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Original Research Article

The Vitamin D Receptor Bsm1 Variant is not Associated With Temporomandibular Disorder With or Without Bruxism

D Vitamini Reseptörü Bsm1 Varyantı, Bruksizm Olan veya Olmayan Temporomandibular Bozuklukla İlişkili Değildir

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ABSTRACT

Aim: Temporomandibular joint disorder (TMD), a set of conditions that affect the temporomandibular joint and related structures, is frequently linked to bruxism. The vitamin D receptor (VDR) affects calcium absorption, bone remodeling, and mineralization rate. The goal of this study was to evaluate the role of the VDR Bsm1 (rs1544410) variant in the susceptibility to bruxism in TMD.

Materials and Method: A total of 321 people [221 TMD patients (135 with bruxism and 86 without bruxism) and 100 healthy controls] were included in the study. The VDR Bsm variant was genotyped using the PCR-RFLP method.

Results: We found no significant difference between the all-TMD patient group and the control group regarding the VDR Bsm1 genotype and allele distribution (p>0.05). There was no deviation from HWE for the VDR variant in groups. There was no relationship between pain characteristics and VDR Bsml genotype distribution in patients with bruxism.

Conclusions: Our results support the conclusion that the VDR Bsm1 variant is not a risk factor for the development of bruxism in TMD. The effect of the VDR Bsm1 variant on the risk of bruxism in TMD should be investigated in studies involving larger populations and other ethnicities.

Keywords: Bruxism; Temporomandibular disorder; PCR-RFLP; Variant; Vitamin D receptor

ÖZET

Amaç: Temporomandibular eklemi ve ilgili yapıları etkileyen bir dizi durum olan temporomandibular eklem bozukluğu (TMD), sıklıkla bruksizm ile bağlantılıdır. D vitamini reseptörü (VDR) kalsiyum emilimini, kemiğin yeniden şekillenmesini ve mineralizasyon hızını etkiler. Bu çalışmanın amacı, VDR Bsm1 (rs1544410) varyantının TMD'de bruksizme duyarlılıktaki rolünü değerlendirmektir.

Gereç ve Yöntem: Çalışmaya toplam 321 kişi [221 TMB hastası (135 bruksizmli ve 86 bruksizmsiz) ve 100 sağlıklı kontrol] dahil edildi. VDR Bsm1 varyantı, PCR-RFLP yöntemi kullanılarak genotiplendi.

Bulgular: Tüm TMD hasta grubu ile kontrol grubu arasında VDR Bsm1 genotipi ve alel dağılımı açısından anlamlı fark bulunmadı (p>0.05). Gruplarda VDR Bsm1 varyantı için HWE'den sapma olmamıştır. Bruksizmli hastalarda ağrı özellikleri ile VDR Bsml genotip dağılımı arasında ilişki yoktu.

Sonuç: Sonuçlarımız, VDR Bsm1 varyantının TMD'de bruksizm gelişimi için bir risk faktörü olmadığı sonucunu desteklemektedir. VDR Bsml varyantının TMD'deki bruksizm riski üzerindeki etkisi, daha büyük popülasyonlar ve diğer etnik kökenleri içeren çalışmalarda araştırılmalıdır.

Anahtar Kelimeler: Bruksizm; D vitamini reseptörü; PCR-RFLP; Temporomandibular eklem hastalığı; Varyant

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INTRODUCTION

Bruxism refers to the chronic, involuntary grinding or clenching of teeth. It commonly occurs during sleep (sleep bruxism) but can also occur while awake (awake bruxism).[1] According to statistics, there is 14.1% sleep bruxism, 28.2% awake bruxism, and 38.8% combined bruxism in the Turkish population.[2] Among all the parafunctional behaviors of the stomatognathic system, bruxism is typically regarded as the most damaging and significant risk factor for temporomandibular disorders (TMD).[3] TMD refers to a group of conditions that affect the temporomandibular joint (TMJ) and the associated muscles, tendons, ligaments, and other structures.[4,5] TMDs affect 5% to 15% of adults and are more prevalent in women between 20 and 40.[6] The etiology, or causes, of TMD are often complex and multifactorial. While the exact cause of TMD is unclear, several factors have been identified as potential contributors to its development.

Vitamin D (VD) is a fat-soluble vitamin that plays a crucial role in regulating calcium and phosphorus levels in the body. It is essential for maintaining bone health, as it promotes calcium absorption from the intestine and helps regulate calcium levels in the bloodstream.[7] Additionally, VD has important functions in the immune system, cell growth, neuromuscular function, and the reduction of inflammation. The effects of VD are mediated by the vitamin D receptor (VDR), a protein found in various tissues throughout the body, including the intestines, bones, immune cells, and many others.[8] There are a few single nucleotide polymorphisms (SNPs) in the VDR gene. The most studied VDR gene variants are ApaI (rs7975232), BsmI (rs1544410), TaqI (rs731236), and FokI (rs10735810). BsmI, TaqI, and ApaI variants are thought to affect VDR expression.[9] The VDR gene variants and changes in VD level have been linked to a number of disorders, including autoimmune, cardiovascular, and recurring infections, osteoarthritis, and osteoporosis.[10,11] In our previous study of the Turkish population, we confirmed a relationship between the VDR Bsm1 variant and TMD.[12] There is currently insufficient evidence to link the VDR Bsm1 variant to bruxism.

Therefore, this study aimed to evaluate the role of the VDR Bsm1 (rs1544410) variant in the susceptibility to bruxism in TMD.

MATERIALS AND METHOD

Study population

This study was approved by the Clinical Trials Publication Ethics Committee at Tokat Gaziosmanpaşa University (2019.83116987-867). A total of 221 TMD patients (135 with bruxism and 86 without bruxism) (46 males, 175 females; mean age±SD years: 29.82±9.742), were included in this prospective case-control research. They were recruited from the Department of Oral and Maxillofacial Surgery at Gaziosmanpasa University in Tokat, Turkey. TMD was diagnosed based on the criteria described by Schiffman *et al*.[13] Evaluation of TMD Axis I assessment includes a TMD pain questionnaire, a TMD symptom questionnaire, demographic information, and examination findings. TMD Axis II assessment includes pain drawing, a chronic pain scale, a jaw function limitation scale, a health questionnaire, and oral habits. Patients with other autoimmune or inflammatory conditions were not included in the study. A thorough physical examination was conducted after a thorough medical history was obtained. A typical questionnaire, including demographic questions and clinical features, was used to interview the subjects. The 100 healthy subjects (31 males, 69 females; mean age±SD years: 30.70±10.068) without a history of any autoimmune or chronic diseases were chosen as controls. The study methodology was explained to each participant, and their written informed consent was collected. This study, which followed the Helsinki Declaration, was authorized by the institutional ethics committee.

Genotyping

All subjects had their blood drawn, and DNA was extracted using a DNA extraction kit (Germany's Sigma-Aldrich) following the manufacturer's instructions. Using the previously described polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique, the VDR Bsm1 variation was genotyped in each patient.[14] The Fermentas restriction enzyme digested the PCR products for an entire night at 37°C. The digested products were seen using UV transillumination after being resolved on 2% agarose gel and stained with ethidium bromide. Bsm1 digestion results in the generation of three genotypes: BB (825 bp), Bb (825, 650, 175 bp), and bb (650, 175 bp). For quality control, 20%

of the samples were randomly selected for repeated detection, and the replicated samples demonstrated 100% consistency.

Statistical analysis

The Statistical Package for the Social Sciences (IBM SPSS Statistics, version 20) and OpenEpi Info software, version 3.01 (www.openepi.com), were used to conduct the statistical analysis. The Hardy-Weinberg equilibrium (HWE) for the distribution of the genotypes of the patients and the controls was assessed using the chi-square (2) test. Using the 2 test or analysis of variance (ANOVA) statistics, the correlations between VDR Bsm1 and the clinical and demographical variables of patients were examined. It was appropriate to compare categorical variables using the 2 test and Fisher's exact test. For the evaluation of risk factors, odds ratios (OR) and 95% confidence intervals (CI) were employed. P values less than 0.05 were regarded as significant for all 2-tailed p values.

RESULTS

In this study, a total of 321 subjects were genotyped for the VDR BsmI variant. The demographical characteristics of patients and controls are shown in Table 1. There was no significant association between TMD patients and the controls according to demographical characteristics (p>0.05).

The genotype and allele distributions of the VDR Bsm1 variant are shown in Table 2. The frequencies of BB, Bb, and bb genotypes of the VDR Bsm1 variant in the patients were 27.1%, 47.5%, and 25.3%; in the controls, they were 31%, 52%, and 17%. B and b allele frequencies were 50.9% and 49.1% in the patient group and 57% and 43% in the control group, respectively. Genotype and allele frequencies did not show any significant differences between all TMD patients and the controls according to the VDR Bsm1 variant (p>0.05). There was no deviation from HWE for the VDR variant in both groups.

Table 1. The demographical characteristics of TMD patients and healthy controls

Demographical characteristics	TMD group n:221	Control group n:100	p
Age, mean ± SD (years)	29.82±9.742	30.70±10.068	0.461
Gender, n (%)			0.066
Male	46 (20.8)	31 (31.0)	
Female	175 (79.2)	69 (69.0)	

Data were analyzed by analysis of variance and χ2 test. TMD: Temporomandibular disorders, SD: standard deviation.

Table 2. Genotype and allele frequencies of VDR Bsm1variant in all TMD patients and control group

VDR Bsm1	TMD group n:221 (%)	Control group n:100 (%)	p	OR (CI 95%)
Genotypes				
BB	60 (27.1)	31 (31.0)	0.253	
Bb	105 (47.5)	52 (52.0)		
bb	56 (25.3)	17 (17.0)		
BB : Bb+bb	60 (27.1) : 161 (72.8)	31 (31.0) : 69 (69.0)	0.478	1.20 (0.71-2.02)
BB+Bb : bb	165 (74.6) : 56 (25.3)	83 (83.0) : 17 (17.0)	0.099	1.65 (0.91-3.09)
Alleles				
B	225 (50.9)	114 (57.0)	0.152	1.28 (0.91-1.79)
b	217 (49.1)	86 (43.0)		
HWE p	0.462	0.543		

Data were analyzed by χ2 test. TMD: Temporomandibular disorders; HWE: Hardy-Weinberg equilibrium

Table 3. Genotype and allele frequencies of VDR Bsm1 variant in patients with bruxism and control group

VDR Bsm1	Patients with bruxism n:135 (%)	Controls n:100 (%)	p	OR (CI 95%)
Genotypes				
BB	35 (25.9)	31 (31.0)	0.352	
Bb	67 (49.6)	52 (52.0)		
bb	33 (24.4)	17 (17.0)		
BB : Bb+bb	35 (25.9) : 100 (74.0)	31 (31.0) : 69 (69.0)	0.392	1.28 (0.72-2.28)
BB+Bb : bb	102 (75.5) : 33 (24.4)	83 (83.0) : 17 (17.0)	0.168	1.58 (0.82-3.08)
Alleles				
B	137 (50.7)	114 (57.0)	0.179	1.29 (0.89-1.86)
b	133 (49.3)	86 (43.0)		

Data were analyzed by χ2 test. TMD: Temporomandibular disorders,

Table 4. Genotype and allele frequencies of VDR Bsm1 variant in TMD patients with and without bruxism

VDR Bsm1	Patients with bruxism n:135 (%)	Patients without bruxism n:86 (%)	p	OR (CI 95%)
Genotypes				
BB	35 (25.9)	25 (29.1)		
Bb	67 (49.6)	38 (44.2)		
bb	33 (24.4)	23 (26.7)	0.730	
BB : Bb+bb	35 (25.9) : 100 (74.0)	25 (29.1) : 61 (70.9)	0.608	1.17 (0.63-2.14)
BB+Bb : bb	102 (75.5) : 33 (24.4)	63 (73.3) : 23 (26.7)	0.702	0.89 (0.48-1.66)
Alleles				
B	137 (50.7)	88 (51.2)	0.931	1.02 (0.69-1.49)
b	133 (49.3)	84 (48.8)		

Data were analyzed by χ2 test. TMD: Temporomandibular disorders.

Table 5. Clinical and demographical characteristics of TMD patients with bruxism stratified according to VDR Bsm1 variant

	***VDR* Bsm1 genotypes**				
Characteristics	**Total n:135**	**BB n:35**	**Bb n:67**	**bb n:33**	**p**
Age, mean ± SD (years)	30.99±11.546	33.63±13.408	30.16±10.773	29.85±10.840	0.290
Gender					
Male	24 (17.8)	4 (11.4)	13 (19.4)	7 (21.2)	0.508
Female	111 (82.2)	31 (88.6)	54 (80.6)	26 (78.8)	
Duration of disease					
< 1 year	63 (46.7)	16 (45.7)	35 (52.2)	12 (36.4)	0.670
1-5 years	39 (28.9)	10 (28.6)	18 (26.9)	11 (33.3)	
> 5 years	33 (24.4)	9 (25.7)	14 (20.9)	10 (30.3)	
Family history of TMD					
Yes	80 (59.3)	17 (48.6)	46 (68.7)	17 (51.5)	0.085
No	55 (40.7)	18 (51.4)	21 (31.3)	16 (48.5)	
Chewing disorders					
Yes	65(48.1)	12 (34.3)	35 (52.2)	18 (54.5)	0.158
No	70 (51.9)	23 (65.7)	32 (47.8)	15 (45.5)	
Sound in TMJ					
Yes	112(83.0)	29 (82.9)	57 (85.1)	26 (78.8)	0.734
No	23 (17.0)	6 (17.1)	10 (14.9)	7 (21.2)	
TMJ locking (open or closed)					
Yes	31 (23.0)	8 (22.9)	17 (25.4)	6 (18.2)	0.724
No	104 (77.0)	27 (77.1)	50 (74.6)	27 (81.8)	

Data were analyzed by analysis of variance and χ2 test. Mean plus standard deviation values are presented for age. SD: standard deviation TMD: Temporomandibular disorders, TMJ: Temporomandibular joint.

Then, we examined the genotype and allele distributions of the VDR Bsm1 variant in TMD patients with bruxism (Table 3). There were 135 patients with bruxism. The prevalence of genotypes of BB, Bb, and bb profiles for the VDR variant was 25.9%, 49.6%, and 24.4%, respectively, in patients with bruxism and 31%, 52%, and 17%, respectively, in the healthy control group. B and b allele frequencies were 50.7% and 49.3% in the patient group with bruxism and 57% and 43% in the control group, respectively. No significant differences were observed between patients with bruxism and healthy controls for the VDR Bsm1 variant genotype and allele frequencies (p>0.05).

Furthermore, we also analyzed if any differences existed in the TMD patients with and without bruxism according to genotype distribution (Table 4). There was no significant difference between patients with and without bruxism according to VDR Bsm1 variant genotypes and allele distributions (p>0.05).

The clinical and demographical characteristics of patients with bruxism were analyzed and stratified according to the VDR Bsm1 variant (Table 5). The genotype distribution of the VDR Bsm1 variant was not different for these features, including age, gender, duration of disease, family history, chewing disorders, sound in the TMJ, and TMJ locking.

We also investigated the relationship between pain characteristics and genotype distribution in 125 patients with bruxism. (Table 6). The pain rating scale was evaluated between 1 and 10. The severity of pain, pain during chewing and speaking, localization of pain, and period of pain were not different in patients with bruxism stratified according to the VDR Bsm1 variant.

Table 6. Clinical characteristics of pain of TMD patients with bruxism stratified according to VDR Bsm1 variant

	VDR Bsm1 genotypes				
Characteristics	**Total n:125**	**BB n:34**	**Bb n:60**	**bb n:31**	**p**
The severity of pain [The Numeric Pain Rating Scale (1-10)], mean ± SD	4.64±2.367	4.32±2.279	5.00±2.343	4.29±2.479	0.265
Pain during chewing and speaking, n (%)					
Yes	86 (68.8)	22 (64.7)	43 (71.7)	21 (67.7)	0.774
No	39 (31.2)	12 (35.3)	17 (28.3)	10 (32.3)	
The localization of pain, n (%)					
Muscle	17 (13.6)	7 (20.6)	9 (15.0)	1 (3.2)	
Joint	44 (35.2)	15 (44.1)	17 (28.3)	12 (38.7)	0.101
Muscle and joint	64 (51.2)	12 (35.3)	34 (56.7)	18 (58.1)	
Period of pain, n (%)					
Chronic	36 (28.8)	7 (20.6)	19 (31.7)	10 (32.3)	
At regular intervals	89 (71.2)	27 (79.4)	41 (68.3)	21 (67.7)	0.463

Data were analyzed by analysis of variance and χ2 test. Mean plus standard deviation values are presented for the severity of pain.
SD: standard deviation, TMD: Temporomandibular disorders

DISCUSSION

Bruxism is a common problem, and it is believed that 85%-90% of the population grinds or clenches their teeth to some extent at some point in their lifetimes.[15] Although several etiologic factors, like stress and occlusal abnormalities, have been proposed, the precise pathophysiology of bruxism is still unknown.[16] There is uncertainty over whether bruxism could be a significant etiologic factor in joint overload, muscle injury, or both. But bruxism has been recognized as a risk factor for TMD as well as masticatory muscle problems.[17] Also, in TMD, degenerative bone changes are found in the bony structures of the TMJ.[18] The exact etiology of TMD is still unknown. According to the results supported by the twin study, it has been reported that genetic variations play a role in the development of TMD in 44% of cases.

VD is important for musculoskeletal disorders. VD deficiency can lead to bone loss, hypocalcemia, and poor muscle strength. A study comparing TMD patients with VD deficiency and TMD patients with average VD levels showed that low serum VD levels have a negative effect on various activities and are associated with TMJ pain.[20] In the study of Alkhatatbeh *et al*., sleep bruxism was associated with VD deficiency and insufficient calcium consumption.[21] In the same study, the control group's 25-hydroxyvitamin D values were considerably higher than those of the sleep bruxism group, whereas both anxiety and depression ratings were higher.[21]

VD in active form exerts its biological effect after binding to VDR. Although regulating bone mineral homeostasis is the primary role of VD, it also inhibits interleukin (IL)-2, contributes to antibody synthesis, promotes lymphocyte proliferation, modulates immunity, and affects cellular differentiation and replication in a variety of target tissues. For these reasons, VD is thought to be a regulator of the immune system.[22] The relationship between VD's influence on immunity and its role in immunological tolerance is demonstrated by the fact that some immune system cells express VDR. Numerous studies have documented the role of VDR in the development of rheumatoid arthritis (RA). In areas of cartilage degradation in RA patients as well as in the rheumatoid synovium, VDR expression has been discovered in macrophages, chondrocytes, and synovial cells.[23] Additionally, in a mouse model of collagen-induced arthritis, VDR agonists were able to control the degree of illness and joint damage[24] and could also lessen the invasive properties of synoviocytes that resembled fibroblasts.[25]

The VDR gene has 11 exons, occupies about 75 kb of genomic DNA, and is located on chromosome 12 q13.11.8 Morrison *et al*. showed for the first time that changes in bone density in healthy individuals are influenced by allelic polymorphisms in VDR-expressing genes.[26] According to Mohammadi *et al*., postmenopausal women who have the VDR Fok1 variant are significantly more likely to have osteoporosis.[27] Additionally, it has been noted that pre- and postmenopausal women with the VDR Fok1 ff genotype have significantly less lumbar spine bone mass than do women with the Ff and FF genotypes. Yılmaz showed that the VDR FokI variant was associated with TMD.[28] But another Turkish study found the VDR Apa1 and Taq1 variants were not linked to TMJ dysfunction or osteoarthritis.[29]

In this study, we evaluated the role of the VDR Bsm1 variant in bruxism in TMD.

Genotype and allele frequencies did not show any significant differences between all TMD patients and the controls, according to the VDR Bsm1 variant. Then we divided the TMD group into two groups, with and without bruxism. There were no statistically significant differences in the genotype and allele frequencies of the VDR Bsm1variant between patients with bruxism and healthy controls ($p>0.05$). In a stratified analysis, TMD patients with and without bruxism had similar distributions of the VDR BsmI genotype and allele distribution. Pain characteristics in patients with bruxism were also not related to the VDR BsmI genotype distribution.

This analysis has several limitations. The first limitation is that only one variant of the VDR was investigated. Other variants of this gene may also contribute to the development of bruxism. The final limitation of this study was the lack of an assessment of VD level.

CONCLUSION

In summary, we conducted the study to investigate the association between the VDR BsmI variant and bruxism in TMD. To the best of our knowledge, this is the first such study in our population. Our results demonstrated no association between the VDR BsmI variant and bruxism in TMD. However, we studied only the ethnically homogenous Turkish population. We believe that a further multi-center study containing a larger number of subjects and the contributions of previous studies may be necessary to evaluate the association between the VDR BsmI variant and predisposition to bruxism more incisively.

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