ORIGINAL ARTICLE

Effect of Vitamin D deficiency treatment on thyroid function and autoimmunity markers in Hashimoto's thyroiditis: A double-blind randomized placebo-controlled clinical trial

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Background: The link between autoimmune thyroid diseases and Vitamin D deficiency has been reported. However, there are controversies in this regard. We conducted a double-blind randomized placebo-controlled clinical trial to investigate the effect of Vitamin D deficiency treatment on thyroid function and autoimmunity marker (thyroid peroxidase antibody [TPO-Ab]) in patients with Hashimoto's thyroiditis. **Materials and Methods:** Fifty-six patients with Hashimoto's thyroiditis and Vitamin D deficiency (25-hydroxyvitamin D level ≤20 ng/mL) were randomly allocated into two groups to receive Vitamin D (50000 IU/week, orally) or placebo for 12 weeks, as Vitamin D-treated (n = 30) and control (n = 26) groups, respectively. TPO-Ab, thyroid-stimulating hormone (TSH), parathormone, calcium, albumin, and creatinine concentrations were compared before and after trial between and within groups. The data were presented as mean (standard error [SE]) and analyzed by appropriate tests. **Results:** Mean (SE) of Vitamin D was increased in Vitamin D-treated group (45.5 [1.8] ng/mL vs. 12.7 [0.7] ng/mL, P = 0.01). Mean (SE) of TPO-Ab did not significantly change in both groups (734 [102.93] IU/mL vs. 820.25 [98.92] IU/mL, P = 0.14 in Vitamin D-treated and 750.03 [108.7] [IU/mL] vs. 838.07 [99.4] [IU/mL] in placebo-treated group, P = 0.15). Mean (SE) of TSH was not changed in both groups after trial, P = 0.4 and P = 0.15 for Vitamin D-treated and control groups, respectively. No significant difference was observed between two study groups in none studied variables (P > 0.05). **Conclusion:** Vitamin D treatment in Vitamin D deficient patients with Hashimoto's thyroiditis could not have significant effect on thyroid function and autoimmunity.

Key words: Autoimmune thyroiditis, clinical trial, Iran, peroxidase, thyroid-stimulating hormone, Vitamin D deficiency

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INTRODUCTION

Vitamin D deficiency is a common medical condition and an important focus of research. Vitamin D has been known for its role in regulation of calcium and bone development since many years ago.[1] Recently, the receptors of 1,25-dihydroxyvitamin D have been found on many cells, including immune cells.[2,3] The expression of 1α hydroxylase (cyp27B1) activity in many of these cells supports[4-6] the idea that the Vitamin D has immunomodulating effects. Several genetic studies have shown an association between gene polymorphism of Vitamin D receptor and of 1α hydroxylase (cyp27B1)[7-10] with autoimmune thyroid diseases (AITDs). However, some papers do not support these associations.[11]

The role of Vitamin D has been suggested in many chronic diseases[12] and immune disorders such as multiple sclerosis,[13,14] rheumatoid arthritis, and type I diabetes mellitus.[15-17] However, the relationship between Vitamin D and AITDs is still a controversial issue.[18] Many studies have already pointed out a relation between low concentration of Vitamin D and AITDs;[19-22] however, the cause and effect relationship is not known. The findings

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of one prospective case-control study wer54e performed in Amsterdam[23] and did not support the association between low Vitamin D level and early stages of thyroid autoimmunity.

Most of the above-mentioned studies have a cross-sectional design, and to our best knowledge, no clinical trials have already been conducted on the effectiveness of Vitamin D treatment among Vitamin D deficient patients with AITDs.

Many of these studies have recommended that interventional clinical trials are necessary to determine the causal effect of Vitamin D deficiency in the pathogenesis of thyroid autoimmune diseases. Therefore, we designed this clinical trial to investigate the effect of Vitamin D deficiency treatment on thyroid function and autoimmunity marker, thyroid peroxidase antibody (TPO-Ab), in patients with Hashimoto's thyroiditis. The results of this study may be helpful to improve the management of AITDs and their prevention in susceptible people.

MATERIALS AND METHODS

Study design and participants

In this double-blind placebo-controlled randomized clinical trial which was conducted from February to July 2015 in Isfahan Endocrine and Metabolism Research Center (IEMRC), 120 hypothyroid or euthyroid adults with positive TPO-Ab were selected by consecutive sampling method. Hypothyroid patients were euthyroid and stable on levothyroxine at least for 6 months or had mild hypothyroidism on enrolment (thyroid-stimulating hormone [TSH] <15 mU/L). Serum Vitamin D levels of selected patients were measured. Those people with 25-hydroxyvitamin D (25[OH] D) ≤20 ng/mL were included in the study. Patients with renal or liver disease, cancer, pregnancy, severe weight loss, and those who were on immunosuppressive medication, insulin, sulfonamides, or any supplement were excluded from the study. Those patients who were on levothyroxine, metformin, or statin treatment enrolled if their medications had been started at least 6 months before enrolment, and no dose adjustment was done during the study period.[24] Study design explained for each person and participants knew that they may receive drug or placebo, and if they were in placebo group after completion of the study, their Vitamin D deficiency would be corrected by treatment. Each participant gave and signed a written informed consent. The research protocol was complied with the ethical standards of Helsinki Declaration (Edinburgh 2000) and approved by Regional Ethics Committee of Isfahan University of Medical Sciences.

The trial also was registered in the Iranian Registry of Clinical trials (IRCT) with the registration number IRCT2014120520216N1.

Procedures and variables assessment

Finally, 65 persons enrolled the study. Participants were randomly allocated using simple randomization to intervention (Vitamin D-treated) and control (placebo-treated) groups. Randomization was performed by a third person, and sealed drug boxes with label A or B were given to each person. Neither patients nor researchers knew the content of the boxes. After trial, the codes were broken. Patients in Vitamin D-treated group (n = 33) were assigned to receive pearls of Vitamin D, 50,000 unit weekly and those in control group (n = 32) were received placebo weekly for 12 weeks [Figure 1]. Both Vitamin D and placebo pearls were provided and manufactured by Zahravi's pharmaceutical company, Tehran-Iran.

Demographic characteristics and medical history of all studied population were recorded. Physical examination was done by an expert endocrinologist. The blood pressure was measure by ERKA sphygmomanometer, weight and height by SECA stadiometer, and waist circumference by tape meter. Body mass index was calculated by dividing weight (kg) by square of height (m^2).

At the beginning and at the end of the trial, two blood samples were taken from each person, one clot and one ethylenediaminetetraacetic acid containing blood sample. Biochemical tests including calcium (Ca), phosphorus (P), albumin, C-reactive protein (CRP), blood urea nitrogen, and creatinine (Cr) were measured on the day of sampling. However, the serum samples taken to measure TPO-Ab, TSH, 25(OH)D, and parathormone (PTH) froze and stored at −20°C to be analyzed at the same time with the second sample at the end of the trial.

Laboratory tests

All biochemical tests were done by photometric assays (BT 2000) using Pars kit (Tehran, Iran). TPO-Ab, PTH, and TSH were

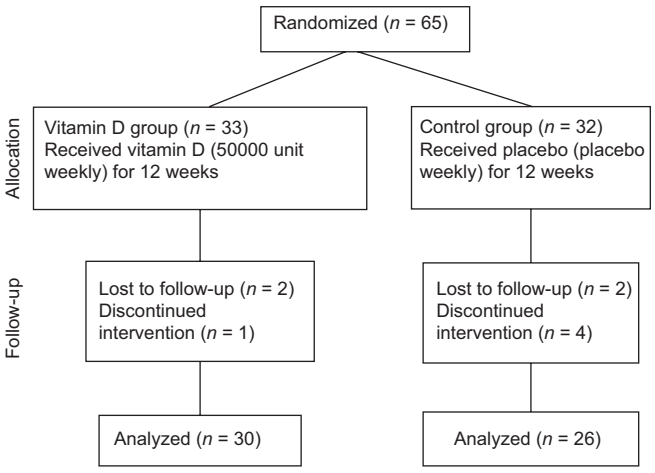

Figure 1: Consort diagram of the study in Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups

measured by chemiluminescent immunoassay method (Advia Centaur CP, Siemens Healthcare Diagnostic Inc., USA).

Vitamin D measured by enzyme-linked immunosorbent assay kit (Immunodiagnostic Systems Limited, UK).

Statistical analysis

Continuous quantitative variables were expressed as mean and standard error of the mean (standard error) and qualitative variables as frequency and percentage. Normality of data was evaluated by Kolmogorov–Smirnov test and normal Q-Q plot. Log transformation was used for skewed data (including TSH, TPO-Ab, and CRP). Paired *t*-test was used for within-group comparisons, and between-group comparison was performed by multivariate analysis of covariance. Box's M-test was used for evaluating homogeneity of covariance matrixes. To compare the qualitative variables, Chi-square test was used. All data analysis was done using SPSS for Windows, version 20 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was statistically significant.

RESULTS

Three persons in Vitamin D-treated group and six persons in placebo-treated group were excluded or dropped. Finally, a total of 30 Vitamin D-treated and 26 placebo-treated participants attended the baseline examination and entered in statistical analysis [Figure 1]. No one developed hypercalcemia during the study.

The clinical characteristics of the study participants are shown in Table 1. Demographic, anthropometric, and laboratory data were not significantly different between Vitamin D- and placebo-treated groups at baseline ($P > 0.05$).

The concentrations of 25(OH)D, TSH, and TPO-Ab at baseline in vitamin D- and placebo-treated groups are presented in Table 1 and Figure 2a-c. The mean of 25(OH)D was 12.76 (0.74) ng/mL and 13.28 (0.86) in Vitamin D- and placebo-treated groups, respectively, at baseline ($P = 0.98$) [Table 1].

The mean of the biochemical measurements including TPO-Ab, TSH, PTH, calcium, albumin, and creatinine in Vitamin D- and placebo-treated groups at baseline and after trial are presented in Table 2.

Within-group comparison in Vitamin D-treated group, showed significant decrease for PTH ($P = 0.001$) but not for TSH, TPO-Ab, or other variables ($P > 0.05$). In placebo-treated group, there was not any significant changes in studied variables ($P > 0.05$).

Between-group analyses showed significant difference only in terms of mean PTH when adjustment was made for baseline values. No significant difference was observed between two study groups in none studied variables ($P > 0.05$).

DISCUSSION

We investigated the effect of Vitamin D treatment on autoimmune thyroid marker (TPO-Ab) and thyroid

Table 1: Demographic and clinical characteristics of Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups

	Placebo group (*n*=26)	Vitamin D group (*n*=30)	*P*
Female sex, *n* (%)	15 (59)	21 (70)	0.31
Levothyroxine consume, *n* (%)	8 (30.8)	13 (45)	0.28
Age, mean (SE), (years)	44.12 (1.56)	43.55 (1.56)	0.81
Weight, mean (SE), (kg)	72.67 (2.12)	71.67 (2.15)	0.74
BMI, mean (SE), (kg/m^2)	26.9 (0.61)	27.48 (0.73)	0.54
SBP, mean (SE), (mmHg)	114.3 (2.37)	119.7 (2.50)	0.12
DBP, mean (SE), (mmHg)	78.47 (1.73)	78.87 (1.66)	0.56
25(OH)D, mean (SE), (ng/mL)	12.76 (0.74)	13.28 (0.86)	0.98
TPO-Ab, mean (SE), (IU/mL)	838.07 (99.37)	820.25 (98.92)	0.97
Ca, mean (SE), (mg/dL)	8.85 (0.13)	9.01 (0.09)	0.20
P, mean (SE), (mg/dL)	3.26 (0.11)	3.53 (0.91)	0.04
Alb, mean (SE), (g/dL)	4.12 (0.05)	4.22 (0.04)	0.12
PTH, mean (SE), (ng/L)	45.45 (3.65)	47.70 (2.8)	0.92
CRP, mean (SE), (mg/dL)	1.16 (0.07)	1.10 (0.06)	0.71
BUN, mean (SE), (mg/dL)	28.22 (1.30)	26.7 (0.8)	0.54
Cr, mean (SE), (mg/dL)	0.88 (0.02)	0.84 (0.02)	0.37
TSH, mean (SE), (mU/L)	3.45 (0.43)	3.30 (0.5)	0.57

P<0.05 were statistically significant. SE = Standard error; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; 25(OH)D = 25-hydroxyvitamin D; TSH = Thyroid-stimulating hormone; TPO-Ab = Thyroid peroxidase antibody; CRP = C-reactive protein; PTH = Parathormone; Ca = Calcium; P = Phosphorus; Alb = Albumin; CRP = C- reactive protein, BUN = Blood urea nitrogen; PTH = Parathormone

Table 2: Mean (standard error) of biochemical parameters at baseline and after trial in Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups

	Vitamin D group (*n*=30)			Placebo group (*n*=26)			$P^{\dagger}$
	Baseline	3 months	P^{+}	Baseline	3 months	P^{+}	
25(OH)D (ng/mL)	12.76 (0.74)	45.53 (1.84)	0.001	13.28 (0.86)	14.92 (1.06)	0.09	0.001
TSH (mU/L)	3.30 (0.5)	3.88 (0.82)	0.40	3.45 (0.43)	2.66 (0.38)	0.09	0.16
TPO-Ab (IU/mL)	820.25 (92)	734 (102.93)	0.138	838.07 (99.37)	750.03 (108.71)	0.15	0.95
CRP (mg/dL)	1.10 (0.06)	1.11 (0.07)	0.89	1.16 (0.07)	1.16 (0.08)	0.97	0.79
PTH (ng/L)	47.7 (2.8)	37.97 (2.26)	0.001	45.45 (3.65)	43.07 (2.27)	0.45	0.05
Ca (mg/dL)	9.01 (0.09)	9.04 (0.05)	0.77	8.85 (0.13)	8.86 (0.1)	0.91	0.19

[+]Resulted from paired *t*-test; [†]Resulted from multivariate analysis of covariance, adjustment was done for baseline values. *P*<0.05 was statistically significant.
25(OH)D = 25-hydroxyvitamin D; TSH = Thyroid-stimulating hormone; TPO-Ab = Thyroid peroxidase antibody; CRP = C-reactive protein; PTH = Parathormone; Ca = Calcium

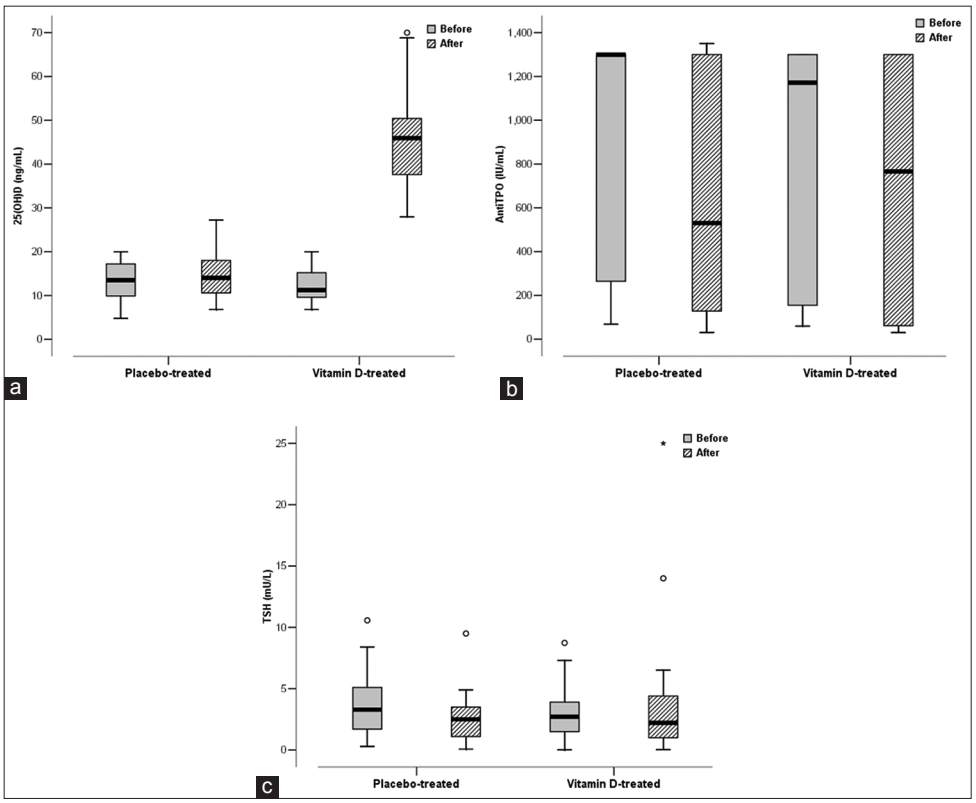

Figure 2: (a) Concentrations of Vitamin D 25-hydroxyvitamin D at baseline and after trial in Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups. (b) Concentration of thyroid peroxidase antibody at baseline and after trial in Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups. (c) Concentrations of thyroid-stimulating hormone at baseline and after trial in Vitamin D deficient, thyroid peroxidase antibody positive, euthyroid or hypothyroid patients, randomized in Vitamin D and placebo groups

function (TSH) in Vitamin D deficient hypothyroid or euthyroid adult patients with positive TPO-Ab. Our results indicated that Vitamin D did not have a significant effect on thyroid function and autoimmunity of studied population.

Kivity *et al*. in a cross-sectional study compared the level of Vitamin D in patients with AITDs, non-AITDs, and healthy people. They showed that the prevalence of Vitamin D deficiency was significantly higher in patients with AITDs than healthy persons. The rate of Vitamin D deficiency was also higher in patients with non-AITDs than healthy population.[25]

Shin *et al*. in Korea studied the association between Vitamin D and TPO-Ab in patients with and without AITDs. They demonstrated that there was a significant negative correlation between Vitamin D level and TPO-Ab in patients with AITDs.[20]

In a study in Turkey, Bozkurt *et al*. studied the relation between Vitamin D deficiency and Hashimoto's thyroiditis. They compared the level of Vitamin D and severity of Vitamin D deficiency between euthyroid patients with Hashimoto's thyroiditis and a healthy control group. Their results pointed out that there was correlation between severity of Vitamin D deficiency and thyroid volume, level

of thyroid autoantibodies as well as duration of Hashimoto's thyroiditis. They concluded that Vitamin D may have potential role both in development and progression of Hashimoto's thyroiditis to hypothyroidism.[21]

In a study in Tehran, Iran, Mansournia *et al*. reached to the similar conclusions. Furthermore, they showed that by 5 ng/mL increases in the level of Vitamin D, the risk of occurrence of Hashimoto's thyroiditis would be decreased by 19%.[26]

Several other studies also reported similar results regarding the inverse association between Vitamin D level and AITDs.[26-30]

On the other hand, some studies did not support the association between Vitamin D and thyroid autoimmunity.[23,31-34] Effraimidis *et al*. have conducted two case–control researches in the framework of Amsterdam AITD cohort study to determine the association between Vitamin D and early stages of thyroid autoimmunity. In one cross-sectional study, they compared the concentration of serum Vitamin D between euthyroid participants with genetic susceptibility for AITDs and negative thyroid antibodies and controls who were healthy women without family history of AITDs. In another longitudinal study, they compared level of Vitamin D between those euthyroid persons with genetic susceptibility for AITDs who developed TPO-Ab and those who did not. Their findings showed higher Vitamin D level in euthyroid participants with genetic susceptibility to AITDs than control group but not any significant differences between patients with newly diagnosed thyroid autoimmunity than control group. They concluded that Vitamin D is not correlate with early stages of thyroid autoimmunity.[23]

D'Aurizio *et al*. did not find any association between low Vitamin D levels and AITDs, too.[31]

The strength of our clinical trial was its novelty. This was the first randomized controlled clinical trial which evaluated the effects of Vitamin D treatment on thyroid autoimmune disease (Hashimoto's thyroiditis), in a prospective manner. We rely on 25(OH)D measurement to define Vitamin D deficiency (≤20 ng/mL) and assessing treatment efficacy with increasing the concentration of 25(OH)D to more than 30 ng/mL. We measured the baseline autoimmune marker and Vitamin D levels at the same time.

The limitations of this study were small sample size and short duration of follow-up period.

We recommend a larger sample size and longer follow-up and enrolment of people with positive family history of AITDs as they are more prone to AITDs and may benefit from potential prevention protocols.

CONCLUSION

The findings of this clinical trial did not support the hypothesis that Vitamin D treatment can improve thyroid autoimmune diseases.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Holick MF. Phylogenetic and evolutionary aspects of Vitamin D from phytoplankton to humans. Vertebrate Endocrinology: Fundamentals and Biomedical Implications. Vol. 3. Orlando: Academic Press; 1989. p. 7-43.
2. Takahashi K, Nakayama Y, Horiuchi H, Ohta T, Komoriya K, Ohmori H, *et al.* Human neutrophils express messenger RNA of Vitamin D receptor and respond to 1alpha, 25-dihydroxyvitamin D3. Immunopharmacol Immunotoxicol 2002;24:335-47.
3. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science 1983;221:1181-3.
4. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: Vitamins A and D take centre stage. Nat Rev Immunol 2008;8:685-98.
5. Hart PH, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: More than just the effects of Vitamin D? Nat Rev Immunol 2011;11:584-96.
6. Holick MF. Vitamin D: Extraskeletal health. Rheum Dis Clin North Am 2012;38:141-60.
7. Pani MA, Knapp M, Donner H, Braun J, Baur MP, Usadel KH, *et al.* Vitamin D receptor allele combinations influence genetic susceptibility to type 1 diabetes in Germans. Diabetes 2000;49:504-7.
8. Pani MA, Seissler J, Usadel KH, Badenhoop K. Vitamin D receptor genotype is associated with Addison's disease. Eur J Endocrinol 2002;147:635-40.
9. Horst-Sikorska W, Ignaszak-Szczepaniak M, Marcinkowska M, Kaczmarek M, Stajgis M, Slomski R. Association analysis of Vitamin D receptor gene polymorphisms with bone mineral density in young women with Graves' disease. Acta Biochim Pol 2008;55:371-80.

10. Stefanic M, Papic S, Suver M, Glavas-Obrovac L, Karner I. Association of vitamin D receptor gene 3'-variants with Hashimoto's thyroiditis in the Croatian population. Int J Immunogenet 2008;35:125-31.
11. Collins JE, Heward JM, Nithiyananthan R, Nejentsev S, Todd JA, Franklyn JA, *et al.* Lack of association of the Vitamin D receptor gene with Graves' disease in UK Caucasians. Clin Endocrinol (Oxf) 2004;60:618-24.
12. Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080S-6S.
13. Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC, *et al.* Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62:60-5.
14. Smolders J, Schuurman KG, van Strien ME, Melief J, Hendrickx D, Hol EM, *et al.* Expression of Vitamin D receptor and metabolizing enzymes in multiple sclerosis-affected brain tissue. J Neuropathol Exp Neurol 2013;72:91-105.
15. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinol Metab Clin North Am 2010;39:419-46.
16. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: A systematic review and meta-analysis. Arch Dis Child 2008;93:512-7.
17. Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy Study Group. Diabetologia 1999;42:51-4.
18. Bizzaro G, Shoenfeld Y. Vitamin D and autoimmune thyroid diseases: Facts and unresolved questions. Immunol Res 2015;61:46-52.
19. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with Vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev 2012;12:127-36.
20. Shin DY, Kim KJ, Kim D, Hwang S, Lee EJ. Low serum Vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. Yonsei Med J 2014;55:476-81.
21. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, *et al.* The association between severity of Vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract 2013;19:479-84.
22. Mackawy AM, Al-Ayed BM, Al-Rashidi BM. Vitamin D deficiency and its association with thyroid disease. Int J Health Sci (Qassim) 2013;7:267-75.
23. Effraimidis G, Badenhoop K, Tijssen JG, Wiersinga WM. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. Eur J Endocrinol 2012;167:43-8.
24. Cardoso-Sánchez LI, Gómez-Díaz RA, Wacher NH. Vitamin D intake associates with insulin resistance in type 2 diabetes, but not in latent autoimmune diabetes in adults. Nutr Res 2015;35:689-99.
25. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, *et al.* Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol 2011;8:243-7.
26. Mansournia N, Mansournia MA, Saeedi S, Dehghan J. The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis. J Endocrinol Invest 2014;37:473-6.
27. Tamer G, Arik S, Tamer I, Coksert D. Relative Vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid 2011;21:891-6.
28. Arslan MS, Topaloglu O, Ucan B, Karakose M, Karbek B, Tutal E, *et al.* Isolated Vitamin D deficiency is not associated with nonthyroidal illness syndrome, but with thyroid autoimmunity. ScientificWorldJournal 2015;2015:239815.
29. Unal AD, Tarcin O, Parildar H, Cigerli O, Eroglu H, Demirag NG. Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. Cent Eur J Immunol 2014;39:493-7.
30. Simsek Y, Cakir I, Yetmis M, Dizdar OS, Baspinar O, Gokay F. Effects of Vitamin D treatment on thyroid autoimmunity. J Res Med Sci 2016;21:85.
31. D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is Vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? Autoimmun Rev 2015;14:363-9.
32. Ma J, Wu D, Li C, Fan C, Chao N, Liu J, *et al.* Lower Serum 25-Hydroxyvitamin D level is associated with 3 types of autoimmune thyroid diseases. Medicine (Baltimore) 2015;94:e1639.
33. Saler T, Keşkek ŞO, Ahbab S, Cakir S, Ortoğlu G, Bankir M, Pamuk OA. Frequency of Hashimoto's thyroiditis in women with Vitamin D deficiency: A cross sectional study. Am J Internal Med 2014;2:44-8.
34. Anaraki PV, Aminorroaya A, Amini M, Feizi A, Iraj B, Tabatabaei A. Effects of Vitamin D deficiency treatment on metabolic markers in Hashimoto thyroiditis patients. J Res Med Sci 2017;22:5.