Evaluation of brain-derived neurotrophic factor and cortisol levels in patients with bruxism

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Abstract

Aim: The purpose of this study was to evaluate brain-derived neurotrophic factor (BDNF) and cortisol levels in patients with bruxism. Relationships between clinical variables (myofacial pain, dental anxiety and masticatory function) and BDNF and cortisol levels were also investigated.

Materials and Methods: In this prospective study, patients were divided into 4 groups according to the severity of bruxism; group I (no bruxism, control group), group II (mild bruxism), group III (moderate bruxism), group IV (severe bruxism). Cortisol and BDNF levels were evaluated from venous blood samples of patients. Myofacial pain was evaluated with the Visual Analogue Scale (VAS), dental anxiety was evaluated with the Modified Dental Anxiety Scale (MDAS), and masticatory function limitation was evaluated with the Jaw Functional Limitation Scale (JFLS).

Results: The study conducted with 75 patients (15 in group I, 20 in group II, 20 in group III, and 20 in group IV) aged 18-64 years. BDNF and cortisol levels increased as the severity of bruxism increased. The cortisol level of group III was significantly higher than that of group I (p=0.008). BDNF and cortisol levels in group IV were significantly higher than group I (p=0.043, p=0.006). VAS, JFLS and MDAS values increased as the severity of bruxism increased. VAS pain scores correlated significantly with BDNF and cortisol levels (r=0.220, p=0.038; r=0.286, p=0.013). MDAS and JFLS values were significantly correlated with cortisol levels (r=0.279, p=0.015; r=0.271, p=0.19).

Conclusion: Plasma BDNF and cortisol levels can contribute to the assessment of bruxism severity and its clinical findings such as myofacial pain, masticatory efficiency and dental anxiety.

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Introduction

Bruxism is a repetitive muscle-jaw activity described as grinding or clenching of the teeth that may appear during the day or during sleep [1]. The average age of onset of bruxism in the population ranges from 17 to 20, and it affects adults, children and both sexes [2]. According to some authors, bruxism is present in 5-8% of adults, with higher rates reported in the literature [3]. Bruxism can lead to problems such as loss of periodontal supporting tissues, mobility, abrasions, and fractures in the teeth. It can also cause pain and noises in masticatory muscles and temporomandibular joint (TMJ) region and headache [4]. Although the etiopathogenesis of bruxism is not fully understood, it is an accepted idea that bruxism develops as a response to anxiety and stress. Psychological stress is considered a major factor that initiates or predetermines bruxism activity during sleep and wakefulness [5]. Hicks and Chancellor [6] stated that there was a relationship between bruxism and stressful lifestyle. Kappe et al. [7] reported that stress and anxiety were the cause of bruxism behaviors and exacerbate their findings. It is also stated that various neurotransmitters (e.g., serotonin, dopamine, norepinephrine) in the central nervous system (CNS) modulate bruxism activity [8]. It has been reported in the literature that bruxism is associated with some stress-related biomarkers such as cortisol and dopamine. Cortisol is commonly known as the "stress hormone," and some research have used alterations in cortisol levels as a determinant of depression, stress and anxiety [9, 10].

Brain-derived neurotrophic factor (BDNF) is a small dimeric neuroprotective protein that belongs to the family...
After the clinical examinations and 20 minutes of rest, myofascial pain, dental anxiety, and masticatory function were chosen as secondary outcome variables including myofascial pain, dental anxiety, and emotional expressions (10 questions). Each question consists of five answers, ranging from 1 'not anxious' to 5 'extremely anxious', resulting in a total score of 5-25 [13]. The Jaw Functional Limitation Scale (JFLS) was used to evaluate the masticatory system limitations that may occur due to bruxism in individuals. The JFLS consists of 20 questions that assess three levels of functional limitation, including vertical jaw mobility (4 questions), mastication (6 questions), verbal and emotional expressions (10 questions). Each question is answered on a numerical rating scale from 0 to 10, with 0 indicating no limitation; 10 indicates serious limitation [14]. Dental anxiety, pain level and JFLS scores were evaluated comparatively between patient groups, and the correlation between these values and cortisol and BDNF levels was investigated.

Materials and Methods

This study was implemented in the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Karadeniz Technical University, and comprised of patients who referred to our department with complaint of bruxism between 2020 and 2021. Patients who demonstrated any of the following criteria were removed from the research: 1) any systematic muscle or joint disease (eg, rheumatoid arthritis, fibromyalgia), 2) serious systemic disease, 3) any neurological disorder (eg, dystonia, trigeminal neuralgia,), 4) psychiatric treatment, 5) breastfeeding, 6) pregnancy, 7) neurological disorder (eg, dystonia, trigeminal neuralgia,), 8) previously treated for bruxism or myofascial pain. This study carried out with the permission of Scientific Research Ethics Committee, Faculty of Medicine, Karadeniz Technical University (2019/196) and implemented in accordance with the ethical guidelines of the Helsinki Declaration. Detailed written informed consent form was provided from all patients before entering the research. Sample size calculation was provided by using G*Power 3.1.9.2 (The G*Power Team, Düsseldorf, Germany). The alpha error=0.05, beta error=0.10 and the effect size was selected as 1 according to the study of Karakoulaki et al. [5]. Considering the potential losses, final sample size was provided as 20 for each bruxism group.

Patients were separated into four groups according to the severity of bruxism: group I, control group; group II, mild bruxism; group III, moderate bruxism; group IV, severe bruxism. The severity of the bruxism was the primary predictor variable. Bruxism level was evaluated with a bruxism scale available in the literature [12]. This scale includes 15 questions. The total score for each patient was obtained according to the answers given by the patients. The severity of bruxism was categorized as mild (score, 3-5 points), moderate (6-10 points), or severe (11 points or higher). The control group consists of individuals who do not have bruxism. Assessment of the BDNF and cortisol levels from blood samples was chosen as the primary outcome variable. Clinical parameters including myofascial pain, dental anxiety and masticatory function were chosen as secondary outcome variables from the patients’ records. After the clinical examinations and 20 minutes of rest, 1.5 ml of venous blood samples were taken from the patients between 9:00 and 11:00 am into tubes without anticoagulant. It was waited for 15 minutes for coagulation and centrifuged at 3000 rpm for 10 minutes. The samples were transferred to eppendorf tubes and stored at -80 °C until further analysis. ELISA human BDNF kit (Boster, California, USA) and ELISA human Cortisol kit (DRG, Marburg, Germany) were used to measure plasma BDNF and cortisol levels in accordance with the manufacturer’s directions. BDNF and cortisol levels of the patient groups were compared.

The myofacial pain levels of the patients were measured on a 10 cm line visual analog scale (VAS), with 10 indicating the worst pain ever and 0 indicating absence of pain. Dental anxieties of the patients were evaluated with the Modified Dental Anxiety Scale (MDAS). It contains five questions. Each question consists of five answers, ranging from 1 'not anxious' to 5 'extremely anxious', resulting in a total score of 5-25 [13]. The Jaw Functional Limitation Scale (JFLS) was used to evaluate the masticatory system limitations that may occur due to bruxism in individuals. The JFLS consists of 20 questions that assess three levels of functional limitation, including vertical jaw mobility (4 questions), mastication (6 questions), verbal and emotional expressions (10 questions). Each question is answered on a numerical rating scale from 0 to 10, with 0 indicating no limitation; 10 indicates serious limitation [14]. Dental anxiety, pain level and JFLS scores were evaluated comparatively between patient groups, and the correlation between these values and cortisol and BDNF levels was investigated.

Statistical analysis

SPSS software for Windows 17.0 was used for the data analysis (SPSS Inc, Chicago, IL, USA). The normality of distribution was determined with Shapiro-Wilk and Kolmogorov Smirnov test. The Kruskal-Wallis and Mann-Whitney U-tests with Bonferroni correction (if needed) were used for intergroup comparisons, Spearman correlation test was used in correlation analysis. For all comparisons, statistical significance was set as p < 0.05.

Results

A total of 75 patients (51 females, 24 males) were enrolled in the study. The study sample consisted of 15 patients in group I (control group), 20 patients in group II (mild bruxism), 20 patients in group III (moderate severe bruxism), and 20 patients in group IV (severe bruxism). The mean age of the individuals participating in the study was 31.19 (18 to 64). Descriptive statistics of the groups are given in Table 1. There was no significant difference between groups with respect to mean age and gender distribution (p > 0.05). The results of comparisons between the primary predictor variables and the primary outcome variables are presented in Table 2. It was observed that BDNF and cortisol levels increased as the severity of bruxism increased. BDNF and cortisol levels were higher in Group II compared to Group I, but this difference was not statistically significant (p=0.805, p=0.314). There was statistically significant difference in cortisol levels between Group III and Group I (p=0.008), but there was no statistically significant difference in BDNF levels (p=0.657). BDNF and cortisol levels in Group IV were significantly higher than Group I (p=0.043, p=0.006).
Table 1. Descriptive statistics.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=15)</th>
<th>Group II (n=20)</th>
<th>Group III (n=20)</th>
<th>Group IV (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>29±6.54</td>
<td>30.45±7.07</td>
<td>30.75±10.05</td>
<td>34±8.9</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>8 (53.3)</td>
<td>11 (55.0)</td>
<td>15 (75.0)</td>
<td>16 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7 (46.7)</td>
<td>9 (45.0)</td>
<td>5 (25.0)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are listed as mean ± standard deviation or number (percentage); n, number; SD, standard deviation.

Table 2. Comparisons between primary predictor variables and primary outcome variables.

<table>
<thead>
<tr>
<th></th>
<th>BDNF</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>2570.96±1548.05</td>
<td>57.76±57.52</td>
</tr>
<tr>
<td>Group II</td>
<td>2041.51±663.62</td>
<td>23.92±15.6</td>
</tr>
<tr>
<td>Group III</td>
<td>2723.08±1906.79</td>
<td>83.5±95.44</td>
</tr>
<tr>
<td>Group IV</td>
<td>2605.42±2554.61</td>
<td>140.77±159.02</td>
</tr>
</tbody>
</table>

Table 3. Comparisons between primary predictor variables and secondary outcome variables.

<table>
<thead>
<tr>
<th></th>
<th>BDNF</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.06±0.25</td>
<td>0.8±1.2</td>
</tr>
<tr>
<td>Group II</td>
<td>1.55±2.18</td>
<td>13.4±15.44</td>
</tr>
<tr>
<td>Group III</td>
<td>4.55±1.76</td>
<td>30.6±17.29</td>
</tr>
<tr>
<td>Group IV</td>
<td>7.6±1.69</td>
<td>39.6±34.88</td>
</tr>
</tbody>
</table>

Table 4. Correlations between clinical variables and BDNF and cortisol levels.

<table>
<thead>
<tr>
<th></th>
<th>BDNF</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JFLS</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>MDAS</td>
<td>r</td>
<td>p</td>
</tr>
</tbody>
</table>

Discussion

Bruxism is a worrying activity because of its devastating consequences such as destruction of teeth and supporting tissues, fracture of restorations, emergence of TMJ and myofascial pains, and induction of temporal tension-type headaches [15]. The formation and pathogenesis of bruxism is thought to be multifactorial, but its etiology is not yet fully understood. Primary etiological factors are occlusal interferences, central or pathophysiological causes involving basal ganglia or brain neurotransmitters, psychosocial effects such as stress or anxiety, genetic factors, and systemic diseases. Alcohol, tobacco, medication, other drugs and use of caffeine are considered as secondary factors [9]. Previous studies have reported that individuals under stress are more likely to exhibit bruxism. The development of bruxism is affected by several factors, such as the capacity of the stomatognathic system to adapt to changing conditions, duration and intensity of etiological factors and their co-occurrence, but chronic stress is the most prominent predisposing factor in the etiology of bruxism [9,16]. In this study, cortisol and BDNF levels, which are stress-related biomarkers, were evaluated in individuals with bruxism.
It has been reported that bruxism is 22% more common in women [17]. This is because of hormonal differences or because women are more likely to express their experiences of pain and seek treatment [18]. It is most common between the ages of 20 and 50 and tends to decrease with age [18]. Similar to the literature, the prevalence of female patients was higher in our study, and the prevalence of female patients increased as the severity of bruxism increased. The majority of patients were between the 2nd and 5th decades in our study, and mean age of the patients was consistent with the literature.

BDNF is the most abundant neurotropic in the CNS and closely related to neural transmission, neural cell survival, and maintenance. Especially in the hippocampus, BDNF secretion changes depending on exercise, stress and learning and plays a critical role in facilitating the formation of neural networks. BDNF is also found elsewhere, including in vascular endothelial cells, lymphocytes, and lacrimal glands [19]. Some studies have shown that the secretion of critical molecules included in the regulation of synaptic plasticity, such as BDNF, is decreased in response to stress [16]. However, it was reported that plasma BDNF level increased due to acute immobilization stress in rats and submandibular glands contributed to this [19]. It was determined in a study that the plasma BDNF level was increased in patients with TMJ disorders [20]. Aizawa et al. [21] showed that NTRK2 and BDNF gene polymorphisms modulate personal responses to stress. This result may be strongly associated with the formation of bruxism [16]. One study reported that polymorphism caused by mutation in the 196th base sequence of the BDNF gene is more common in individuals with bruxism than in the control group [16]. In another study, it was reported that chronic stress markedly elevated the plasma BDNF concentration in rats [19]. Increased plasma BDNF level may play critical roles in maintaining homeostasis under stress [19]. According to our results, as the severity of bruxism increased, the plasma BDNF level also increased. Because BDNF is able to cross the blood-brain barrier, it is possible that circulating BDNF contributes to the maintenance and function of neural cells. Therefore, the increase in plasma BDNF level could be an important neuroprotective reaction under chronic stress [19].

Cortisol is the main steroid hormone released from the zona fascicular layer of the adrenal cortex, belonging to the glucocorticoid hormone group. The hypothalamic-pituitary-adrenocortical axis is activated when humans are under stress, resulting in an increase in cortical secretion [9]. Cortisol secretion is in a daily rhythm and the highest concentration is recorded around 9am. It is also considered the “stress hormone” because its levels in the saliva and blood increase significantly in stressful situations [9].

Many studies in the literature have reported that bruxism activity is related to psychological stress and cortisol levels [9, 22]. Previous studies examining the relationship between stress and bruxism through stress-related biomarkers (α-amylase and cortisol) have reported that patients with bruxism show higher cortisol levels than normal individuals [22]. In our study, cortisol level in patients with bruxism were higher than in control group, and it was seen that cortisol levels increased as the severity of bruxism increased.

It is stated in the literature that bruxism is a significant risk factor for TMJ disorders and myofascial pains. Patients commonly complain about headache, neck pain, earache, and other facial pain [23]. Villarosa et al. [24] stated that bruxism leads to significant pain in the masseter muscle areas. Allen et al. [25] reported that bruxism is related to common symptoms of TMJ disorders [23]. In our study, it was observed that patients with bruxism had higher pain scores compared to the control group, and pain scores increased as the severity of bruxism increased. BDNF is one of the neuropeptides that play a critical role in the development of hyperalgesia and pain [20]. BDNF is involved in the pathophysiology of burning mouth syndrome, migraine pain and other headaches due to elevated plasma and saliva concentration during active pain periods [20]. It has been stated that the plasma BDNF level is increased in patients with TMJ disorders and myalgia [20]. In addition, one study reported that serum cortisol level was higher in patients with myofascial pain dysfunction compared to the control group [26]. Similarly, a significant correlation was determined between pain scores and BDNF and cortisol levels in this study.

Fear and anxiety about dental treatments is a major problem for many patients and can interfere with treatment, some patients avoid dentists because of their extreme fear [13]. It is not surprising that individuals with high dental anxiety often experience oral health problems [27]. MDAS is a reliable method for assessing dental anxiety and is a quick and effective tool for researchers. It is also useful in evaluating psychometric properties [13]. Montero et al. [28] reported in their study that patients with bruxism had higher MDAS scores. Winocur et al. [29] showed an important relationship between bruxism and dental anxiety in their study on 480 adult patients. It has been reported that the association between bruxism and dental anxiety may be an indirect manifestation of stress associated with the oral cavity [29]. Similarly, it was determined that MDAS scores increased as the severity of bruxism increased in this study. Alfayad et al. [10] reported that dental anxiety increases the serum cortisol level. According to our results, significant correlation was found between MDAS scores and plasma cortisol level, but no correlation was found with BDNF level.

The nonfunctional mandibular movements observed in bruxism produce an abnormal effect on the masticatory muscles and cause painful symptoms, hyperfunction, and decreased coordination when the force exceeds the adaptive capacity of the stomatognathic system [30]. The Jaw Functional Limitation Scale assesses limitations on jaw mobility, mastication, and verbal and emotional expressions [14]. It has been used in many studies in the literature to evaluate the limitations of masticatory muscles. In our study, we used JFLS to evaluate the limitations that may occur in the stomatognathic system due to bruxism. According to our results, JFLS scores increased as the severity of bruxism increased. It is thought that myofascial pains that increase with the severity of bruxism and TMJ-muscle pain that increases during jaw movements are reflected in JFLS scores. Accordingly, there was a significant correlation between JFLS scores and cortisol levels.
However, no correlation was found between JFLS scores and BDNF level. This can be explained by the fact that the relationship between BDNF level and masticatory system limitations is more complex.

The limitation of the study was that individual factors (patient age, gender, educational status, etc.) that may affect BDNF and cortisol levels were not taken into account. These individual factors could affect BDNF and cortisol levels, as well as VAS pain, MDAS and JFLS values.

Conclusion

According to the study results, plasma cortisol and BDNF levels increased as the severity of bruxism increased. A significant correlation was determined between BDNF levels and VAS pain values. It was determined that cortisol level was significantly correlated VAS pain, MDAS and JFLS values. These findings showed that plasma cortisol and BDNF levels could contribute to the evaluation of bruxism severity and its clinical findings such as myofacial pain, masticatory efficiency and dental anxiety.

Acknowledgment

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Ethics approval

This study was approved by the Karadeniz Technical University, Faculty of Medicine, Scientific Research Ethics Committee (2019/196) and conducted in accordance with the ethical principles of the Declaration of Helsinki.

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