ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship Between Serum Vitamin D Levels and Thyroid Function Tests in Euthyroid and Hypothyroid Patients with Elevated Anti-TPO

Anti-TPO Yüksekliği Olan Ötiroid ve Hipotiroidili Hastalarda Vitamin D Düzeyleri ile Tiroid Fonksiyon Testleri Arasındaki İlişki

Lütfiye Seçil Deniz Balyen

Department of Internal Medicine, Faculty of Medicine, Kafkas University, Kars, Turkey

ABSTRACT

Aim: *The results of studies that investigate relationship between "autoimmune thyroid diseases (AITDs)" and serum vitamin D values are inconsistent. The study aimed to evaluate association between serum vitamin D levels and thyroid function tests in euthyroid and hypothyroid patients with elevated thyroid peroxidase antibodies (anti-TPO).*

Material and Method: *Our research was carried out by examining the file records of 21 patients with the concurrent measurement of Vitamin D and thyroid function tests who identified anti-TPO positivity. The participants were divided into two groups according to serum vitamin D levels: group 1 (patients who had serum vitamin D levels of ≥20 ng/mL) and group 2 (patients who had insufficient or deficient vitamin D levels of <20 ng/mL).*

Results: *Anti-TPO levels (median (min-max)) were lower in group 1 (149.3 (29.7-388.1) IU/mL) than in group 2 (287.7 (141.5-794.6) IU/mL). Serum thyroid-stimulating hormone (TSH) and serum free thyroxine (fT4) levels were no different among the groups. Serum anti-TPO were positively correlated with TSH (r=0.731, p= 0.005) and negatively with vitamin D (r=-0.484, p=0.026).*

Conclusion: *Decreased serum vitamin D levels can contribute to the pathogenesis of AITDs. Further researches are necessary to fully illuminate the role of vitamin D levels in autoimmune thyroiditis.*

Key words: *vitamin D; autoimmune thyroiditis; thyroid function tests*

ÖZET

Amaç: *Otoimmun tiroid hastalıkları (AITD) ile vitamin D seviyeleri arasındaki ilişkiyi araştıran çalışmaların sonuçları tutarsızdır. Bizim çalışmamızın amacı, tiroid peroksidaz antikorları (anti-TPO) yükselmiş olan hipotiroid veya ötiroid hastalarda vitamin D seviyeleri ile tiroid fonksiyon testleri arasındaki ilişkiyi değerlendirmekti.*

Materyal ve Metot: *Bu çalışma, anti-TPO pozitifliği saptanan ve vitamin D seviyeleri ile tiroid fonksiyon testleri eş zamanlı olarak ölçülen 21 hastanın dosya kayıtları incelenerek gerçekleştirildi. Katılımcılar vitamin D seviyelerine göre 2 gruba ayrıldı: grup 1 (optimal vitamin D seviyelerine (≥20 ng/mL) sahip olan hastalar) ve grup 2 (yetersiz veya eksik vitamin D seviyelerine (<20 ng/mL) sahip olan hastalar).*

Bulgular: *Anti-TPO seviyeleri (median (min-max)) grup 1'de (149.3 (29.7-388.1) IU/mL), grup 2'dekine göre (287.7 (141.5-794.6) IU/mL) daha düşüktü (p=0.036). Tiroid stimulan hormon (TSH) ve serbest tiroksin (fT4) seviyeleri gruplar arasında farklı değildi. Anti-TPO seviyeleri TSH ile pozitif olarak (r=0.731, p= 0.005), vitamin D ile negatif olarak (r=-0.484, p=0.026) korele idi.*

Sonuç: *Düşük vitamin D seviyeleri AITD'lerin patogenezine katkıda bulunabilir veya bir nedenden ziyade otoimmun hastalık sürecinin bir sonucu olabilir. Otoimmun tiroiditte vitamin D seviyelerinin rolünü tam olarak aydınlatabilmek için daha ileri araştırmalar gereklidir.*

Anahtar kelimeler: *vitamin D; otoimmun tiroidit; tiroid fonksiyon testleri*

Introduction

Hypothyroidism, thyroid hormone deficiency, is a common pathological condition. Its prevalence is 0.2% to 5.3% in Europe and 0.3% to 3.7% in the United States. It is seen more often in women, elders, white individuals, and patients with autoimmune endocrinopathies, autoimmune gastric atrophy, type 1 diabetes mellitus (DM), and coeliac disease. Hypothyroidism can be overt (clinical), defined as high serum thyroid-stimulating hormone (TSH) and low serum free thyroxine (fT4) concentrations or can be mild/subclinical, defined as high TSH and normal fT4 concentrations. Hashimoto's disease is a

İletişim/Contact: *Lütfiye Seçil Deniz Balyen, Department of Internal Medicine, Faculty of Medicine, Kafkas University, Kars, Turkey* • ***Tel:*** *0533 616 92 29* • ***E-mail:*** *lsdbalyen@gmail.com* • ***Geliş/Received:*** *16.06.2019* • ***Kabul/Accepted:*** *03.01.2020*

ORCID: *Lütfiye Seçil Deniz Balyen, 0000-0002-8072-6543*

chronic, autoimmune inflammatory disease of thyroid and the leading cause of hypothyroidism in developed countries. The pathogenesis of this disease is closely related to formation of antithyroid antibodies that attack thyroid struma. Thyroid peroxidase antibodies (anti-TPO) is existent in most patients with autoimmune thyroiditis and in approximately 11% of the general population. The mechanisms of autoimmune thyroiditis are not fully understood, however it has been claimed that some genetic and environmental factors such as vitamin D deficiency/insufficiency can be connected with development of autoimmune thyroiditis[1-4].

The effect on the musculoskeletal system of Vitamin D is its canonical role. However, the importance of serum vitamin D levels in terms of extraskeletal health has become focus area for researchers, especially in the last decades. The immune system cells (e.g. macrophages and lymphocytes) express the vitamin D receptor (VDR) and thereby are modulated by Vitamin D. The insufficiency or deficiency of Vitamin D have been detected as risk factors for a variety of autoimmune diseases, including rheumatoid arthritis (RA) and insulin dependent DM[5-7].

The findings of studies that investigate relationship between autoimmune thyroid disorders and serum vitamin D values are inconsistent[5,8]. The goal of the study was to comment association between serum vitamin D values and thyroid function tests in euthyroid and hypothyroid patients with elevated anti-TPO.

Material and Method

The research was put into practice by examining the file records of the patients who applied to the Polyclinic of Internal Medicine of our Faculty of Medicine between 2014 to 2017 and who identified anti-TPO positivity. The inclusion criteria of the study were: (a) an adult older than 18 years and (b) persons with the concurrent measurement of Vitamin D (25-(OH)-D3) and thyroid function tests. The exclusion criteria included: individuals with hyperthyroidism or taking thyroid hormone replacement therapy (HRT), inadequate data, subjects diagnosed of having other thyroid diseases or chronic diseases including RA and DM. The study was approved by the Local Research Ethics Committee of our Faculty of Medicine (13.12.2017/10). The participants were divided into two groups with regards to serum vitamin D values[9]: group 1 (patients who had serum vitamin D values of ≥20 ng/mL) and group 2 (patients who had insufficient or deficient Vitamin D values of <20 ng/mL). TSH, fT4, anti-TPO, and serum vitamin D levels were quantified by using Beckman Coulter UniCel DxI 600 device (Beckman Coulter Diagnostics, USA).

Statistical Analyses

Statistical analyses were achieved by using commercial software (SPSS version 20, IBM Corp., USA). Continuous variables were compared with the Mann-Withney U test and were predicated as median (minimum-maximum). Spearman's correlation test formed an estimate of the correlations. A p value lower than 0.05 was interpreted as statistically significant.

Results

All patients were women. Patients with optimal vitamin D levels (n=10) had median (min-max) age of 29 (22-75) years and patients with insufficient or deficient Vitamin D levels (n=11) had age of 36 (20-65) years. Statistically, the difference in terms of ages was not significant (p=0.863). Anti-TPO levels (median (min-max)) were lower in group 1 (149.3 (29.7-388.1) IU/mL) than in group 2 (287.7 (141.5-794.6) IU/mL; p=0.036) (Figure 1). fT4 and TSH values were no different among two groups (Table 1). Anti-TPO values were positively correlated with TSH (r=0.731, p= 0.005) and negatively with vitamin D (r=-0.484, p=0.026) (Figure 2). There was no correlation among the other parameters. A post hoc power analysis performed for anti-TPO levels in the groups showed that power of the study was 69%.

Discussion

Thyroperoxidase (TPO) is both an enzyme responsible from thyroid hormone biosynthesis and an autoantigen associated with autoimmune thyroid diseases (AITD)[10]. Genetic factors are responsible for approximately 70% of AITDs, while environmental factors contribute for about 30% to AITDs[11]. More than half of the world population have low vitamin D values[12]. Its prevalence is increasing globally[12]. Vitamin D modulates immune functions and its lack is associated with an escalated risk for autoimmunity and with enhanced susceptibility to infections[13]. Also, vitamin D supplementation might improve immune functions, prevent autoimmune disorders, and create a defense against infections[13].

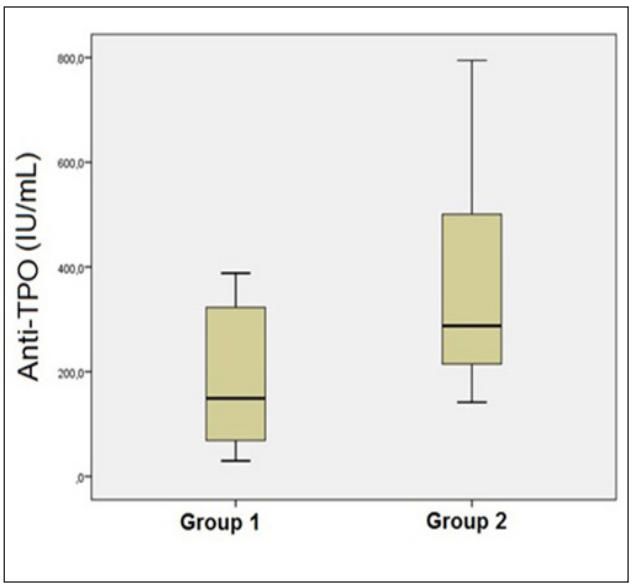

Figure 1. *Anti-TPO levels in the study groups.*

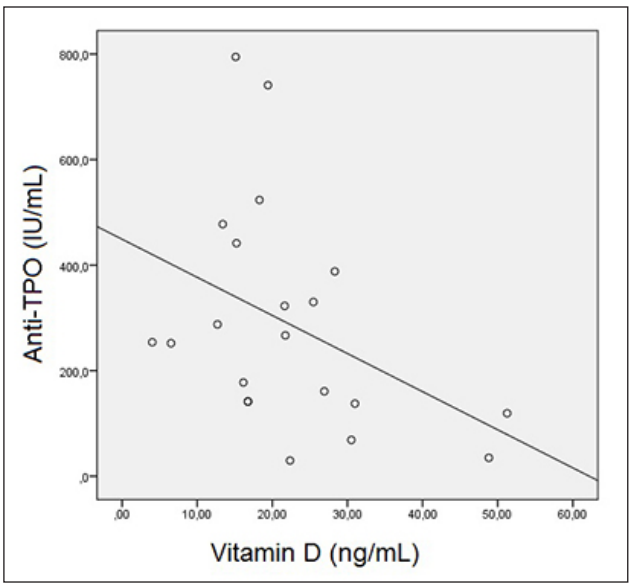

Figure 2. *The correlation between anti-TPO and vitamin D.*

Table 1. *Vitamin D, anti-TPO, TSH, and fT4 levels in the study groups*

	Group 1 (n=10)	Group 2 (n=11)	p
Vitamin D (ng/mL)	27.6 (21.6-51.3)	15.2 (4.0-19.4)	0.000
anti-TPO (IU/mL)	149.3 (29.7-388.1)	287.7 (141.5-794.6)	0.036
TSH (μIU/mL)	1.39 (0.77-1.78)	2.13 (0.59-9.10)	0.295
fT4 (ng/dL)	0.84 (0.71-1.03)	0.73 (0.68-0.99)	0.366

anti-TPO: thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone; fT4: free thyroxine. Data in the table have been expressed as the median (minimum-maximum).

We determined that anti-TPO values are lower in patients with optimal serum vitamin D values compared to that of patients with insufficient or deficient serum vitamin D values and that as serum vitamin D values increase, serum anti-TPO levels decrease. The results clearly point out that Vitamin D can pressure autoimmunity. Previous researches have shown that there is a relationship between vitamin D deficiency and autoimmune thyroiditis development. Recently, Nalbant et al.[14] reported that insufficient vitamin D levels might decrease blood supply to thyroid and that anti-TPO levels were higher in patients who had vitamin D deficient in HT. They put forward that reduction of blood supply to thyroid can clarify the increased anti-TPO levels and impaired immune-modulation, which are seen in vitamin D deficiency. Vitamin D has important effects on T helper cell type 1 (Th1), Th2, Th9, and Th17 and IL-4, IL-10, IL-17, and IFN-gamma secretion, explaining how vitamin D insufficiency or deficiency contribute to immune thyroid disease development[15,16]. Also, it has been shown that polymorphisms of VDR is significantly associated with autoimmune thyroid diseases[17]. Our results agree with previous studies that have indicated that serum vitamin D insufficiency or deficiency is an important risk factor for positive thyroid antibodies[18,19].

The fact that low serum vitamin D values can contribute to the pathogenesis of AITDs made think that vitamin D administration can be a part of their treatment. Simsek et al.[20] have found that vitamin D supplementation reduced thyroid antibody titers (serum anti-TPO and thyroglobulin antibody) in patient with vitamin D deficient. Similarly, Krysiak et al.[3,4] have determined that there is a favourable effect of vitamin D on thyroid autoimmunity. However, there are many studies that have reported that vitamin D treatment cannot

improve thyroid function and autoimmunity associated with thyroid[21-23]. In a recently-reported study, it has been found that vitamin D levels are similar in patients with HT and the healthy control group[8]. Moreover, it has been suggested that low vitamin D values may be a result of autoimmune processes rather than an etiological factor[24]. Consequently, further researches are necessary to fully illuminate the role of vitamin D levels in autoimmune thyroiditis and its causal effect.

References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017;390(10101):1550–62.
2. Mincer DL. Thyroid, Hashimoto thyroiditis. Treasure Island (FL): StatPearls Publishing; 2017.
3. Krysiak R, Szkrobka W, Okopien B. The effect of vitamin D and selenomethionine on thyroid antibody titers, hypothalamic-pituitary-thyroid axis activity and thyroid function tests in men with Hashimoto's thyroiditis: A pilot study. Pharmacol Rep 2019;71(2):243–7.
4. Krysiak R, Kowalcze K, Okopien B. The effect of vitamin D on thyroid autoimmunity in euthyroid men with autoimmune thyroiditis and testosterone deficiency. Pharmacol Rep 2019;71(5):798–803.
5. Wiersinga WM. Clinical relevance of environmental factors in the pathogenesis of autoimmune thyroid disease. Endocrinol Metab (Seoul)2016;31(2):213–22.
6. Kmiec P, Sworczak K. Vitamin D in thyroid disorders. Exp Clin Endocrinol Diabetes 2015;123(7):386–93.
7. Erdoğdu Hİ, Atalay E. Relationship between high erythrocyte sedimentation rate and 25-hydroxy vitamin D and C-reactive protein levels. Sakarya Med J 2018;8:798–805.
8. Botelho IMB, Moura Neto A, 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(10):1029–37.
9. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc 2011;86(1):50–60.
10. Ruf J, Carayon P. Structural and functional aspects of thyroid peroxidase. Arch Biochem Biophys 2006;445(2):269–77.
11. Wiersinga WM. Thyroid autoimmunity. Endocr Dev 2014;26:139–57.
12. Wimalawansa SJ, Razzaque DMS, Al-Daghri NM. Calcium and vitamin D in human health: hype or real? J Steroid Biochem Mol Biol 2017;S0960–0760(17):30381–3.
13. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of immune function by vitamin D and its use in diseases of immunity. Endocrinol Metab Clin North Am 2017;46(4):1061–94.
14. Nalbant A, Aydin A, Karacan A, Onmez A, Tamer A, Cinemre H. Association of vitamin D insufficiency/deficiency with thyroid artery Doppler ultrasonography in patients with Hashimoto thyroiditis. Pak J Med Sci 2017;33(2):295–9.
15. Palmer MT, Lee YK, Maynard CL, Oliver JR, Bikle DD, Jetten AM, et al. Lineage-specific effects of 1, 25-dihydroxyvitamin D(3)on the development of effector CD4 T cells. J Biol Chem 2011;286(2):997–1004.
16. Wang J, Lv S, Chen G, Gao C, He J, Zhong H, et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. Nutrients 2015;7(4):2485–98.
17. Feng M, Li H, Chen SF, Li WF, Zhang FB. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. Endocrine 2013;43(2):318–26.
18. Wang X, Zynat J, Guo Y, Osiman R, Tuhuti A, Zhao H, et al. Low serum vitamin d is associated with anti-thyroid-globulin antibody in female individuals. Int J Endocrinol 2015;2015:285290.
19. Lacka K, Maciejewski A. Vitamin D in the etiopathogenesis of autoimmune thyroiditis. Pol Merkur Lekarski 2013;34(203):281–5.
20. Simsek Y, Cakır I, Yetmis M, Dizdar OS, Baspinar O, Gokay F. Effects of vitamin D treatment on thyroid autoimmunity. J Res Med Sci 2016;21:85.
21. 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.
22. Vahabi Anaraki P, Aminorroaya A, Amini M, Momeni F, Feizi A, Iraj B, et al. Effect of vitamin D deficiency treatment on thyroid function and autoimmunity markers in Hashimoto's thyroiditis: A double-blind randomized placebo-controlled clinical trial. J Res Med Sci 2017;22:103.
23. Vondra K, Bilek R, Matucha P, Salatova M, Vosatkova M, Starka L, et al. Vitamin D supplementation changed relationships, not levels of metabolic-hormonal parameters in autoimmune thyroiditis. Physiol Res 2017;66(Supplementum 3): S409-S417.
24. Hu S, Rayman MP. Multiple nutritional factors and the risk of hashimoto's thyroiditis. Thyroid 2017; 27(5):597–610.