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Research article

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Relationship between vitamin D receptor gene polymorphisms and vitamin D levels in children

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Ethics Committee Approval
Approval for this study was obtained from the Ethics Committee of Kafkas University Faculty of Medicine with the decision number 11 of the document dated 31.10.2018 and numbered 177. Informed consent was obtained from each participating child and their parents by providing detailed information about the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Vitamin D exerts its effects in the body through its receptors. Polymorphisms in vitamin D Receptor (VDR) gene are known to cause certain diseases and affect vitamin D levels. In this study, we planned to examine the relationship between vitamin D levels and Vitamin D gene polymorphisms among children.

Methods: The study group included 124 healthy children living in the same region. Vitamin D (VitD), Parathyroid Hormone (PTH), Alkaline phosphatase (ALP), Calcium (Ca), Phosphorus (P) and Magnesium (Mg) were examined in the blood samples taken. In terms of measured Vitamin D levels, children were divided into group 1 (Vitamin D < 20 ng/mL) and group 2 (Vitamin D ≥ 20 ng/mL). Deoxyribonucleic Acid (DNA) was isolated from the serum sample, VDR ApaI and TaqI polymorphisms were determined by Polymerase Chain Reaction (PCR) method, and comparisons were made between groups.

Results: The overall mean age of the children included in the study was 8.11 (4.98) years. The mean ages of participants in Groups 1 and 2 were 9.38 (4.87) years and 6.38 (4.62) years, respectively (P=0.091). The mean vitamin D levels of Groups 1, 2 and overall were 13.82 (3.29) ng/mL, 33.96 (20.47) ng/mL, and 23.49 (21.54) ng/mL, respectively (P=0.509). The two groups were similar in terms of serum ALP, PTH, Ca, Mg and P levels (P>0.05 for all). VDR polymorphisms were found to have no effect on Vitamin D levels.

Conclusion: In our study, no relationship was found between the genotypes of ApaI and TaqI polymorphisms and Vitamin D levels. This study is important in terms of remarking the fact that Vitamin D deficiency is still a public health problem and its contributions to VDR gene polymorphism research.

Keywords: Vitamin D, Vitamin D receptor, Polymorphism

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Introduction

Vitamin D is mainly synthesized in the skin by way of ultraviolet-B (UV-B) rays from sunlight, but also partially ingested from vegetable and animal foods. It is activated in our body after being hydroxylated in the liver first, then the kidney, and besides its many effects in our body, it mainly affects the calcium (Ca^{+2}) metabolism [1,2]. It was demonstrated that Vitamin D receptor (VDR) resides in the immune system, as well as many tissues such as blood cells and the central nervous system [3].

The function of Vitamin D in our body is mediated by VDR. Many polymorphisms were identified in studies examining the VDR gene, i.e., ApaI, TaqI, FokI and BsmI polymorphisms [4]. There are studies investigating the relationship between Vitamin D levels and VDR gene polymorphisms, and different results have been obtained in different populations [5-9].

In our study, we aimed to determine the frequency of VDR Apa and Taq polymorphisms, their genotype typology in healthy children and relationship with serum vitamin D levels.

Materials and methods

A total of 124 healthy children aged 12 months-18 years who visited Kafkas University Faculty of Medicine, General Pediatrics Outpatient Clinic for routine checkup, had no complaints and normal physical examination findings, had not used daily or depot vitamin D preparations within the last 3 months and not lived in any place other than the place of residence within the last 6 months were included in this study. A total of 72 children with vitamin D insufficiency, deficiency and severe deficiency based on blood samples obtained in routine examinations, and 52 children with normal vitamin D values were included in the study on a voluntary basis.

Approval for this thesis study was obtained from the Ethics Committee of Kafkas University Faculty of Medicine with the decision number 11 of the document dated 31.10.2018 and numbered 177. Informed consent was obtained from each participating child and their parents by providing detailed information about the study.

Those with a condition requiring hospitalization, without an informed consent form obtained from their parents and those who did not want to participate in the study, those with a known chronic disease, clinical complaints of Vitamin D deficiency or excess, abnormal physical examination findings, those who have used depot or daily doses of Vitamin D preparations within the last 3 months, and those who have lived in another region within the last 6 months were excluded from the study. Ca^{+2}, P, ALP, Mg and PTH levels were examined simultaneously with vitamin D levels.

After the biochemical parameters were examined, the remaining serum samples were stored in Eppendorf tubes in a -20°C deep freezer until genetic analysis. DNA was isolated from stored samples and ApaI and TaqI gen polymorphisms were studied (Figure 1, 2).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20 was used for the analysis of the data. Two groups were formed in terms of Vitamin D level: Group 1 included children with Vitamin D < 20 ng/mL and group 2 included those with Vitamin D ≥ 20 ng/mL. Visual graphics (Histogram) and the Kolmogorov-Smirnov test were used to check whether parameters complied with normal distribution. The relationship between the genotype and allele distributions of TaqI and ApaI polymorphisms and Vitamin D levels of the two groups was evaluated by Pearson's Chi-Square test. The vitamin D results of the groups with ApaI and TaqI polymorphisms were evaluated with the ANOVA test. $P<0.05$ values were considered statistically significant in all tests.

Results

The mean age of 124 healthy children participating in the study was 8.11 (4.98) years. Groups 1 and 2 (9.38 (4.87) years vs. 6.38 (4.62) years) and females and males (8.47 (5.33) years vs. 7.86 (4.74) years) were similar in terms of age ($P=0.091$ and $P=0.603$, respectively). There were 36 females and 36 males in Group 1, and 14 females and 38 males in Group 2.

Figure 1: A: Cutting with ApaI among children with Vitamin D < 20ng/mL, B: Cutting with ApaI among children with Vitamin D ≥20ng/ml

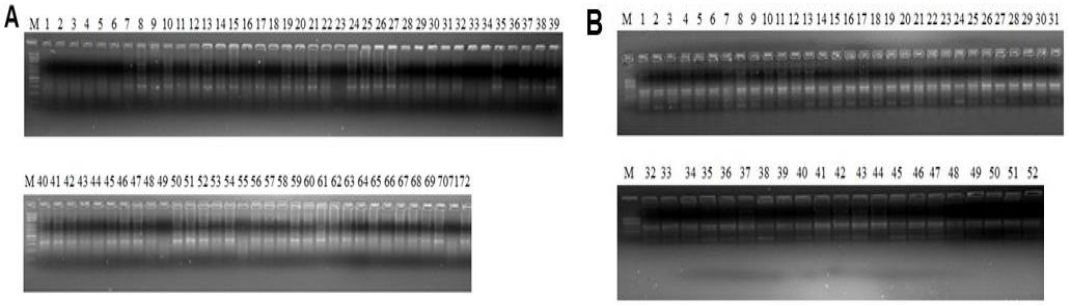
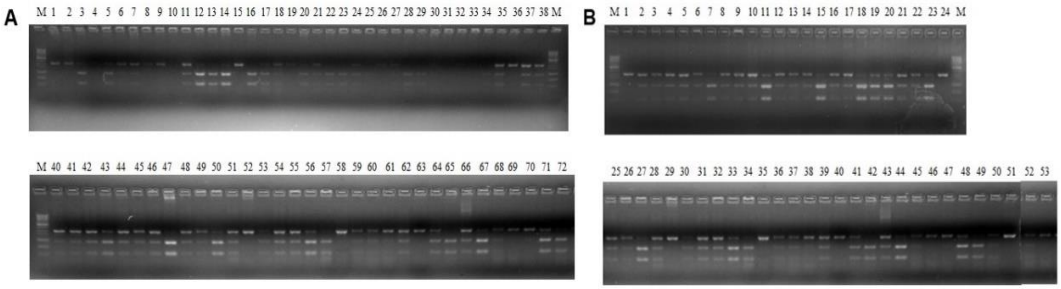


Figure 2: A: Cutting with TaqI among children with Vitamin D < 20ng/mL, B: Cutting with TaqI among children with Vitamin D ≥ 20 ng/mL



The mean vitamin D levels in Groups 1, 2 and overall were 13.82 (3.29) ng/ml, 33.96 (20.47) ng/ml, and 23.49(21.54) ng/ml, respectively, with no significant difference between the groups (P=0.509). The lowest and highest vitamin D level among all children were 5 ng/ml and 116 ng/ml, respectively. The mean vitamin D levels of male and female children were 24.73 (17.64) ng/ml, and 18.62 (14.69) ng/ml, respectively (P<0.001) (Table 1).

In terms of ApaI polymorphism, 32% had AA genotype, 57% had Aa genotype, and 11% had aa genotype. For TaqI polymorphism, 42% had TT genotype, 48% had Tt genotype, 10% had tt genotype (Table 2).

Table 1: Mean 25(OH) D3 across all population and genders

Group	25(OH)D3 Average	n	*P*-value
Vitamin D <20 ng/mL	13.82 (3.29)	72 (58%)	
Vitamin D≥20ng/mL	33.96 (20.47)	52 (42%)	0.509
All Population	23.49 (21.54)	124 (100%)	
Males (all population)	24.73 (17.64)	74 (59.7%)	
Females (all population)	18.62 (14.69)	50 (40.3%)	0.001

Table 2: Distribution of ApaI, TaqI polymorphism genotypes among the groups and overall

	Vitamin D <20ng/mL (n=72)	Vitamin D ≥20ng/mL (n=52)	*P*-value	All Population (n=124)	Total %	Girl (n=50)	Boy (n=74)	*P*-value
ApaI								
AA	25 (35%)	15 (29%)		40	32	18	22	
Aa	40 (55%)	31 (60%)	0.777	71	57	28	43	0.656
aa	7 (10%)	6 (11%)		13	11	4	9	
TaqI								
TT	31 (43%)	21 (40%)		52	42	19	33	
Tt	34 (47%)	25 (48%)	0.927	59	48	28	31	0.175
tt	7 (10%)	6 (12%)		13	10	3	10	

In Group 1, 35% had AA, 55% had Aa, 10% had aa, 43% had TT, 47% had Tt, and 10% had tt genotypes. The rates of AA, Aa, aa, TT, Tt and tt genotypes in Group 2 were 29%, 60%, 11%, 40%, 48% and 12%, respectively (Table 2).

Vitamin D levels among these genotypes were as follows: 19.58 ng/mL in AA, 22.94 ng/mL in Aa, 26.85 ng/mL in aa, 20.69 ng/mL in TT, 24.10 ng/mL in Tt, and 20.23 ng/mL in tt. Vitamin D levels did not significantly differ according to ApaI and TaqI genotypes (P=0.348, P=0.509, respectively) (Table 3).

Table 3: Relationship between Vitamin D level and ApaI and TaqI polymorphisms genotypes

	AA	Aa	aa	*P*-value
Vitamin D(ng/mL)	19.58 (10.38)	22.94 (17.13)	26.85 (27.45)	0.348
	TT	Tt	tt	
	20.69 (12.66)	24.10 (20.32)	20.23 (12.51)	0.509

Discussion

According to studies conducted in different age groups of many societies, Vitamin D insufficiency and deficiency are at a remarkable level all over the world [10-13]. Research in Turkey showed that rates of overall vitamin D deficiency and insufficiency were 51.8% and 20.7%, respectively. The mean vitamin D level in deficient individuals was 18.7 (6.8) ng/mL in Erzurum, and 52% of children aged between 2-4 years, 62.5% of children aged between 5-8 years and 63% of children aged between 9-12 years were vitamin D deficient [14,15].

In the present study, mean Vitamin D levels were 23.49 ng/mL. Among 124 children, Vitamin D levels were below 20 ng/mL in 72 (58%) cases and within normal limits in 52 (42%). None had severe deficiency or intoxication, while vitamin D levels of 34.7% were deficient, 23.4% were insufficient, 41.4% were normal, and 0.8% were excess (Table 4). In this respect, this study was compatible with other studies conducted in our region in terms of Vitamin D deficiency/insufficiency.

Table 4: Overall Distribution of Vitamin D

	n	%
Severe Deficiency (<5 ng/mL)	0	0
Deficiency (5-15 ng/mL)	43	34.7
Insufficiency (15-20 ng/mL)	29	23.4
Normal (20-100 ng/mL)	51	41.1
Excess (100-150 ng/mL)	1	00.8
Intoxication (>150 ng/mL)	0	0

The females included in our study had significantly lower vitamin D levels compared to females. Vitamin D deficiency affects females more often because of the traditional lifestyle in Turkey. In a study conducted with 14.091 participants in USA to set forth the correlation between Vitamin D levels and gender, the mean levels of vitamin D among male and female children were 31.37 ng/mL and 28.72 ng/mL, respectively, which significantly differed [16]. In a study conducted in Kocaeli region in Turkey, the 25-OH level in 50% of female students was below 10 ng/mL, while this rate was between 3 and 13% in other students [17]. Both in the present study and in studies conducted in Turkey and other countries, vitamin D levels of females are lower compared to males.

Genetic factors controlling vitamin D levels play an important role in vitamin D deficiency. Many polymorphisms were identified in studies conducted on the VDR gene, i.e., ApaI, TaqI, FokI and BsmI [18]. In their study on FokI, ApaI and TaqI polymorphisms in the VDR Gene among 100 healthy Turkish individuals, Dayangaç et al. [19] documented the rates of AA, Aa, aa, TT, Tt and tt as 30%, 55%, 15%, 35%, 49%, and 16%, respectively. In another polymorphism study conducted with a healthy population in India, TT, Tt, tt, AA, Aa and aa genotypes were 49%, 40%, 11%, 36%, 44% and 20%, respectively [20].

In a VDR Apal and Taql polymorphism study conducted with a healthy population in Iran, AA, Aa, aa, TT, Tt and tt genotypes for ApaI and TaqI were 42%, 47%, 10%, 36%, 58%, and 6%, respectively [21]. Our results were like those obtained by Dayangaç et al. [19]. At this point, it is evident that the study population reflects the genetic profile of Turkey and demonstrates similarities in terms of polymorphism and genotype rates with the studies performed in the healthy population in various countries.

There are many studies regarding the correlation between VDR gene polymorphisms and vitamin D levels in the world and in Turkey; nevertheless, the results were inconsistent with each other. The relationship between Vitamin D levels and polymorphisms in the VDR gene was demonstrated in certain studies [5-9, 22-25]. Contrarily, studies with no evident correlation on this issue were conducted both abroad and in Turkey. For example, no significant difference was found between Vitamin D levels with respect to TaqI polymorphisms in India [26]. VDR polymorphisms (BsmI, TaqI, ApaI) were not associated with Vitamin D levels in patients diagnosed with Graves' disease in Egypt [27]. In the studies conducted by Maalmi et al. [28] on children with asthma in Tunisia, Elrawi et al. [29] on patients with hypothyroidism, and Faghfouri et al. [30] on patients with autoimmune thyroiditis in Iran, no relationship was found between Vitamin D levels and VDR gene polymorphisms. In Turkey, no significant association was found between Vitamin D levels and FokI polymorphism among major depression patients [31]. In a study evaluating 84 pediatric patients with a diagnosis of Hashimoto's Thyroiditis, VDR polymorphisms and vitamin D levels were not related [32, 33].

This study demonstrated that ApaI and TaqI VDR gene polymorphisms do not pose a risk for Vitamin D deficiency and insufficiency, similar to studies that did not detect a relationship between VDR gene polymorphisms and vitamin D levels in the literature.

Limitations

Although VDR has different genetic polymorphisms, this study was conducted with two. The failure to include other polymorphisms can be considered as the limitation of this study.

Conclusion

Vitamin D deficiency is still an important societal problem today. The study group only includes healthy children and has a wide age range (12 months-18 years). The study population is sufficient compared to other studies, and it is the first VDR gene polymorphism study conducted in the relevant region. In light of all these data, it is thought that the study will contribute to further studies to be conducted in this regard.

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References

1. Gupta A, Thompson PD. The relationship of Vitamin D deficiency to statin myopathy. Atherosclerosis. 2011;215(1):23-9.
2. Gürel G, Karadöl M, Çölgeçen E. A case-control study on rosacea and vitamin D levels. J Surg Med. 2018;2(3):269-72.
3. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80:1678-88.
4. Valdivielso J.M, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006;371(1-2):1-12.
5. Junaid K, Rehman A, Jolliffe DA, Wood K, Martineau AR. High prevalence of Vitamin D deficiency among women of child-bearing age in 45 Lahore Pakistan, associating with lack of sun exposure and illiteracy. BMC Womens Health. 2015; 12,15:83.
6. Thanapirom K, Suksawatamnuay S, Sukeepaisarnjaroen W, Tangkijvanich P, Treeprasertsuk S, Thaimai P, et al. Vitamin D-related gene polymorphism predict treatment response to pegylated interferon-based therapy in Thai chronic hepatitis C patients. BMC Gastroenterology. 2017;17:54.
7. Zheng SZ, Zhang DG, Wu H, Jiang LJ, Jin J, Lin XQ, et al. The association between Vitamin D receptor polymorphisms and serum 25 hydroxy Vitamin D levels with ulcerative colitis in Chinese Han population. Clin Res Hepatol Gastroenterol. 2017;41(1):110-7.
8. Bhanushali AA, Lajpal N, Kulkarni SS, Chavan SS, Bagadi SS, Das BR.
9. Frequency of fokI and taqI polymorphism of Vitamin D receptor gene in Indian population and its association with 25-hydroxyVitamin D levels. Indian J Hum Genet. 2009;15(3):108–13.
10. Smolders J, Damoiseaux J, Menheere P, Tervaert JW, Hupperts R. Fok-I
11. vitamin D receptor gene polymorphism (rs10735810) and Vitamin D metabolism in multiple sclerosis. J Neuroimmunol. 2009;207(1–2):117–21.
12. Demiral M, Sırmagül B, Kırel B. Endokrin polikliniğine başvuran çocuklarda D vitamini düzeyleri. J Curr Pediatr. 2016;14:60-6.
13. Taşkıran B, Cansu GB. Güneydoğu bölgesinde erişkinlerde D Vitamini eksikliği. Osmangazi Journal of Medicine. 2016;39:13-20.
14. Aykal G, Cerit N, Tekeli SÖ. Ameliyathane personelinde D vitamini eksikliği ve yetersizliği prevalansı. Türk Klinik Biyokimya Derg. 2016;14:18-26.
15. Cashman KD, Dowling KG, Skrabakova Z, Kiely M, Lamberg-Allardt C, Durazo-Arvizu RA, et al. Vitamin D deficiency in Europa: pandemic? Am J Clin Nutr. 2016;103:1033-44.
16. Uçar F, Taşlıpınar MY, Soydaş AÖ, Özcan N. Ankara Etlik İhtisas Eğitim Araştırma Hastanesi'ne başvuran hastalarda 25-OH Vitamin D düzeyleri. Eur J Basic Med Sci. 2012;2:12-5.
17. Güllük İ, Alp H. 2-12 yaş arası sağlıklı çocuklarda d vitamini düzeyleri ve etkileyen faktörler. Atatürk Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Uzmanlık tezi, (Danışman: Prof. Dr. Handan ALP). Erzurum, 2017.
18. Black PN, Scragg R. Relationship between serum 25-hydroxy Vitamin d and pulmonary function in the third national health and nutrition examination survey.
19. Chest. 2005;128(6):3792-8.
20. Hatun S, Islam O, Cizmecioglu F, Kara B, Babaoğlu K, Berk F, et al. Subclinical Vitamin D deficiency is increased in adolescent girls who wear concealing clothing. J Nutr. 2005 Feb;135(2):218-22.
21. Jose MV, Elvira F. Vitamin D receptor polymorphisms and diseases. Clinica Chimica Acta. 2006;371:1-12.
22. Dayangaç D, Özaydın E, Özbaş Gerçeker F, Coşkun T, Erdem Yurter H. Sağlıklı Türk Populasyonunda Vitamin D Reseptör (VDR) Gen Polimorfizm Analizi. Türk Biyokimya Dergisi. 2002;27:11-6.
23. Bid HK, Mishra DK, Mittal RD. Vitamin-D receptor (VDR) gene (Fok-I, Taq-I and Apa-I) polymorphisms in healthy individuals from North Indian population. 2005.
24. Haddad S. Vitamin-D receptor (VDR) gene polymorphisms (Taq-I &Apa-I) in Syrian healthy population. Meta gene. 2014;2:646-50.
25. Santos BR, Mascarenhas LP, Satler F, Boguszewski MC, Spritzer PM. Vitamin D deficiency in girls from South Brazil: a cross-sectional study on prevalence and association with vitamin D receptor gene variants. BMC pediatrics. 2012;12(1):62.
26. Kitanaka S, Isojima T, Takaki M, Numakura C, Hayasaka K, Igarashi T. Association of Vitamin D-related gene polymorphisms with manifestation of Vitamin D deficiency in children. Endocr J. 2012;59(11):1007-14.
27. Dipanshu S, Chakravorty R. Genetic polymorphism in the Vitamin D receptor gene and 25-hydroxy Vitamin D serum levels in east Indian women with polycystic ovary syndrome. J Mol Biomark Diagn. 2015;6(247):2.
28. Yıldırım M, Kurtulgan HK, Şahin A. Vitamin D deficiency, myopathy and VDR gene polymorphism in a young woman. Cumhuriyet Medical Journal. 2015;37(2):164-6.
29. Rao Vupputuri M, Goswami R, Gupta N, Ray D, Tandon N, Kumar N. Prevalence and functional significance of 25-hydroxyVitamin D deficiency and Vitamin D receptor gene polymorphisms in Asian Indians. The American journal of clinical nutrition. 2006;83(6):1411-9.
30. Abd El Gawad SS, Abdul Samee ER, Metwali AA, Abd El Gawad MS. Vitamin D receptor gene polymorphism and its association with 1,25-dihydroxy vitamin D (3) inpatients with Graves disease in an Egyptian population: a pilot study. Endocr Pract. 2012;18(2):132-9.
31. Maalmi H, Sassi FH, Berraies A, Ammar J, Hamzaoui K, Hamzaoui A. Association of vitamin D receptor gene polymorphisms with susceptibility to asthma in Tunisian children: A case control study. Hum Immunol. 2013;74(2):234-40.
32. El Rawi HA, Ghanem NS, El Sayed NM, Ali HM, Rashed LA, Mansour MM. Study of Vitamin D Level and Vitamin D Receptor Polymorphism in Hypothyroid Egyptian Patients. Journal of thyroid research. 2019;1-10.
33. Faghfouri AH, Bagheri M, Mehdizadeh A, Ayremlou P, Zarrin R. Vitamin D Level and Vitamin D Receptor Gene Polymorphisms in Iranian Azeri Turkish Patients With Autoimmune Thyroid Diseases. Acta Medica Iranica. 2018;508-15.
34. Şahin Can M, Baykan H, Baykan Ö, Erensoy N, Karlıdere T. Vitamin D levels and vitamin D receptor gene polymorphism in major depression. Psychiatria Danubina. 2017;29(2):179-85.
35. Guleryuz B, Akin F, Tunc Ata M, Mergen Dalyanoglu M, Turgut S. Vitamin-D receptor (VDR) gene polymorphisms (TaqI, FokI) in Turkish patients with Hashimoto's thyroiditis: relationship to the levels of Vit-D and cytokines. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2016;16(2):131-9.
36. Yıldız İ, Ünüvar E, Zeybek Ü, Toptaş B, Cacina C, Toprak S, et al. Çocuklarda Yineleyen Tonsillofarenjitte D Vitamininin Rolü. Journal of the Child/Cocuk Dergisi. 2012;12(3):132-8.

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