Biomedical Research 2017; 28 (20): 8795-8800 *ISSN 0970-938X*
www.biomedres.info

Impact of glucocorticoid receptor gene *Bcl-1* variant on temporomandibular disorders.

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Abstract

Objectives: Temporomandibular Disorders (TMD) constitute a heterogeneous group of disorders characterized by alterations in mandibular movement. The aim of this study was to investigate the association between the *Bcl1* variant of *NR3C1* gene and TMD susceptibility in Turkish population.
Method: *NR3C1* gene BcI1 variant of 100 TMD patients and 105 healthy controls was genotyped by polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP).
Results: There was also no significant difference in regard to genotype and allele frequencies between the patients and the controls (OR 0.216 (95% Cl: 0.85-2.04); p=0.216). However, present study found that numeric pain rating scale was higher in patients with CC and CG genotypes.
Discussion: Although the *NR3C1 Bcl1* variant did not show any difference between the TMD and the control groups, we thought that this variant could be correlated with pain intensity in patients. Further studies with different ethnic subjects are needed to confirm the results.

Keywords: Temporomandibular disorders, Glucocorticoid receptor gene, *Bcl1* variant.

Accepted on September 27, 2017

Introduction

Temporomandibular disorders (TMD) are a kind of disease group that manifest itself as musculoskeletal and neuromuscular conditions [1]. It is characterized by recurrent or chronic pain in the temporomandibular region, disc displacement with clicking and crepitus noises produced during mandibular movement. The clear etiology of TMD has not been established yet. It is believed that genetic risk factors can play a role in the etiology of TMD, as suggested by a twin study that ascribed 44% of TMD to genetic inheritance of variations [2]. In epidemiologic studies, it has been shown that women have a higher risk for TMD [3].

Glucocorticoids (GCs) play a crucial role in the regulation of several processes in the human body. They display their influences by binding to the glucocorticoid receptor [4]. The human glucocorticoid receptor gene (NR3C1) is localized on chromosome 5q31-32, includes 9 exons and it regulates the coding of the NR3C1 protein, which binds glucocorticoid hormones in the liver, muscle, and vasculature, affecting the metabolism and the cardiovascular function [5]. GCs may lower inflammatory gene expression by interfering with the inflammatory transcription factors and by facilitating the transcription of genes with anti-inflammatory activity. Inflammatory proteins cause an increase in bone turnover by inducing osteoclastic activity. The amount of Glucocorticoid receptors, which could be affected by the polymorphisms on *NR3C1* gene, will determine the amount of free GCs and consequently the amount of inflammatory proteins [6]. The increase in inflammatory proteins may lead to TMD as well as to other joint disorders. On the other hand, TMD is also thought to be one of the physical results of stress. Stress is one of the causes of elevated free cortisol levels. Cortisol, the basic glucocorticoid in circulating, shows its effect by binding especially the glucocotiocid receptors in the hippocampus [7].

The *NR3C1* gene has several polymorphic sites. The *Bcl1* variant (rs41423247) of the *NR3C1* gene, a C to G substitution located in intron 2, is correlated with the enhanced glucocorticoid sensitivity and higher cortisol levels [8].

The aim of this present study was to investigate the association between *Bcl1* variant of *NR3C1* gene and TMD susceptibility in a Turkish population.

Methods

Study population

One hundred patients with TMD (77 females and 23 males; aged 18-71) were included in the study. Patients were recruited from the Department of Oral and Maxillofacial Surgery during the eight months period between July 2015 to March 2016. The diagnosis of TMD was based on the criteria described by Schiffman et al. (Table 1) [9]. A detailed medical history was taken, followed by a complete oral examination. Additionally, a control group consisting of 105 unrelated healthy subjects (69 females and 36 males; aged between 19 and 69) with similar ethnic background and residing in the same geographic area with the patients was formed. Subjects with no evidence of chronic disease were included in the control group. Informed written consent was obtained from each subject according to the Declaration of Helsinki, and design of the work (15-KAEK-124) was approved by the Local Ethical Committee.

Table 1. *The diagnosis of TMD patients according to criteria described by Schiffman et al. [8].*

Criteria	TMD patients
	n=100 (%)
Temporomandibular joint (TMJ) disorders	42 (42.0)
Masticatory muscle disorders	2 (2.0)
TMJ disorders+Masticatory muscle disorders	5 (5.0)
TMJ disorders+Headache	38 (38.0)
Masticatory muscle disorders+Headache	3 (3.0)
TMJ disorders+Masticatory muscle disorders+Headache	10 (10.0)

Molecular analysis

Blood samples were collected in Ethylene Diamine Tetra-Acetic acid (EDTA)-coated tubes from the patients with TMD and control subjects, and stored at -20°C until use. Genomic DNA was extracted using commercial kit (Sigma–Aldrich, Taufkirchen, Germany) according to manufacturer protocol. The BclI variant in the intron 2 of *NR3C1* gene was evaluated using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. PCR reaction was performed as described previously [10]. PCR products were cut with Ksp 221 restriction enzyme (Sigma-Aldrich, Taufkirchen, Germany). Then, the digestion products were separated on 3% agarose gels stained with ethidium bromide and photographed with a standard ultraviolet transilluminator. Wild-type (CC) individuals had 2 fragments of 90 and 116 bp. Individuals with the GG genotype had an uncut fragment of 206 bp. The heterozygotes (GC) had fragments of 90, 116, and 206 bp.

Table 2. *The demographical characteristics of TMD patients and healthy controls.*

Demographical characteristics	TMD patients	Healthy controls	p
	n=100	n=105	
Age, mean ± SD (y)	34.92 ± 13.343	36.76 ± 11.255	0.286
Gender, n (%)			0.09
Male	23 (23.0)	36 (34.3)	
Female	77 (77.0)	69 (65.7)	

Data were analyzed by analysis of variance and χ^2 test. TMD: Temporomandibular Disorders; SD: Standard Deviation.

Statistical analysis

All statistical analyses were performed using IBM SPSS 20.0 and OpenEpi 2.3.1 software. Continuous data were presented as mean ± SD (standard deviation). Chi square test was used to detect the significance of differences in the allele frequencies and genotype distributions between the two study groups. The association between *Bcl1* variant and the clinical and demographic characteristics of patients and clinical characteristics of pain of TMD patients were analyzed by using χ^2 test or analysis of variance (ANOVA) statistics. Hardy-Weinberg equilibrium test was performed for both study groups. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated. A p value of <0.05 was considered statistically significant.

Table 3. *Genotype and allele frequencies of NR3C1 Bcl1 variant in patient and control groups.*

Polymorphism	Patients n=100 (%)	Controls n=105 (%)	p	OR (CI 95%)
Genotypes				
CC	57 (57.0)	52 (49.5)	0.482	
CG	36 (36.0)	42 (40.0)		
GG	7 (7.0)	11 (10.5)		
CC:CG+GG	57 (57.0):43 (43.0)	52 (49.5):53 (50.5)	0.285	1.35 (0.78-2.35)
CC+CG:GG	93 (93.0):7 (7.0)	94 (89.5):11 (10.5)	0.379	1.55 (0.57-4.42)
Alleles				
C	150 (75.0)	146 (69.5)	0.216	1.31 (0.85-2.04)
G	50 (25.0)	64 (30.5)		

Data were analyzed by χ^2 test.

Results

Two hundred and five Turkish individuals (105 controls and 100 patients) participated in the study. There were 69 female and 36 male participants in the control group, and the patient group consisted of 77 females and 23 males. The females constituted the majority of cases in both patient and control groups. The mean age was 34.92 ± 13.343 and 36.76 ± 11.255 in the patient and in the control group, respectively. The demographic features of the study subjects are shown in Table 2.

Table 4. *Clinical and demographical characteristics of TMD patients stratified according to NR3C1 Bcl1 variant.*

		NR3C1 Bcl1 variant			
Characteristics	**Total n=100**	**CC n=57**	**CG n=36**	**GG n=7**	**P value**
Age, mean ± SD (y)	34.92 ± 13.343	33.88 ± 12.490	36.67 ± 13.879	34.43 ± 18.137	0.619
Gender, n (%)					
Male	23 (23.0)	15 (26.3)	7 (19.4)	1 (14.3)	0.634
Female	77 (77.0)	42 (73.7)	29 (80.6)	6 (85.7)	
Duration of disease, n (%)					
<1 y	27 (27.0)	18 (31.6)	6 (16.7)	3 (42.9)	0.374
1-5 y	36 (36.0)	21 (36.8)	13 (36.1)	2 (28.6)	
>5 y	37 (37.0)	18 (31.6)	17 (47.2)	2 (28.6)	
Family history of TMD, n (%)					
Yes	49 (49.0)	24 (42.1)	22 (61.1)	3 (42.9)	0.192
No	51 (51.0)	33 (57.9)	14 (38.9)	4 (57.1)	
History of systemic disease, n (%)					
Yes	63 (63.0)	40 (70.2)	18 (50.0)	5 (71.4)	0.13
No	37 (37.0)	17 (29.8)	18 (50.0)	2 (28.6)	
Bruxism, n (%)					
Yes	55 (55.0)	31 (54.4)	21 (58.3)	3 (42.9)	0.746
No	45 (45.0)	26 (45.6)	15 (41.7)	4 (57.1)	
Eating disorders, n (%)					
Yes	33 (33.0)	15 (26.3)	16 (44.4)	2 (28.6)	0.188
No	67 (67.0)	42 (73.7)	20 (55.6)	5 (71.4)	
Sound in TMJ (jaw joint clicking or popping), n (%)					
Yes	73 (73.0)	42 (73.7)	25 (69.4)	6 (85.7)	0.664
No	27 (27.0)	15 (26.3)	11 (30.6)	1 (14.3)	
TMJ locking (open or closed), n (%)					
Yes	8 (8.0)	5 (8.8)	2 (5.6)	1 (14.3)	0.7
No	92 (92.0)	52 (91.2)	34 (94.4)	6 (85.7)	

Data were analyzed by analysis of variance and χ^2 test. Mean plus standard deviation values are presented for age. TMD: Temporomandibular Disorders; TMJ: Temporomandibular Joint; SD: Standard Deviation.

Genotypic and allelic distributions of the *NR3C1 Bcl1* variant in patient and control groups are presented in Table 3. The CC, CG, GG genotypes of the NR3C1 *Bcl1* variant were observed in 49.5%, 40.0%, and 10.5% of control subjects and in 57%, 36% and 7.0% of patients, respectively. Genotype distribution did not show any significant difference between patients and controls according to NR3C1 *Bcl1* variant (p>0.05). The frequency of *Bcl1* C allele was 75% (n=150) and that of G allele was 25% (n=50) in the patient group. There were not any significant differences of allele frequencies between patients and controls (OR 0.216 (95% Cl: 0.85-2.04); p=0.216).

Table 5. *Clinical characteristics of pain of TMD patients stratified according to NR3C1 Bcl1 variant.*

		NR3C1 Bcl1 variant			
Characteristics	**Total n=89**	**CC n=48**	**CG n=34**	**GG n=7**	**P value**
The severity of pain (The numeric pain rating scale (1-10)), mean ± SD	3.89 ± 1.957	3.77 ± 1.753	4.35 ± 2.116	2.43 ± 1.902	0.048
Pain during sleep, n (%)					
Yes	49 (55.1)	27 (56.3)	20 (58.8)	2 (28.6)	0.332
No	40 (44.9)	21 (43.7)	14 (41.2)	5 (71.4)	
Pain during chewing and speaking, n (%)					
Yes	55 (61.8)	31 (64.6)	22 (64.7)	2 (28.6)	0.169
No	34 (38.2)	17 (35.4)	12 (35.3)	5 (71.4)	
The localization of pain, n (%)					
Muscle	9 (10.1)	5 (10.4)	4 (11.8)	0	0.866

Joint	69 (77.5)	38 (79.2)	25 (73.5)	6 (85.7)	
Muscle and joint	11 (12.4)	5 (10.4)	5 (14.7)	1 (14.3)	
Period of pain, n (%)					
Chronic	27 (30.3)	10 (20.8)	15 (44.1)	2 (28.6)	0.077
At regular intervals	62 (69.7)	38 (79.2)	19 (55.9)	5 (71.4)	
Factors that trigger pain					
Movement	53 (59.6)	26 (54.2)	21 (61.8)	6 (85.7)	0.48
Cold	17 (19.1)	11 (22.9)	5 (14.7)	1 (14.3)	
Movement and cold	19 (31.3)	11 (22.9)	8 (23.5)	0	
Types of pain					
Blunt	43 (48.3)	23 (47.9)	16 (47.1)	4 (57.1)	0.859
Sharp	43 (48.3)	24 (50.0)	16 (47.1)	3 (42.9)	
Pulse type	3 (3.4)	1 (2.1)	2 (5.9)	0	
The duration of pain					
<1 h	39 (43.8)	21 (43.8)	14 (41.2)	4 (57.1)	0.935
≥ 1 h	39 (43.8)	21 (43.8)	16 (47.1)	2 (28.6)	
Constant	11 (12.4)	6 (12.5)	4 (11.8)	1 (14.3)	

Data were analyzed by analysis of variance and χ^2 test. Mean plus standard deviation values are presented for the severity of pain. TMD: Temporomandibular Disorders; SD: Standard Deviation. The results that are statistically significant are shown in boldface.

Furthermore, this present study also analyzed if any differences existed in clinical and demographic characteristics of patients according to genotype distribution. The clinical and demographic characteristics according to genotype distribution are presented in Table 4. There was not any significant difference between genotype and age, gender, disease duration, or clinical parameters such as bruxism, jaw joint clicking or popping, joint locking and sounds related to these findings ($p>0.05$).

Clinical characteristics of pain of TMD patients were stratified according to *NR3C1 Bcl1* variant are shown in Table 5. Pain intensity in patients was measured using the numeric pain rating scale (NPRS) (1-10). A "numeric pain" score ranging from 0 (no pain) to 10 (maximum pain) was constructed. Eleven patients who had rare pain were not evaluated. In terms of correlation between genotype distribution of the *NR3C1 Bcl1* variant and clinical parameters such as pain during sleep, chewing or speaking, pain localization, pain period, factors that trigger pain, pain type and pain duration, present study didn't find any statistical significance among the groups as well. However, we noted a significant association of *NR3C1 Bcl1* variant with numeric pain rating scale ($p=0.048$). The numeric pain rating score was higher in patients with CC and CG genotype.

Discussion

GCs are an essential class of endogenous steroid hormones that modulate vital biological processes such as growth, development, metabolism, behavior and apoptosis [11]. They have been considered to hinder activation of the hypothalamic-pituitary-adrenocortical (HPA) axis through a delayed feedback system that is regulated by GC levels and that involves genomic changes. The glucocorticoid receptor, a 94kD cytosolic protein, mediates the physiological effects of GCs. NR3C1, also known as glucocorticoid receptor gene, has been widely studied in various inflammatory and autoimmune diseases such as Graves opthalmopathy, asthma, cystic fibrosis, and inflammatory bowel disease [12-15]. There are several variants in the *NR3C1* gene. *NR3C1 Bcl1* variant has been associated with hypersensitivity to GCs and regulation of the HPA axis activity [8]. The *Bcl1* variant acts as part of a conserved haplotype and has frequently been associated with mood and mental diseases [16]. Numerous studies suggested associations of this haplotype with alterations in metabolism including hyperinsulinemia, increased abdominal fat, higher mass index (BMI), raised leptin levels, and larger increases in body weight after experimentally induced overfeeding, in C genotype carriers [17]. Watt et al. noticed that the higher allele of *Bcl1* variant is more frequent in individuals genetically predisposed to develop hypertension [18].

The temporomandibular joint, which is one of the most complicated joints in human body, plays an important role in functions such as jaw motion, speaking, chewing, and swallowing. TMD is a common term covering a number of clinical conditions that involve the masticatory masculature, the temporomandibular joint, and the related structures. Even though clear etiology of TMD has not been established, there is

a common belief for a bio-psychosocial and multifactorial background, indicating the complex interaction between biological mechanism, mental conditions and psychological traits, environmental factors, and macro-microtrauma [19].

TMD can lead to pain and functional impairment, impede quality of life and frequently result in depressive symptoms [20]. Recent studies suggest that shifted basal and stress-induced HPA activity can be associated with painful idiopathic conditions like fibromyalgia and irritable bowel syndrome [21,22]. These clinical conditions may be also associated with inter-individual variations in HPA axis activity and modified glucocorticoid impacts. TMD is often seen together with other psychosomatic symptoms such as sleep disorders, headache, fatigue, and depression, all of which belong to somatic syndromes [23]. It was also reported that the NR3C1 major allele exists in higher frequency in patients with chronic fatigue syndrome [24]. Rossum et al. reported that the *NR3C1 Bcl1* variant is associated with major depression [25].

No association was found between adult/juvenile rheumatoid arthritis (RA) and the *NR3C1 Bcl1* variant in studies conducted on the basis of thought that inappropriately low endogenous cortisol production and impaired HPA axis response involved in pathogenesis of RA [10,26,27]. Holliday et al. investigated whether genetic variations that play a role in HPA axis affect the predisposition to musculoskeletal pain, however, they did not find any correlation between the NR3C1 variants and musculoskeletal pain [28]. The *NR3C1* gene was one of the genes that was evaluated in OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) trial, in which 358 genes were investigated to illuminate the basis of TMD in recent years [29].

In present study, *Bcl1* variant of *NR3C1* was genotyped in a group of patients with TMD to analyze the correlation between the genotypes and the clinico-pathologic features of the patients. The current data suggested that this variant do not affect the development and clinical course of TMD in Turkish population (Table 3). However, this present study found that numeric pain scale was significantly higher in patients with *NR3C1 Bcl1* CC and CG genotype (Table 5).

Although current data did not support that the *Bcl1* variant of the *NR3C1* gene is associated with TMD susceptibility, these findings serve to advise that the *Bcl1* variant of the *NR3C1* gene may affect pain intensity in TMD patients. However, further studies with a larger sample size are needed to verify these findings.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Ethical Approval

This work (15-KAEK-124) was approved by the Local Ethical Committee.

Acknowledgment

None

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