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ORIGINAL ARTICLE

Comparison of Vitamin D Levels in Patients with Chronic Lymphocytic Thyroiditis and the Normal Population, and the Role of Vitamin D on Autoimmunity

Kronik Lenfositik Tiroiditli Olgular ve Normal Populasyonda D Vitamini Düzeylerinin Karşılaştırılması ve Otoimmünite Üzerindeki Rolü

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ABSTRACT

Background: The effects of vitamin D on calcium homeostasis and bone metabolism have been investigated for many years. However, studies conducted in the last 20-25 years have shown that vitamin D has many functions beyond calcium metabolism. It is now known that vitamin D deficiency has a role in the formation of autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis and other diseases including diabetes, many types of cancer, and heart disease. The aim of this study was to compare the vitamin D levels of patients with Hashimoto's thyroiditis and healthy subjects and to evaluate possible relationships between vitamin D and other parameters.
Methods: This single-centre study was conducted at Izmir Bozyaka Training and Research Hospital. The participants (n=80) were divided into two groups with one group consisting of patients with the diagnosis of Hashimoto's thyroiditis (patient group, n=40) and one group consisting of healthy volunteers (control group, n=40). The patient group and control group were compared in terms of vitamin D levels. Thyroid-stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), anti-Tg, anti-TPO, age, and body mass index (BMI) were also measured and compared.
Results: The mean vitamin D level was 18.0±3.0 ng/mL and the median vitamin D level was 16.7 ng/mL (6.5-41 ng/mL) in the control group. The mean vitamin D level was 16.1±7.6 ng/mL and the median vitamin D value was 14.85 ng/mL (0.18-35.50 ng/mL) in the patient group. There was no statistically significant difference between the two groups in terms of vitamin D levels (p=0.305). When Thyroid-stimulating hormone (TSH), free T3 (FT3), free T4 (FT4) and body mass index (BMI) were examined, once again, no statistical difference was found between the groups. In addition, no statistically significant positive or negative correlation was found between vitamin D level and any other parameters.
Conclusion: Our study showed a numerical reduction in vitamin D levels between the patient and control groups; however, our data cannot evaluate potential relationships between vitamin D levels and Hashimoto's thyroiditis.

Keywords: BMI; Hashimoto's thyroiditis; TSH; Vitamin D

ÖZ

Amaç: D vitamininin kalsiyum homeostazı ve kemik metabolizması üzerindeki etkileri uzun yıllardır araştırılmaktadır. Ancak son 20-25 yılda yapılan çalışmalar, D vitamininin kalsiyum metabolizması dışında birçok işlevi olduğunu göstermiştir. Günümüzde D vitamini eksikliğinin diyabet, birçok kanser türü, kalp hastalıkları yanı sıra inflamatuar barsak hastalığı, romatoid artrit, multipl skleroz gibi otoimmün hastalıkların formasyonunda rolü olduğu bilinmektedir. Bu çalışmada amaç Hashimoto tiroiditi olan hastalar ve sağlıklı deneklerin D vitamini düzeylerini karşılaştırmak ve D vitamini ile diğer parametlerinin olası ilişkisini değerlendirmek olarak belirlendi.
Gereç ve Yöntem: Çalışma tek merkezde, İzmir Bozyaka Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Katılımcılar (n=80) Hashimoto tiroiditi tanılı hastalardan oluşan grup (hasta grubu, n=40) ve sağlıklı gönüllülerden oluşan grup (kontrol grubu, n=40) olmak üzere ikiye ayrıldı. Hasta grubu ve kontrol grubu vitamin D düzeyleri açısından karşılaştırıldı. Ayrıca tiroid stimüle edici hormon (TSH), serbest T3 (FT3), serbest T4 (FT4), anti-Tg (anti T), anti-TPO (anti M), yaş, vücut kitle indeksi (VKİ) değişkenleri de incelendi ve değerlendirildi.
Bulgular: Kontrol grubu (n=40) ve hasta grubu (n=40) D vitamini açısından karşılaştırıldığında: Kontrol grubunda ortalama D vitamini değeri 18.0±3.0 ng/ml ve medyan D vitamini değeri 16.7 ng/ml (6,5-41 ng/ml) saptandı. Hasta grubunda ortalama D vitamini değeri 16.1 ± 7.6 ng/ml ve medyan D vitamini değeri 14.85 ng/ml (0.18-35.50 ng/ml) saptandı. D vitamini açısından iki grup arasında istatistiksel olarak anlamlı fark tespit edilmedi (p=0,305). TSH, FT3, FT4 ve VKİ parametreleri incelendiğinde iki grup arasında D vitamini gibi istatistiksel olarak fark tespit edilmedi. Ayrıca D vitamini ile diğer parametreler arasında negatif ya da pozitif istatistiki olarak anlamlı korelasyon saptanmadı.
Sonuç: Çalışmamızda hasta ve kontrol grubu arasında D vitamini düzeyleri açısından sayısal olarak bir fark saptandıysa da bu istatistiki olarak anlamlı değildi . Ayrıca D vitamini düzeyi ile Hashimoto tiroiditi parametreleri arasında korelasyon saptanmadı. Çalışmamızın verileri ile D vitamini düzeyi ile Hashimoto tiroiditi arasındaki olası ilişkiyi tamamen değelendirmek mümkün olmayacaktır. Bizim çalışmamızın Hashımoto tiroditi ile D vitamini eksikliği arasındaki ilişkiyi daha kapsamlı bir şekilde araştıracak çalışmalar için yardımcı olacağını düşünmekteyiz.

Anahtar Kelimeler: VKİ; Hashimoto tiroiditi; TSH; Vitamin D

Introduction

Vitamin D is a fat-soluble vitamin. Very few foods naturally contain vitamin D and dermal synthesis is the major natural source of the vitamin (1). This synthesized substance is a precursor and it requires two enzymatic conversions to active metabolites. Vitamin D is converted enzymatically in the liver to 25-hydroxyvitamin D (25OHD), the major circulating form of vitamin D, and in the kidneys to 1,25-dihydroxyvitamin D, the active form of vitamin D. The chemical structure of the active form of vitamin D is similar to that of steroid

hormones (2).

The effects of vitamin D on calcium homeostasis and bone metabolism have been investigated for many years. However, studies conducted in the last 20-25 years have shown that vitamin D has many functions beyond calcium metabolism (3). It is now known that vitamin D deficiency has a role in the formation of autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis and other diseases including diabetes, many types of cancer, and heart disease (4-6).

The discovery of vitamin D receptors (VDRs) in many tissues has led to research the role of vitamin D in the diseases mentioned above. The fact that VDRs have been identified in almost all immune system cells, and especially in antigen-presenting cells such as active T and B lymphocytes, active macrophages, and dendritic cells, confirms the role of vitamin D in immune regulation (7-8).

Hashimoto's thyroiditis is the most common autoimmune thyroiditis and the most common cause of hypothyroidism. It is clinically characterized by gradual thyroid failure with or without goitre formation due to lymphocytic infiltration and autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells (9). Based on the effects of vitamin D on the immune system, vitamin D may have a role in the pathogenesis of Hashimoto's thyroiditis. Moreover, studies have found that VDR polymorphism increases the frequency of Hashimoto's thyroiditis (10).

The aim of this study was to compare the vitamin D levels of patients with Hashimoto's thyroiditis and healthy subjects and to evaluate possible relationships between vitamin D and other parameters.

Methods

We conducted this cross-sectional study in accordance with the principles of the Declaration of Helsinki. All participating patients provided written informed consent. The single-centre study was conducted at Izmir Bozyaka Training and Research Hospital and approval for the study was obtained from the local ethics committee of the hospital. The participants were divided into two groups; one group comprising patients with a diagnosis of Hashimoto's thyroiditis (patient group, n=40) and one group comprising healthy volunteers (control group, n=40). Eligible participants for the patient group were females who had ultrasonographic results consistent with chronic thyroiditis and serological antibody positivity (anti-Tg and anti-TPO).

Inclusion criteria for the patient group were the age of 16-50 years, ultrasonographic results consistent with chronic thyroiditis, and serological antibody positivity (anti-Tg and anti-TPO). Inclusion criteria for the healthy volunteers in the control group were the age of 16-50 years, normal thyroid ultrasound, and normal antibody levels (anti-Tg and anti-TPO). The exclusion criteria of the study were diabetes mellitus, chronic kidney or liver failure, cancer, not being euthyroid, body mass index (BMI) of >30 kg/$m^{2,}$ metabolic bone disease, autoimmune diseases other than thyroiditis, postmenopausal status, being male, and using antiepileptics, oral contraceptives, osteoporosis treatment, or calcium and vitamin D supplements. Patients with BMI of >30 kg/m2 were not included in the study because obesity has been shown to have a negative relationship with vitamin D in previous studies.

The patient and control groups were compared in terms of vitamin D levels. Thyroid-stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), anti-Tg, anti-TPO, age, and BMI were also measured and compared. All participants were given an appointment and asked to come to the appointment in the morning after 12 hours of fasting. Blood samples were taken from the antecubital vein for FT3, FT4, TSH, anti-Tg, anti-TPO, and vitamin D levels. For 25OHD, the electrochemiluminescence immunoassay method was used with an Elecsys 2010 device.

Vitamin D levels of <20 ng/mL were accepted as signifying severe deficiency, levels of 21-31 ng/mL as deficiency, and levels of >32 ng/mL as normal. The demographic data of the participants included in the study were recorded and detailed physical examinations were performed. Basic laboratory findings were recorded from the patients' files or other health documents. Body weight and height were measured by the same person using standard measuring instruments while participants were wearing indoor clothing and standing. BMI was calculated by dividing the participant's weight by the square of the height (weight/height2, kg/m2) using the Quetelet index.

The obtained data were analysed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The t-test was used to compare the means of two independent groups. The Cohen method was used to measure the effect size of the parameter of vitamin D (Cohen's *d*). For correlation analysis, distribution tests were performed and Spearman correlation coefficients were calculated. Values of $p<0.05$ were considered statistically significant. Means were presented with standard deviation values.

Results

A total of 80 participants, 40 in the patient group and 40 in the control group, were included in this study. Age and other parameters of the control and patient groups are shown in Table 1. The mean vitamin D level was 18.0±3.0 ng/mL and the median vitamin D level was 16.7 ng/mL (6.5-41 ng/mL) in the control group. The mean vitamin D level was 16.1±7.6 ng/mL and the median vitamin D level was 14.85 ng/mL (0.18-35.50 ng/mL) in the patient group (Table 1). There was no statistically significant difference between the two

groups in terms of vitamin D (p=0.305). When TSH, FT3, FT4, and BMI were examined, once again, no statistical difference was found between the two groups (Table 1). In the analysis of Cohen's effect size for vitamin D, the *d* value was 0.23. Accordingly, the effect size of the study was evaluated as low.

As a result of Spearman correlation tests, no statistically positive or negative correlation was found between vitamin D level and any other parameters (p>0.05). Statistically, all parameters were evaluated independently of one another. The negative correlation between vitamin D and antibodies (anti-Tg and anti-TPO) reported in some studies could not be demonstrated in this work.

Table 1: Values of variables in the groups

	Patient group (n=40)	*Control group (n=40)*	*Significance (p-value)**
Age, years, median (range)	34 (18-49)	27 (16-49)	0.128
Vitamin D, ng/mL, median (range)	14.850 (0.18-35.5)	16.700 (6.5-41)	0.305
BMI, kg/m², median (range)	25 (15.70-29.9)	22.535 (18.50-28.57)	0.316
TSH, mIU/L, median (range)	2.27 (0.41-4.9)	1.56 (0.55-3.95)	0.075
FT4, ng/dL, median (range)	0.81 (0.62-1.21)	0.86 (0.59-1.14)	0.908
FT3, pg/mL, median (range)	2.94 (2.37-3.71)	3.055 (2.51-4.04)	0.703

* The p-value shows whether there is a statistical difference between the two groups.

BMI = Body mass index, TSH = Thyroid-stimulating hormone, FT4 = Free T4, FT3 = Free T3.

Discussion

Vitamin D deficiency is an important public health problem in Turkey. In a previous study, Erkal et al. showed that 25OHD levels were below 25 ng/mL in 78% of Turkish people, regardless of where in the country they lived (11). In addition, there are previous studies showing a relationship between vitamin D deficiency and autoimmunity, but there is no definitive evidence to date showing the relationship between Hashimoto's thyroiditis and vitamin D. In our study, no significant difference was found between the patient and control groups in terms of vitamin D levels. In addition, no correlation was found between vitamin D level and Hashimoto's thyroiditis parameters. The results of our study are not sufficient to allow a definitive evaluation of the relationship between vitamin D level and Hashimoto's thyroiditis.

Hashimoto's thyroiditis occurs as a result of interactions of genetic and environmental factors (12). The role of genetic factors is one of the most researched aspects of Hashimoto's thyroiditis and vitamin D is among the relevant factors. 1,25-Dihydroxyvitamin D is the most active form of vitamin D and it has been shown to effectively prevent the development of autoimmune thyroiditis in animal models (13).

Lin et al. investigated the role of VDR polymorphism in 109 patients with Hashimoto's thyroiditis in their study in Taiwan. As a result, it was determined that the risk of developing Hashimoto's thyroiditis is higher in Chinese individuals who carry the C/C homozygous form of the VDR Fok I polymorphism localized in exon 2 (10). Stefanic et al., in a study including 145 Croatian patients with Hashimoto's thyroiditis haplotype variants and alleles involving the VDR gene 3' region, showed that these imbalances may have a pathogenic role (14).

Contrary to the studies mentioned above, there are also studies showing that vitamin D levels in Hashimoto's thyroiditis are unrelated to the disorder. In the study of Botelho et al., vitamin D levels were found to be similar in healthy volunteers and patients with Hashimoto's thyroiditis (15). In addition, those authors emphasized that it is not known whether low vitamin D is the cause or the result of autoimmunity and that larger studies on this subject are needed.

Most studies show that vitamin D has a role in Hashimoto's thyroiditis. In our study, we investigated the level of vitamin D in Hashimoto's thyroiditis. While the mean vitamin D level was 16.19 ng/mL in the patient group, it was 18.02 ng/mL in the control group. There was no significant difference between the groups in this regard (p=0.305) and the vitamin D levels of both groups revealed deficiencies. The fact that most of these participants had vitamin D deficiency shows that vitamin D deficiency is still a public health problem that should be taken seriously in Turkiye.

There are many personal and environmental factors

that affect vitamin D levels. Vitamin D levels are highest at the end of summer and lowest at the end of winter (16). The fact that most of the participants' measurements were taken in winter was a limiting aspect of our study. The second important limitation was the low number of patients. Conducting a similar study in summer with a larger number of participants may produce different results.

One of the personal factors affecting vitamin D level is clothing style. Clothing is an important barrier between UV rays and the skin. Particularly in research conducted in Arab countries, it is reported that, in spite of abundant sunlight, traditional clothing styles prevent adequate sun exposure and cause vitamin D deficiency (17). Thus, another reason for the low levels of vitamin D in our study may be differences in clothing styles.

There have also been studies showing the relationship between vitamin D deficiency and Hashimoto's thyroiditis with vitamin D therapy. In the study conducted by Chahardoli et al., patients with Hashimoto's thyroiditis were given vitamin D treatment for three months and the authors observed significant decreases in anti-Tg and TSH levels (18). However, they did not detect any significant changes in FT3 or FT4 levels. For this reason, they suggested that vitamin D can be used as a treatment during periods of disease exacerbation.

In our study, we could not detect a negative or positive correlation between thyroid autoantibodies and vitamin D. In their study, however, Bozkurt et al. found a negative correlation between vitamin D levels and antibody levels (19). Such a correlation detected in that study and other previous studies shows the immunomodulatory role of vitamin D (20-21). Thyroid antigen-specific T helper cells stimulate B lymphocytes and cause the synthesis of antibodies responsible for thyroid damage and infiltration (22). T helper and macrophage cells have more VDRs than lymphocytes (23). They reduce the release of IL-2, IL-5, IFN-γ, and TNF-a by active vitamin D in T cells, thus reducing the general immune response and the antibody-mediated immune response (24). The decrease in the activation of T lymphocytes, which express VDRs at high levels, together with vitamin D may explain this correlation.

Conclusion

In our study, although there was a numerical difference in vitamin D levels between the patient and control groups, it was not statistically significant. In addition, no correlation was found between vitamin D level and Hashimoto's thyroiditis parameters. With the data of our study, it is not possible to evaluate potential relationships between vitamin D level and Hashimoto's thyroiditis. However, our study may be helpful for future research investigating the relationship between Hashimoto's thyroiditis and vitamin D deficiency more comprehensively.

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