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The Paradigm of Autoimmunity: Is Vitamin D the New Player?

Otoimünite Paradigması: D Vitamini Yeni Oyuncu mu?

Gülbüz Sezgin[1], Eşref M. Özer[2], Oya Uygur Bayramiçli[3], Feride Sinem Akgün[4], Fehime Benli Aksungar[5], Selim Nalbant[1]
[1]Departments of Internal Medicine, [2]Endocrinology, [3]Gastroenterology, and [4]Emergency, Maltepe University, Medical School, Istanbul.
[5]Biochemistry Department of Acıbadem University, Medical School, Istanbul.
Correspondance: Gülbüz Sezgin Maltepe University Faculty of Medicine Department of Internal Medicine, 34843, Maltepe, Istanbul, Turkey, E-mail: gulbuz.sezgin@maltepe.edu.tr

ABSTRACT

Aim: Vitamin D is necessary for the bone and mineral homeostasis and has also immune regulatory and anti-inflammatory functions. It has been hypothesized that there is a relation between vitamin D deficiency or insufficiency and autoimmune thyroiditis. We aim that to show any relationship between vitamin D deficiency and thyroid autoimmunity.

Material and Methods: This prospective study is performed between August 2010 and May 2011 at the Department of Internal Medicine, Endocrinology and Emergency Medicine of Maltepe University, School pof Medicine Hospital. The Ethics Committee of Maltepe University Medical Faculty approved the study.274 patients with Hashimoto's thyroiditiswere evaluated prospectively for vitamin D, TSH, anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin (anti-Tg).The correlation between vitamin D and autoimmune parameters is analyzed.

Results: According to vitamin D levels there is a statistically significant difference between anti-TPO levels ($p=0.024$; $p<0.05$). Anti-TPO levels of patients with a vitamin D level between 4-10 ng/ml are higher than that of the patients with a vitamin D level of 10.01-20 ng/ml and 20 ng/ml and over. Anti-Tg and TSH levels are not statistically significantly different according to vitamin D levels ($p=0.550$; $p=0.554$; $p>0.05$). There is also no difference in TSH levels according to vitamin D subgroups ($p=0.177$; $p>0.05$).

Conclusion: In patients with Hashimoto's thyroiditis there is a positive correlation between vitamin D level and anti-TPO but not anti-Tg.

Keywords: nazolabiyal, V-Y ilerletme flebi, ortayüz defekti, ektropiyon

ÖZET

Amaç: Vitamin D, kemik ve mineral homeostazı için gereklidir ve aynı zamanda immunregülatör ve anti-inflamatuar fonksiyonları vardır. Vitamin D eksikliği veya yetersizliği ile otoimmün tiroiditler arasında ilişki olduğu hipotezi öne sürülmüştür. Bu çalışmada Vitamin D eksikliği ile tiroid otoimmünitesi arasında ilişki olup olmadığını göstermeyi amaçladık.

Materyal- Metod: Çalışmamız Ağustos 2010 ile mayıs 2011 yılları arasında Maltepe Üniversitesi Eğitim ve Araştırma Hastanesi İç Hastalıkları, Endokrinoloji ve Acil servis bölümlerinde prospektif olarak yapılmıştır. Maltepe Üniversitesi Tıp Fakültesi Etik Kurul Komitesinden onay alınmıştır.Hashimoto tiroiditi olan 274 hastada Vitamin D, TSH, anti Tiroid Peroksidaz Antikoru (Anti-TPO) ve anti Tiroglobulin (Anti-Tg) seviyeleri ölçülmüştür. Vitamin D ile otoimmün parametreler arasındaki korelasyon incelenmiştir.

Bulgular: Vitamin D ile anti-TPO seviyeleri arasında istatistiksel olarak anlamlı bir ilişki vardır ($p=0.024$; $p<0.05$). Vitamin D seviyesi4-10 ng/m olan hastaların Anti-TPO değerleri ile D vitaminiseviyesi10.01-20 ng/ml, 20 ng/ml ve üzeri olan hastalardan daha yüksektir. Anti-Tg ve TSH seviyeleri D vitamin düzeylerine gore istatistiksel olarak anlamlı derecede farklı değildir ($p=0.550$, $p=0.554$; $p>0.05$).D vitamini alt gruplarına gore TSH seviyelerinde de anlamlı bir farklılık yoktur ($p=0.177$; $p>0.05$).

Sonuç: Hashimoto Tiroiditi olan hastalarda Vitamin D ile anti TPO arasında pozitif korelasyon tespit edilirken anti Tg ile bu korelasyon gözlenmedi.

Anahtar kelimeler: Vitamin D, Tiroid otoimmünitesi, Anti-Tg, Anti-TPO

INTRODUCTION

Vitamin D is not a regular vitamin but a steroid hormone which is necessary for the bone and mineral homeostasis and has also immune-regulatory and anti-inflammatory functions (1,2).

1, 25 –Dihydroxyvitamin D is transported to target tissues with vitamin D binding protein (DBP). Active vitamin D shows its effect on target cells with the Vitamin D receptors (VDR) which are found in cytoplasm and nucleus. VDR is expressed in bowel, bone, kidney cells but exists also in skin, breast , pituitary gland, parathyroid glands, pancreatic beta cells, gonads, brain, muscle cells, circulating monocytes and active B and T lymphocytes and these cells also produce 1,25 –Dihydroxyvitamin D (2,3). In recent years the effect of vitamin D on immune system has been discovered. The recognition of vitamin D receptors on mononuclear cells in peripheral blood led to the discovery of its role on the regulation of the immune system (4,5). The role of vitamin D in the prevention of some cancers, autoimmunity, cardiovascular and infectious diseases has been shown in many studies along with its role in calcium and bone homeostasis (6,7,8). Vitamin D deficiency has also a correlation with the increase in the incidence of autoimmune diseases like type I diabetes mellitus, rheumatoid arthritis, SLE, multiple sclerosis, Sjögren's syndrome, thyroiditis and inflammatory bowel disease (9,10,11,12).Hashimoto's thyroiditis (HT) is an autoimmune disease which is more prevalent in women and is characterized by enlargement of the gland due to lymphocytic infiltration and the production of auto antibodies. Genetic and environmental factors have been implicated in the development of the disease [13]. Recent research suggests that factors leading to low levels of vitamin D and to a decrease in the functions of vitamin D (VDR gene polymorphism, disorders of the vitamin D binding protein) can increase the risk of Hashimoto's thyroiditis. Vitamin D does not only inhibit dendritic cells activated by the T cell, but also inhibits the production of cytokines, interferon-g, interleukin 2 from the T helper cells (Th) and the increase of B cells; it also induces B cell apoptosis and plays a role in the development of HT (14,15). We studied vitamin D levels in patients with autoimmune thyroiditis and looked for a relation between vitamin D deficiency and thyroid auto antibodies.

MATERIAL AND METHOD

This prospective study was conducted between August 2010 and May 2011 at the Department of Internal Medicine and Endocrinology of Maltepe University Medical Faculty Hospital and 274 patients were studied prospectively. The Ethics Committee of Maltepe University Medical Faculty approved the study. 274 patients followed up with the diagnosis of Hashimoto's thyroiditis formed the study group and age, gender, height and body weight, BMI were recorded. At the recruitment the aim of the study and the protocol was explained to the patients and written informed consent was taken from all of them .The next day 12 hour fasting state ante brachial vein blood samples were taken and analyzed for vitamin D, TSH, anti-TPO, anti-Tg antibodies at the Department of Biochemistry. Inclusion criteria; all patients between the ages of 17-83 with the diagnosis of autoimmune thyroiditis who accepted to participate in the study were included. Exclusion criteria were malignancies and other diseases causing Vitamin D deficiencies (such as asthma, chronic renal failure, and malabsorption). Vitamin D, TSH, anti-TPO and anti-Tg antibodies were analyzed (Roche-DiagnosticsGmbH, Mannheim, Germany) using Cobase411 device by electrochemiluminescence. Calcium and phosphorous wereanalyzed (Siemens Healthcare DiagnosticsInc. Newark, USA) using a clinical chemical analyzer (Dimension RXL Max) andorto-cresolphtalein colorimetric method and phosphomolybdate method, respectively. Statistical analysis wasperformedusing "Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Statistical Software Utah, USA". Mann Whitney U Test and Pearson's Ki-Square Test were used for data analysis.Spearman's Correlation Analysis was used for the evaluation of relationship between the parameters. $P < 0.05$ is considered significant.

RESULTS

The study cohort included 274 patients with a mean age of 51.99 ±17.92 years (females 74.1 % females [n=203] and males 25.9 % [n=71]). Vitamin D levels varied between 4 and 113.3 ng/ml with a mean value of 11.73±10.59 ng/ml and a median of 9.41 ng/ml. Vitamin D levels were between 4-10 ng/ml in 52.2 % of patients (n=143), between 10.01-20 ng/ml in 33.7% (n= 95) and over 20 ng/ml in 13.1 % (n=36). Anti-TPO levels were between 0.22 IU/ml and 969 IU/ml with a mean value of 44.89±104.98 IU/ml and a median of 16.06 IU/ml. Anti-Tg levels were between 1.40 IU/ml and 4000 IU/ml with a mean value of 94.96±346.17 IU/ml and a median of 21.58 IU/ml. TSH levels were between 0.01 μIU/ml and 15 μIU/ml with a mean value of 2.20±1.69 μIU/ml and a median of 1.72 μIU/ml. (Table 1)

There is a statistically significant difference between the age groups according to vitamin D levels ($p=0.002$; $p<0.01$). Patients with a vitamin D level between 10.01-20 ng/ml are significantly younger in comparison to the patients with a vitamin D level between 4-10 ng/ml and 20 ng/ml and over ($p=0.028$; $p=0.004$; $p<0.05$). There is no difference betweenpatients with a vitamin D level of 4-10 ng/ml and of >20 ng/ml ($p=0.273$; $p>0.05$). There is a statistically significant difference between males and females according to vitamin D levels ($p=0.005$; $p<0.01$). A level of 4-10ng/ml is seen significantly more in women (Table1). According to vitamin D

levels there is a statistically significant difference between Anti-TPO levels (p=0.024; p<0.05). Anti-TPO levels of patients with a vitamin D level between 4-10 ng/ml are higher than patients with a vitamin D level of 10.01-20 ng/ml and of >20 ng/ml. There is also no difference in anti-TPO levels according to vitamin D subgroups (p=0.138; p>0.05). Anti-Tg and TSH levels are not statistically significantly different according to vitamin D levels (p=0.550; p=0.554; p>0.05). There is also no difference in TSH levels according to vitamin D subgroups (p=0.177; p>0.05) (Table 2). There is a weak negative correlation between the age and vitamin D levels (12.4 %) (r:-0.124; p=0.041; p<0.05). There is a weak positive correlation of 14.5 % between Anti-TPO levels and vitamin D levels (r: 0.165; p=0.006; p<0.01). There is no statistically significant correlation between vitamin D levels and Anti-Tg (p>0.059) (Table 3). There is a statistically significant difference in TPO values according to age groups (p=0.047; p<0.05). In dual comparisons Anti-TPO levels of the patients younger than 35 is significantly lower than the patients between 35-50 years of age (p=0.018; p<0.05); Anti-TPO levels of other groups are not statistically significant (p=0.341; p=0.062; p>0.05).There is no statistically significant difference in Tg values according to age groups (p=0.413; p>0.05). There is a statistically significant difference in TSH values according to age groups (p=0.036; p<0.05). TSH values of patients younger than 35 is significantly higher than the patients between 35-50 and over 50 (p=0.026; p=0.024; p<0.05) (Table 4).

DISCUSSION

Thyroid diseases are very common and autoimmune thyroid diseases are the most frequent autoimmune diseases. Autoimmune thyroid diseases have a prevalence of 5 % in general [16]. This prevalence is 1-2 % in men and 7-9 % in women (17). Autoimmune thyroid disease and vitamin D deficiency are more common in women. In a study by Hekimsoy et al, it has been shown that vitamin D deficiency is more common in Turkish women in comparison to other countries (18). Our study confirms that vitamin D levels are statistically significantly higher in men in comparison to women (p<0.01).The pathogenesis of autoimmune diseases is multifactorial as other autoimmune diseases. Hashimoto's thyroiditis is caused by an interaction of genetic and environmental factors. Most of the studies involved genetic factors but in recent years, studies arguing a pathogenetic role of vitamin D deficiency in Hashimoto's thyroiditis have been carried out (19). Vitamin D has regulatory effects on inflammatory responses and autoimmunity. In experimental animal models vitamin D inhibits the development of autoimmunity and inhibits HLA class II expression (20, 21). It also inhibits the production of cytokines, interferon-g, interleukin 2 from the T helper cells (Th) and the increase of B cells; it also induces B cell apoptosis and plays a role in the development of HT (15). 1,25 –Dihydroxyvitamin D is the best parameter of the whole vitamin D pool of the body. Normal serum concentration varies between 30- 80 ng/ml (20- 200 nmol/L) and has a half-life of 21 day (22,2). Mean serum concentration <20 ng/ml is defined as deficient, a level between 21-29 ng/ml moderate and a level >30ng/ml is defined as normal (23).In many studies the correlation between vitamin deficiency and insufficiency and autoimmune thyroiditis has been shown. Kivity et al said that the prevalence of vitamin D deficiency is higher in autoimmune thyroid disease and the presences of thyroid antibodies are more prominent in vitamin D deficient patients (24).In our study according to vitamin D levels there is a statistically significant difference between Anti-TPO levels (p<0,05). According to vitamin D levels there wasn't any statistically significant difference between anti thyroglobulin levels (p>0,05).Hashimoto's thyroiditis is diagnosed by the presence of auto antibodies and ultrasound evaluation. But the determination of the initiation of autoimmunity can be best defined histopathologically. Tamer et al,observed that in Hashimoto's thyroiditis, the prevalence of vitamin D deficiency was higher in comparison to healthy people (15). This might be caused by the high prevalence of vitamin D deficiency in the Turkish population.In our study in patients with a vitamin D level between 4-10 ng/ml there was a positive correlation between vitamin D deficiency and Hashimoto'sthyroiditis. Shin et al also found out that Anti-TPO and vitamin D deficiency were significantly correlated in patients with a vitamin D level <20 ng/ml.In fact, the correlation between 25(OH) D3level and anti-TPO is also seen in vitamin D level within the range of vitamin D deficiency as defined by a recent guideline on bone metabolism, suggesting a need of a different reference value of vitamin D for this extra-skeletal effect (25). In accordance with increasing age the prevalence of vitamin D deficiency also increases and with replacement treatment age-related macular degeneration decreases (26). In our study we observed that vitamin D deficiency increased with age vitamin D, and we believe that replacement treatment should be recommended for the prevention of chronic diseases in elderly people (27).In a study on patients with thyroid dysfunction it has been shown that with increasing vitamin D level, TSH gets lower (28). We couldn't find any correlation between TSH levels and vitamin D levels. In this study we aimed to evaluate the relation between vitamin D deficiency and thyroid auto antibodies and there was a positive relation between Anti-TPO and vitamin D level and no relation between Anti-Tg and vitamin D level.

		Overall	Vitamin D			p
			4-10 (ng/ml) (n=143)	10.01-20(ng/ml) (n=95)	> 20 (ng/ml) (n=36)	
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age (years)		51.99±17.92	53.41±17.24	47.40±17.52	58.47±19.15	[a]0.002**
Vitamin D		11.73±10.60	5.24±1.98	14.70±2.77	29.66±17.68	-
		n (%)	n (%)	n (%)	n (%)	
Gender	Females	203 (74.1)	117 (81.8)	60 (63.2)	26 (72.2)	[b]**0.005****
	Males	71 (25.9)	26 (18.2)	35 (36.8)	10 (27.8)	
Age (years)	<35	49 (17.9)	23 (16.1)	24 (25.3)	2 (5.6)	
	35-50	79 (28.8)	31 (21.7)	35 (36.8)	13 (36.1)	[b]**0.001****
	> 50	146 (53.3)	89 (62.2)	36 (37.9)	21 (58.3)	

[a]Oneway Anova Test [b]Pearson Ki-square Test **p<0.05

Table 1: Demographic data of the patients according to vitamin D levels

		Overall	Vitamin D			p
			4-10 (ng/ml)	10.01- 20 (ng/ml)	> 20 (ng/ml)	
		Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	
Anti-TPO (IU/ml)		44.89±104.98 (16.1)	39.85±93.70 (13.6)	43.80±109.38 (18.2)	67.78±132.55 (17.1)	[c]0.024*
Anti-Tg		94.96±346.17 (21.6)	129.05±448.99 (21.5)	51.91±84.42 (23.2)	37.80±50.91 (20.1)	[c]0.550
TSH		2.20±1.69 (1.7)	2.19±1.87 (1.7)	2.09±1.36 (1.8)	2.51±1.77 (2.2)	[c]0.554
		n (%)	n (%)	n (%)	n (%)	
Anti TPO	Normal	234 (85.4)	126 (88.1)	81 (85.3)	27 (75.0)	[b]0.138
	Positive	40 (14.6)	17 (11.9)	14 (14.7)	9 (25.0)	
TSH	Low	13 (4.7)	10 (7.0)	2 (2.1)	1 (2.8)	
	Normal	252 (92.0)	127 (88.8)	92 (96.8)	33 (91.7)	[d]0.177
	High	9 (3.3)	6 (4.2)	1 (1.1)	2 (5.6)	

[b]Pearson Ki-kare Test [c]Kruskal Wallis Test
[d]Fisher-Freeman-HaltonTest *p<0.05

Table 2: Thyroid functions according to Vitamin D levels

	Vitamin D	
	r	**p**
Age	-0.124	**0.041***
Anti-TPO (IU/ml)	0.165	**0.006****
Anti-Tg (n=170)	0.001	**0.991**
TSH	0.086	**0.155**

r: Spearman's correlations *p<0,05 **p<0,01

Table 3: Parameters according to Vitamin D

	Age			ᶜp
	< 35 years	**35-50 years**	**>50 years**	
	Mean±SD (Median)	**Mean±SD (Median)**	**Mean±SD (Median)**	
Anti-TPO (IU/ml)	24,71±43,46 (14,1)	63,50±149,59 (17,6)	41,59±88,03 (15,6)	**0,047***
Anti-Tg	44,89±82,77 (19,9)	54,88±82,41 (24)	129,87±455,35 (21,4)	**0,413**
TSH	2,51±1,43 (2,2)	2,04±1,30 (1,6)	2,18±1,94 (1,6)	**0,036***

cKruskal Wallis Test *p<0.05

Table 4: Thyroid function tests according to age groups

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