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The association between vitamin D and Hashimoto's thyroiditis

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Abstract

Hashimoto's thyroiditis is probably the most common autoimmune disease treated in endocrinology clinics. It is still contraversial whether vitamin D deficiency is a cause or result of Hashimoto's throiditis. However pleiotropic effects of vitamin D have been described recently in many studies that its deficiency could be a predisposing factor for autoimmune diseases. This clinical research aims to show the relationship between vitamin D deficiency and Hashimoto thyroiditis. One hundred twenty six participants who admitted to family medicine clinics in year 2017 during a 6 months period of time at Izmir Katip Celebi University Hospital in Turkey were included in our cross sectional study. Openepi sample size calculator predicted 95% of confidence interval, 80% of power and 5% of tolerence with consisting a number of 38 individuals in each group. Patients were grouped as previously diagnosed Hashimoto's thyroiditis, newly diagnosed Hashimoto's thyroiditis and healthy individuals. After supplying reserved participants which consist of 10% of the total, 42 individuals recruited in each group. Vitamin D levels were significantly lower in both previously diagnosed Hashimoto and newly diagnosed Hashimoto groups than control group with values of 12.62ng/dl, 11.76ng/dl and 15.03ng/dl respectively ($p < 0.05$). Vitamin D insufficiency found to be correlated with TSH, fT4, anti-TPO, anti-Tg, kreatin, PTH levels, BMI, smoking and female gender ($p < 0.05$). Multiple regression analysis of these parameters via retrospective elimination method showed that vitamin D is negatively correlated with BMI and anti-Tg. On the other a positive correlation with fT4 was also shown in the study. Vitamin D deficiency may be a predisposing factor for Hashimoto's disease.

Keywords: Vitamin D deficiency, hashimoto disease, thyroiditis, autoimmune, antibodies

Introduction

Vitamin D deficiency is a public health issue throughout the world and found to be associated with a wide variety of chronic diseases such as cancer, cardiovascular diseases, metabolic diseases, infectious diseases, autoimmune diseases and even mortality [1]. Although frequency of vitamin D insufficiency changes by the location of countries its prevelance was reported to be higher than 93% worldwide with a cut off value of 20 ng/mL [2,3]. Furthermore vitamin D deficiency is more prevalent in populations with Hashimoto's disease compared to healthy individuals [4-8]. Hashimoto's autoimmune thyroid disease which is probably the most common autoimmune disease, is also among the most common endocrine disorder worldwide [9]. The prevalence of Hashimoto's disease is now estimated to be 10-12% in general population [6,10-12]. Anti TPO antibody positivity which is found to be present in nearly 21% of the population was reported more frequent in people with lower vitamin D levels [13,14]. Vitamin D seems to prevent steps towards thyroid damage and antibody production [8]. by inhibiting dendritic cell dependent T-cell activation and stimulating CD4 T cells [9].

Thyroid gland infiltration by lymphocytes ends with chronic damage causing hormone deficiency in Hashimoto's disease [15]. It is thought that a T-cell originated immune disfunction which occurs through interaction of sensitive genes and environmental factors, is the cause of progressive tissue destruction [6,16]. Factors likely to play a role in the etiology are dietary iodine intake, smoking, alcohol, yersinia enterocolitika and viral infections, selenium deficiency, stress, cytokine therapy, estrogen therapy, pregnancy, female gender, fertility and age [15]. However there is a few case control study representing association between vitamin D deficiency and Hashimoto's thyroiditis. A number of studies reported a significant negative correlation between serum 25 (OH) D and anti-TPO but it is still of concern whether vitamin D deficiency is a cause or result of Hashimoto thyroiditis [16,17].

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We claim that vitamin D might play a role at pathogenesis of Hashimoto's thyroiditis. This clinical research aims to show the relationship between D vitamin deficiency and Hashimoto's thyroiditis through comparison the presence of autoantibody with vitamin D levels between groups.

Materials and Methods

Design of the Study

'Openepi sample size calculator' is used for calculating the sample size. Because of the prevalence of vitamin D deficiency is 92% in patients with Hashimoto disease and is 63% in healthy population, sample size of 114 individual is calculated with 95% CI, 80% power, %5 tolerence with a minimum 38 individual in each group [18]. Candidates who were between 18-85 years old whom with either anti TPO antibody or anti TG antibody are included the study. Patients with any disease or use of agents affecting bone metabolism were excluded. Other criterias for exclusion were history of thyroidectomy, pregnancy and lactating. 12 participants which is 10% of total was calculated for backup. With the addition of this supply 42 individuals recruited in each group reaching a number of 126 totally. Izmir, a seaside city of Turkey which is available for sunshine exposure in the summer was the study center.

Participants were divided into 3 groups. The first group consists of patients who were previously diagnosed with Hashimoto's disease regardless of being on treatment. Patients who are diagnosed recently were in the second group. And the third group with healthy individuals defined as control. TSH was not taken into consideration while grouping. Abbott Architect appliance was used to detect vitamin D level using chemiluminescent microparticle immunoassay (CMIA) method in our study.

Hashimoto disease was diagnosed by the presence of either anti TPO antibody or anti TG antibody(anti-TPO:0-57U/ml; anti-TG: 0-60U/ml) [19].

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Statistical Analyse

SPSS 20 demo pack program was used for statistical analyses. Mean, median, standard deviation, smallest-largest values were collected as numerical variables and numbers, ratios, percentages were colected as categorical variables from study and were used for descriptive analysis. Normal distribution of data was tested by visual (histogram and probability) and analytical method (Kolmogorov Smirnov). Chi-square, One-Way Anova, Kruskal-Wallis and Mann Whitney U analytical tests were used for comparisons between groups in accordance with the variable feature. Leneve test was used to evaluate the homogeneity of variances. Relationships between groups were evaluated by correlation and linear regression. Values with a p value of less than 0.05 were considered statistically significant.

Results

Individuals in each group was equally distributed with a percentage of 33.3 % (n:42). There was no statistically significant difference between the groups according to BMI, educational status, gender, smoking. As seen in Table 1 a statistical difference was observed between groups in terms of age (p = 0.011). This difference was originated between patients who were previously diagnosed Hashimoto and control group (p <0.017).

Table 1. Demographic Data

	Previously diagnosed Hashimoto (n=42)	Newly diagnosed Hashimoto (n=42)	Control Group (n=42)	Statistical Analysis	
	Mean ±SD	Mean ±SD	Mean ±SD		
Age	44±12.31	38.38±12.34	36.71±9.68		
	n(%)	n(%)	n(%)	X2	P
Gender					
Men	7(29.2)	5(20.8)	12(50)	4.015	0.134
Women	35(34.3)	37(36.3)	30(29.4)		
Educational Status					
Primary school or below	21(47.7)	10(22.7)	13(29.6)	16.115	0.03
Secondary school or high school	13(37.1)	16(45,7)	6(17.2)		
University level or above	8(17)	16(34.1)	23(48.9)		
Smoker					
Yes	12(31.6)	13(34.2)	13(34.2)	0.075	0.963
No	30(34.1)	29(33)	29(33)		
Body Mass Index (BMI)					
Underweight	1(25)	2(50)	1(25)	8.372	0.212
Normal	9(20.9)	17(39.5)	17(39.5)		
Overweight	16(36.4)	11(25)	17(38.6)		
Obese	16(45.7)	12(34.3)	7(20)		

Table 2 shows the average vitamin D levels of 12.62 ng/ml, 11.76 mg/ and 15.03 mg / dl in previously diagnosed Hashimoto group, newly diagnosed Hashimoto group and control groups respectively.

Post Hoc analysis of laboratory values that may be associated with vitamin D are given in Table 3. While TSH, fT3, anti-TPO, anti-Tg, vitamin D and PTH levels were statically significant ($p < 0.05$), fT4, creatin, BUN, ALP, FPG, calcium, and phosphorus values were not ($p > 0.05$).

Table 2. Vitamin D Status in the Population

	Previously diagnosed patients	Newly diagnosed patients	Control group	Total
Severe deficiency	45.2% (n:19)	40.5% (n:17)	28.6% (n:12)	38.1% (n:48)
Deficiency	42.9% (n:18)	52.4% (n:22)	52.4% (n:12)	49.2% (n:62)
Sufficiency	7.1% (n:3)	4.8% (n:2)	14.3% (n:12)	8.7% (n:11)
Normal	4.8% (n:2)	2.4% (n:1)	4.8% (n:12)	4.0% (n:5)
Average vitamin D	12.6 mg/dL	11.76mg/dL	15.3mg/dL	12.26mg/dl

Table 3. Relationship Between Groups in Terms of Numerical Parameters

	Previously Diagnosed Hashimoto (n=42)		Newly diagnosed Hashimoto (n=42)		Control Group (n=42)				Newly-Prevouly Diagnosed Hashimoto	Previously Diagnosed Hashimoto	Control Group
Anova	**Medium**	**Sd**	**Medium**	**Sd**	**Medium**	**Sd**	**F**	**P**		**Tukey**	
Age	44.00	12.31	38.38	12.24	36.71	9.68	4.643	0.011	0.068	0.012	0.784
BMI	28.75	5.28	26.14	5.17	25.98	3.93	4.343	0.150	0.039	0.026	0.986
fT4	1.06	0.23	0.99	0.17	1.08	0.13	2.728	0.069	0.206	0.860	0.070
Creatinin	0.72	0.13	0.70	0.09	0.72	0.09	0.489	0.615	0.748	0.975	0.614
BUN	11.40	3.32	11.16	3.01	10.40	3.005	1.167	0.315	0.935	0.313	0.507
Calcium	9.00	0.46	9.00	0.42	9.03	0.38	0.090	0.914	0.994	0.950	0.912
Phosphorus	3.47	039	3.54	0.51	3.60	0.61	0.659	0.519	0.812	0.487	0.856
ALP	70.71	19.89	66.11	23.72	61.14	12.61	2.582	0.080	0.522	0.064	0.467

	Previously Diagnosed Hashimoto (n=42)			Newly diagnosed Hashimoto (n=42			Control Group (n=42)							
Kruskal Wallis	**Med.**	**Min**	**Max**	**Med.**	**Min**	**Max**	**Med.**	**Min**	**Max**	**X2**	**P**	**Mann-Whitney U**		
TSH	2.88	<0.01	105.65	2.95	0.18	37.59	1.62	0.16	6.80	14.905	0.001	0.893	0.001	<0.001
fT3	2.86	2.13	8.74	3.04	1.6	4.00	3.06	2.42	3.68	13.681	0.001	0.003	0.001	0.932
AntiTPO	439.55	28.00	1300	1300	28	16664	28.00	28.00	28.00	65.590	<0.001	0.217	<0.001	<0.001
AntiTg	74.05	15.00	500	114.9	15	156700	15.00	15.00	21.60	68.878	<0.001	0.170	<0.001	<0.001
FBG	88.00	71.00	136.00	90	68	114	86,50	73.00	147	1.066	0.587	0.490	0.629	0.343
Vitamin D	11.00	4.80	36.70	10.75	3.40	40.80	13.70	5.20	35.10	6.432	0.040	0.893	0.043	0.019
PTH	53.7	17.00	236	47.7	19.1	101	35.2	15.1	92.5	13.131	0.001	0.129	<0.001	0.029

*Post Hoc analysis ($p<0.017$)

Demographic datas related to vitamin D levels are shown in Table 4. Although a negative correlation between vitamin D level and age was detected it was not statistically significant(Spearman rho = -0.052, p = 0.559). Vitamin D level was lower in smokers when compared to non-smokers. A significant, low level positive correlation between smoking and vitamin D levels was detected (Spearman rho = 0.237, p = 0.007). Body weight was also found to be associated with levels of vitamin D. Higher BMI was correlated with lower vitamin D levels. Low level significant negative correlation was found between BMI and vitamin D level. (Spearman rho = -0.245, p = 0.006). It was found that vitamin D level was lower in women than in men (Spearman rho = -0.226, p = 0.011) . Correlation between laboratory values and vitamin D is shown in Table 5. While TSH, fT4, PTH, anti-TPO and anti TG levels were significantly correlated with vitamin D level there was no such a significant correlation between fT3, FBG, BUN, calcium, phosphorus, ALP and vitamin D levels (p> 0.05). Spearrman correlation analysis showed a correlation between smoking, gender, BMI, TSH, fT4, Anti-TPO, Anti-Tg, kreatine, PTH and vitamin D. By using multiple regression analysis a significant but negative correlation between both BMI (Beta: -0.261 min: -0.505, max: -0.018, p: 0.036) (Figure 2), and anti-Tg (Beta: -0.011 min: -0.021, max: - 0.002, p: 0.016) and vitamin D was determined. On the other hand a positive significant correlation with fT4 was also determined(Beta = 6.374, min = 0.018 max = 12.370, p = 0.049).

Table 4. Correlation between demographic data and vitamin D level

	Vitamin D Level	
	Rho	**P**
Age	-0.052	0.559
Smoking	0.237	0.007
BMI	-0.245	0.006
Gender	-0.226	0.011

Rho: Spearman correlation factor. P<0.05

Table 5. Correlation between laboratory values and vitamin D

	Vitamin D Level	
	Rho	**P**
TSH	-0.213	0.017
fT4	0.211	0.018
fT3	0.057	0.524
FBG	-0.084	0.348
Creatinie	0.249	0.005
BUN	0.035	0.694
Calcium	0.174	0.051
Phosphorus	-0.077	0.390
PTH	-0.195	0.029
ALP	0.003	0.976
Anti-TPO	-0.287	0.001
Anti-Tg	-0.239	0.007

Rho: Spearman correlation factor. P<0.05

Discussion

Although 25 (OH) D levels between 10 ng/ml and 30 ng/ml are suggested for the diagnosis of vitamin D insufficiency in humans [20-22]. There is still no consensus on which level is considered to be optimal for skeletal and extra-skeletal effects [23]. However healthy levels of vitamin D for optimal health benefits encompassing immune functions as well are mentioned to be between 40-60 ng/dL ranges [24]. We applied a cut off value of 30 mg/dl for insufficiency in the study. Apart from the effects on bone, other physiological effects of vitamin D are stimulating the insulin production, regulating activated T and B lymphocyte functions, increasing cardiac muscle contractibility, preventing the development of inflammatory bowel diseases, and increasing thyroid stimulating hormone (TSH) release [25]. In our study the association between Hashimoto's autoimmune thyroidits and vitamin D deficiency is investigated through parameters such as anti –TPO, anti-TG, TSH, fT4 and fT3 that are related to thyroid dysfunction.

Higher TSH levels even with normal free T3 and fT4 levels indicate thyroid hypofunction. Presence of autoantibodies such as anti-TPO and anti-TG that are directed to thyroid gland reminds the diagnosis of Hashimoto's thyroiditis. We diagnosed participants with Hashimoto's disease if any of these autoantibodies is present independent of TSH levels. Vitamin D levels are found to be lower in people with hypothroidism [26]. Vitamin D level in Hashimoto population was also found lower in studies done by Tamer et al., Nalan et al. and Maciejewski et al. with percentages of 92%, 93.4% and 100% respectively [6,13,15,18]. In our study, similar to the literature, vitamin D levels were found to be lower in patients with Hashimoto thyroiditis than healthy individuals. Vitamin d deficiency in the Hashimoto group was 97.7% [6,9,27,28]. We also found a negative correlation between vitamin D and TSH levels, which is consistent with the literatüre [9,28,29]. Lower autoantibody levels in population with higher vitamin D levels could be interpreted as a result of immunomodulatory effect of vitamin D which is also shown in some other studies [9,17,30,31]. In our study, we found a significant negative correlation similar to these findings. While some experts did not report any correlation with free thyroid hormone levels and vitamin D we showed that fT4 levels were lower in people with low vitamin D levels [9].

Demographic values such as age, gender, smoking and weight are evalulated in study. Female dominance is known in Hashimoto disease and parallel to literatüre with a similar percentage that is 85% of individuals in our Hashimoto groups were female [10,15]. Although Prasad et al. stated that the vitamin D level is lower in women compared to men and Katrinakı et al. stated that this difference disappeared after the age of 50 [22,27]. We found lower vitamin D levels in women than men in our study. In accordance with some studies in literature a decrease in vitamin D level by age was shown in our study as well but it was not istatically significant [22,32].

While vitamin D deficiency prone to be higher among smokers, Hashimoto's thyroiditis and thyroid peroxidase antibody levels have been reported to be lower [33-35]. In our study there were no statistically difference between groups in terms of smoker numbers in each group. So smoking is not considered as a factor causing a change on vitamin D levels within the groups.

Low levels of calcitriol triggers the secretion of PTH [36]. Similar with InCHIANTI study, we found PTH levels higher in vitamin D deficient population [40]. Exposure to sunlight at an appropriate location sufficiently is the primary source of vitamin D [37,38]. In a study conducted in the island of Crete located at similar latitudes with our center, the vitamin deficiency was reported to be 85% [22]. While it was reported 77.4% in a previous study [18], we found that vitamin D insufficiency prevelance was 96% with a cut off value of <30ng / ml. Accordingly, while the serious deficiency of vitamin D (<10ng / ml) was stated as 21% in the study of Katrinakı et al.'s it was found to be 38.1% in our study [22].

Patients with Hashimoto thyroiditis who are diagnosed formerly found to have severe vitamin D deficiency more frequent than newly diagnosed group [9, 30]. We found that severe vitamin D deficiency was 45.2% in the previously diagnosed Hashimoto group, 40.4% in the newly diagnosed Hashimoto group and 28.5% in the control group.

Because of vitamin D is being held in adipose tissue, obese people have less vitamin D in their blood than those of with normal weight [25]. We found a significant and inverse association between BMI and vitamin D in accordance with the literature [39,40].

With all these findings mentioned above we consider that vitamin D could play a role in the pathogenesis of Hashimoto diasease.

Conclusion

Vitamin D deficiency may be a predisposing factor for Hashimoto's disease. Considering a wide variety of disorders associated with vitamin D deficiency, the addition of vitamin D to the nutrients can be an acceptable option for improving public health.

Conflict of interests
The authors declare that they have no conflicts of interest concerning this article.

Financial Disclosure
All authors have read and approved the final form of this article.

Ethical approval
The İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee granted the ethics committee approval with the approval date 22.12.2016 and number 163.

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