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Association of pain intensity, pain-related disability, and depression with hypothalamus–pituitary–adrenal axis function in female patients with chronic temporomandibular disorders

Kyung B. Jo[a], Young J. Lee[a], Il G. Lee[b], Sang C. Lee[c], Jai Y. Park[d], Ryun S. Ahn[c,*]

[a] Graduate School of Integrative Medicine, CHA University, Seoul, Republic of Korea
[b] Department of Dental Surgery, The Armed Forces Dental Hospital, Seoul, Republic of Korea
[c] Research Center for Chronic Pain and Integrative Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea
[d] Department of Anesthesiology and Pain Medicine, The Armed Forces Capital Hospital, Seoul, Republic of Korea

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ABSTRACT

Patients with temporomandibular disorders (TMD) commonly experience myofascial and joint pain, pain-related disability, and other pain conditions including depression. The present study was carried out to explore the function of the hypothalamus–pituitary–adrenal (HPA) axis in relation to variables of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis II and comorbid depression in female patients with TMD. Cortisol and dehydroepiandrosterone (DHEA) levels were determined in saliva samples that had been collected at various periods after waking (0, 30, and 60 min) and at nighttime (2100–2200 h) from 52 female patients with chronic TMD pain and age- and gender-matched controls ($n = 54$, 20–40 years old). There were no significant differences in the levels and diurnal patterns of cortisol and DHEA secretion between groups of patients with TMD and controls. In patients, the cortisol awakening response (CAR) or diurnal cortisol rhythm were not associated with any variables of the RDC/TMD Axis II or the Beck Depression Inventory (BDI)-II total scores. However, the ratio of overall cortisol secretion within the first hour after waking (CARauc) to overall DHEA secretion during the post-waking period ($Dauc_{awk}$), defined as $CARauc/Dauc_{awk}$, was significantly associated with pain-related RDC/TMD variables (pain intensity and pain-related disability) and BDI-II total scores. Pain intensity and pain-related disability scores were also significantly associated with BDI-II total scores. These results indicated that an increase in molar cortisol/DHEA ratio due to the dissociation between cortisol and DHEA secretion was associated with pain intensity, pain-related disability, and depression in female patients with TMD.

1. Introduction

Temporomandibular disorder (TMD) is a collective term used to describe clinical problems involving the temporomandibular joint, muscles of mastication, or combined muscle–joint disorders (Dworkin and LeResche, 1992). Specific signs or symptoms of TMD may include pain, restricted mandibular movement, and noises from the temporomandibular joints during jaw movement (Herb et al., 2006). TMD pain has been described as a dull, throbbing, or constant aching pain, and it may include a background burning sensation, which is elicited on jaw opening or aggravated by increased jaw functions, such as wide opening of the mouth, yawning, talking, or chewing (Wright and North, 2009). The prevalence of chronic TMD pain (pain lasting for at least 6 months) has been reported by 8% of males and 15% of females, and is highest among 25–44-year-olds, with 10% of that population being males and 18% females (Von Korff et al., 1988). In addition to pain, most patients with chronic TMD pain often suffer from comorbidities. Previous studies have shown that chronic TMD pain is comorbid with other pain conditions such as fibromyalgia, headaches, and back pain (Lim et al., 2011); psychiatric and psychosomatic disorders such as depression and somatization (Yap et al., 2002); and pain-related behavioral and psychosocial disturbances (Manfredini et al., 2010; Reissmann et al., 2008). The number of comorbidities has been demonstrated to be associated with pain-related variables such as pain intensity, pain duration, or both (Dahan et al., 2015).

The hypothalamic paraventricular nucleus (PVN) plays a central role in the integration of circadian and stress signals (Herman et al.,

* Corresponding author.
E-mail addresses: ryunsup@gmail.com, ryunsup@yahoo.co.kr (R.S. Ahn).

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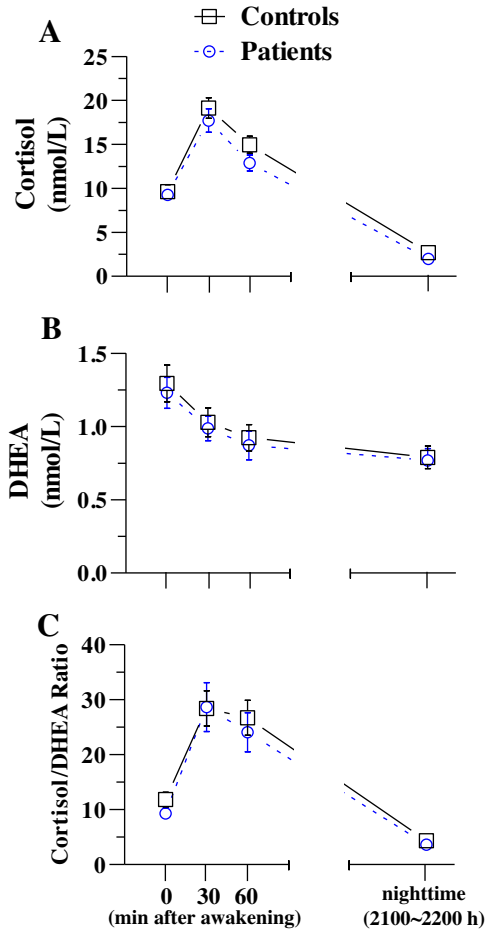

Fig. 1. Cortisol, dehydroepiandrosterone (DHEA), and cortisol/DHEA ratio profiles in patients with chronic TMD pain and healthy controls. Cortisol and DHEA concentrations were determined in saliva samples that were collected at various periods after waking (0, 30, and 60 min) and at nighttime. Samples were obtained from non-pregnant, reproductive-aged female patients with chronic TMD pain ($n = 52$) and age- and gender-matched healthy controls ($n = 54$). The molar cortisol-to-DHEA ratio was calculated from cortisol and DHEA concentrations at each time point. All data are expressed as the mean ± standard error of the mean (SEM).

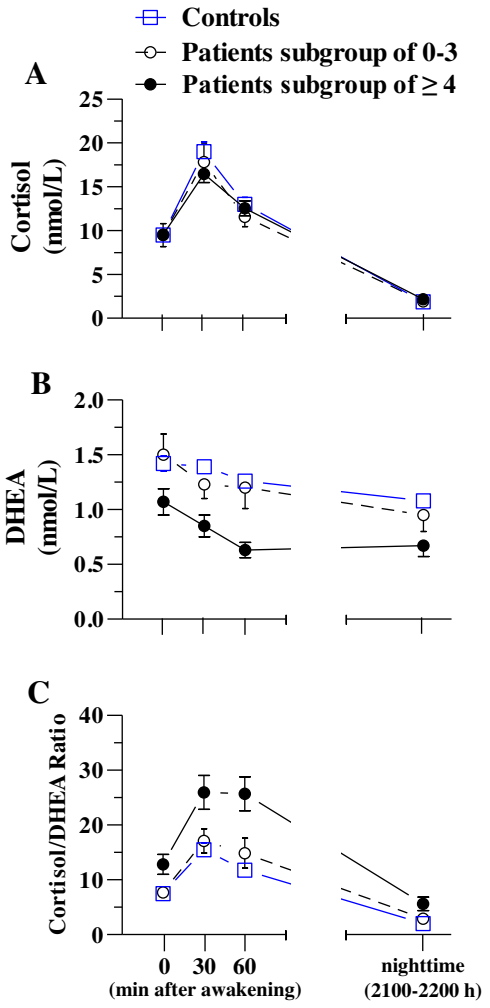

Fig. 2. Cortisol, dehydroepiandrosterone (DHEA), and cortisol/DHEA ratio profiles in patient subgroups: 0–3 and ≥4. Patients were classified into two subgroups based on the recommended cut-off value for the BDI-II affective subscale of 0–3 (subgroup 0–3, $n = 22$) and BDI-II affective subscale scores of 4 or more (subgroup ≥ 4, $n = 30$). Cortisol, DHEA, and cortisol/DHEA ratio profiles in the patient subgroups and healthy controls are presented in Fig. 2A, B and C, respectively. All data are expressed as the mean ± standard error of the mean (SEM).

2003). Neurons in the PVN transmit the integrated signals to other brain regions and peripheral tissues via neurotransmitters, the autonomic nerve system, and the hypothalamus–pituitary–adrenal (HPA) axis (Herman et al., 2002). Cortisol secretion in the HPA axis is characterized by a pronounced diurnal rhythm; a robust increase in cortisol levels within the first hour after waking (called the cortisol awakening response, CAR), and a subsequent decline over the remainder of the day, reaching a nadir at midnight (Weitzman et al., 1971; Pruessner et al., 1997). Because endogenous and exogenous stresses can influence CAR and diurnal cortisol rhythm, these are used as reliable indices for determination of HPA axis function (Adam and Kumari, 2009). A heightened CAR and/or flattened diurnal cortisol rhythm has been demonstrated in patients with chronic pain conditions, such as complex regional pain syndrome and shoulder and neck pain (Neeck et al., 1990; Park and Ahn, 2012).

Along with cortisol, dehydroepiandrosterone (DHEA) is produced in the adrenal cortex in response to adrenocorticotropic hormone (ACTH) and it exhibits the myriad physiological anti-glucocorticoid actions (Kalimi et al., 1994). The concentrations of DHEA in the blood oscillate in parallel with those of cortisol under ACTH stimulation and acute stress conditions (Arvat et al., 2000; Lennartsson et al., 2012), but elevation in cortisol-to-DHEA ratio resulting from reduced DHEA concentrations with either no change or elevation in cortisol concentrations has openly been observed in subjects who are suffering from chronic stress and medical illness (Sollberger and Ehlert, 2016). The elevated cortisol-to-DHEA ratio implies an alteration in adrenocortical steroid secretion toward cortisol secretion and a relative dominance of cortisol actions and functional hypercortisolemic status (Goodyer et al., 1998), and this phenomenon has been demonstrated to be associated with the length of depressive period in non-medicated depressive patients (Young et al., 2002) and the degree of perceived pain-related stress in patients with irritable bowel syndrome (Sugaya et al., 2015).

Given the higher stress levels in patients with TMD pain compared with pain-free subjects, as determined by the Trier Inventory for Chronic Stress (Schmitter et al., 2010), it is reasonable to expect that hormone secretions in the each level of the HPA axis in patients with chronic TMD pain may be different from those in pain-free subjects. However, previous studies have shown no difference in basal cortisol levels (Nilsson and Dahlstrom, 2010), CAR, and diurnal cortisol rhythm (Galli et al., 2009) between groups of patients with TMD and pain-free subjects. Meanwhile, the HPA axis function in patients with chronic pain is susceptible to pain-related comorbid conditions such as psychiatric and psychosomatic disorders and pain-caused physical disabilities. For instance, an altered