be associated with an increased risk of disease developing, whereas there was a highly significant increase in the levels of TSH, IL-8, and anti-TPO antibodies. More studies are needed to delineate further the pathophysiologic mechanisms of thyroid involvement and the related role of vitamin D status. In addition, long-term studies of thyroid dysfunction in Hashimoto's thyroiditis patients would be informative Majority of patients had un insufficient VD levels. VD may have a role in the pathogenesis of the disease which presumably causes high levels of TPO-Ab.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Weetman AP. An update on the pathogenesis of Hashimoto's thyroiditis. J Endocrinol Invest 2021;44:883-90.
2. Guan H, de Morais NS, Stuart J, Ahmadi S, Marqusee E, Kim MI, *et al*. Discordance of serological and sonographic markers for Hashimoto's thyroiditis with gold standard histopathology. Eur J Endocrinol 2019;181:539-44.
3. Sur ML, Gaga R, Lazăr C, Lazea C. Genetic and environmental factors in the pathophysiology of Hashimoto's thyroiditis. Pediatr Endocrinol Rev 2020;17:343-8.
4. DeGiorgio CM, Hertling D, Curtis A, Murray D, Markovic D. Safety and tolerability of Vitamin D3 5000 IU/day in epilepsy. Epilepsy Behav 2019;94:195-7.
5. Carlberg C. Vitamin D: a micronutrient regulating genes. Curr Pharm Des 2019;25:1740-6.
6. Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, *et al*; American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-39.
7. Travaglino A, Pace M, Varricchio S, Insabato L, Giordano C, Picardi M, *et al*. Hashimoto thyroiditis in primary thyroid non-Hodgkin lymphoma: a systematic review and meta-analysis. Am J Clin Pathol 2020;153:156-64.
8. Miteva MZ, Nonchev BI, Orbetzova MM, Stoencheva SD. Vitamin D and autoimmune thyroid diseases: a review. Folia Med (Plovdiv) 2020;62:223-9.
9. Muscogiuri G, Mari D, Prolo S, Fatti LM, Cantone MC, Garagnani P, *et al*. 25 hydroxyvitamin D deficiency and its relationship to autoimmune thyroid disease in the elderly. Int J Environ Res Public Health 2016;13:850.
10. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010;10:482-96.
11. Behera KK, Saharia GK, Hota D, Sahoo DP, Sethy M, Srinivasan A. Effect of Vitamin D supplementation on thyroid autoimmunity among subjects of autoimmune thyroid disease in a coastal province of India: A randomized open-label trial. Niger Med J 2020;61:237-40.
12. Planck T, Shahida B, Malm J, Manjer J. Vitamin D in Graves disease: levels, correlation with laboratory and clinical parameters, and genetics. Eur Thyroid J 2018;7:27-33.
13. Vondra K, Stárka L, Hampl R. Vitamin D and thyroid diseases. Physiol Res 2015;64:S95-S100.
14. Nodehi M, Ajami A, Izad M, Asgarian Omran H, Chahardoli R, Amouzegar A, *et al*. Effects of vitamin D supplements on frequency of CD4+ T-cell subsets in women with Hashimoto's thyroiditis: a double-blind placebo-controlled study. Eur J Clin Nutr 2019;73:1236-43.
15. Turashvili N, Javashvili L, Giorgadze E. Vitamin D deficiency is more common in women with autoimmune thyroiditis: A retrospective Study. Int J Endocrinol 2021;2021:2021.
16. Tompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. 2e Lancet 2018;391:1622-36.
17. Ke W, Sun T, Zhang Y, He L, Wu Q, Liu J, *et al*. 25-Hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. Endocr J 2017;64:581-7.
18. Štefanić M, Tokić S. Serum 25-hydoxyvitamin D concentrations in relation to Hashimoto's thyroiditis: A systematic review, meta-analysis and meta-regression of observational studies. Eur J Nutr 2020;59:859-72.
19. Jia R. Observation on the efficacy of calcitriol combined with levothyroxine sodium tablets in Hashimoto's thyroiditis with hypothyroidism. J Med Forum 2020;41:133-5.
20. Chahardoli R, Saboor-Yaraghi AA, Amouzegar A, Khalili D, Vakili AZ, Azizi F. Can supplementation with vitamin D modify thyroid autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and thyroid profile (T3, T4, TSH) in Hashimoto's thyroiditis? A double blind, randomized clinical trial. Horm Metab Res 2019;51:296-301.
21. Botelho IM, Neto AM, Silva CA, Tambascia MA, Alegre SM, Zantut-Wittmann DE. Vitamin D in Hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status. Endocr J 2018;65:1029-37.
22. Zhang J, Chen Y, Li H, Li H. Effects of vitamin D on thyroid autoimmunity markers in Hashimoto's thyroiditis: Systematic review and meta-analysis. J Int Med Res 2021;49:3000605211060675.
23. Xu J, Huang G, Weng L, Gong L, Mao Y, Li Y, *et al*. Low serum interleukin-38 levels in patients with Graves' disease and Hashimoto's thyroiditis. J Clin Lab Anal 2022;36:e24101.
24. Babić Leko M, Jureško I, Rozić I, Pleić N, Gunjača I, Zemunik T. Vitamin D and the Thyroid: A Critical Review of the Current Evidence. Int J Mol Sci 2023;24:3586.
25. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, *et al*. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Pract Res Clin Endocrinol Metab 2019;33:101367.
26. Ramhøj L, Svingen T, Frädrich C, Rijntjes E, Wirth EK, Pedersen K, *et al*. Perinatal exposure to the thyroperoxidase inhibitors methimazole and amitrole perturbs thyroid hormone system signaling and alters motor activity in rat offspring. Toxicol Lett 2022;354:44-55.
27. Ercoli T, Defazio G, Muroni A. Cerebellar syndrome associated with thyroid disorders. Cerebellum (London, England) 2019;18:932-40.
28. Ercoli T, Defazio G, Muroni A. Status epilepticus in Hashimoto's encephalopathy. Seizure 2019;70:1-5.
29. Xie L, Huang Z, Li H, Liu X, Zheng SG, Su W. IL-38: a new player in inflammatory autoimmune disorders. Biomolecules 2019;9:345.
30. Saleem K, Alhadrawy MK, Abood AH, HUSSAIN HM. Evaluation Levels of Immunoglobin G and Lipid Profile in Patients Infected with Hyatid Cyst in Al-najaf Governate, Iraq. Asian J Microbiol Biotechnol Environ Sci 2016;18:101-4.
31. Siddiq A, Naveed AK, Ghaffar N, Aamir M, Ahmed N. Association of Pro-Inflammatory Cytokines with Vitamin D in Hashimoto's Thyroid Autoimmune Disease. Medicina (Kaunas, Lithuania) 2023;59:853.
32. Provatopoulou X, Georgiadou D, Sergentanis TN, Kalogera E, Spyridakis J, Gounaris A, *et al*. Interleukins as markers of inflammation in malignant and benign thyroid disease. Inflamm Res 2014;63:667-74.
33. Kshetrimayum V, Usha SM, Vijayalakshmi P. A study of hs-CRP and lipid profile in hypothyroid adults at tertiary care hospital. Int J Clin Biochem and Res 2019;6:303-10.